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Research Article

Some features of the immune system response in the new coronavirus infection COVID-19

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AIM: to study the cytokine link of immunity in patients with the new coronavirus infection COVID-19 and the possibility of using these data to predict the risk of lung tissue damage.

MATERIALS AND METHODS: Patients with diagnosed new coronavirus infection COVID-19 were divided into 4 groups depending on the severity of the disease: 1 — asymptomatic patients; 2 — patients with lung tissue damage in the amount of 25%; 3 — patients with lung tissue damage 50%; 4 — patients with lung tissue damage 75% (according to the results computed tomography). Immunological studies were performed upon admission to the clinic, then after 7 days and before discharge. The concentration of cytokines in blood serum was studied by the method of solid-phase enzyme immunoassay using kits manufactured by Vector Best.

RESULTS: In all groups, a low content of proinflammatory cytokines was found: tumor necrosis factor and interferon-γ, interleukin-1, and interleukin-2. The median level of interleukin-6 in all groups during the entire follow-up period was within the normal range, however, in some patients, there was a multiple excess of its concentration. In groups with 50% and 75% lung tissue damage, an increase in the concentration of interleukin-8 was shown. Statistically significant differences were noted only for the level of interleukin-8 between the group with an asymptomatic form of infection and the CT-2 and CT-3 groups. It was found that the concentration of interleukin-1 below 3.58 pg/ml is a significant risk factor for severe disease. In all groups of subjects, low levels of interleukin-4 and interleukin-10 were noted, while there was no significant difference between the groups. Positive correlations were revealed between the degree of lung tissue damage and the level of interleukins 6, 2, and 8. Negative correlations were established between the degree of lung tissue damage and the content of interleukin-1.

CONCLUSION: There was no significant activation of the cytokine link of adaptive antiviral immunity in the examined contingent. Serum cytokine levels were within normal values and had no significant intergroup differences. An increase in IL-8 in groups with clinically pronounced signs of infection indicates the activation of indicators characterizing innate immunity.

Keywords: anti-inflammatory cytokines; asymptomatic course; COVID-19; cytokine profile; lung tissue lesion; pro-inflammatory cytokines; T-cells.

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Научная статья

Некоторые особенности реагирования иммунной системы при новой коронавирусной инфекции COVID-19

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Цель: изучение цитокинового звена иммунитета у больных новой коронавирусной инфекцией COVID-19 и возможности использования этих данных для прогнозирования риска развития поражения легочной ткани.

Материалы и методы. Пациенты с диагностированной новой коронавирусной инфекцией COVID-19 были разделены на 4 группы в зависимости от степени тяжести заболевания: 1 — бессимптомные больные; 2 — больные с поражением легочной ткани в объеме 25 %; 3 — больные с поражением легочной ткани 50 %; 4 — больные с поражением легочной ткани 75 % (по результатам компьютерной томографии). Иммунологические исследования проводили при поступлении в клинику, затем через 7 дней и перед выпиской. Изучали концентрацию цитокинов в сыворотке крови методом твердофазного иммуноферментного анализа с применением наборов производства «Вектор Бест».

Результаты. Во всех группах установлено низкое содержание провоспалительных цитокинов: фактора некроза опухоли, интерферрона-γ, интерлейкинов 1 и 2. Медианный уровень интерлейкина-6 во всех группах в течение всего времени наблюдения находился в пределах нормы, однако у отдельных больных наблюдалось многократное превышение его концентрации. В группах с 50 и 75 % поражением легочной ткани показано увеличение концентрации интерлейкина-8. Статистически значимые различия отмечены только для уровня интерлейкина-8 между группой с бессимптомной формой инфекции и группами КТ-2 и КТ-3. Установлено, что концентрация интерлейкина-1 ниже 3,58 пг/мл является значимым фактором риска тяжелого течения заболевания. Во всех группах обследуемых отмечено низкое содержание интерлейкинов 4 и 10, при этом значимой разницы между группами не отмечено. Выявлены положительные корреляционные связи между степенью поражения легочной ткани и уровнем интерлейкинов 6, 2 и 8. Установлены отрицательные корреляционные связи между степенью поражения легочной ткани и содержанием интерлейкина-1.

Заключение. У обследованного контингента не выявлено достоверной активации цитокинового звена адаптивного противовирусного иммунитета. Уровни цитокинов в сыворотке крови находились в пределах нормальных значений и не имели значимых межгрупповых различий. Увеличение IL-8 в группах с клинически выраженными признаками инфекции свидетельствует об активации показателей, характеризующих врожденный иммунитет.

Ключевые слова: бессимптомное течение; поражение легочной ткани; провоспалительные цитокины противовоспалительные цитокины; Т-клетки, цитокиновый профиль COVID-19.

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BACKGROUND

The results of scientific research concerning the coronavirus infection and coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remain relevant to date [1–3]. Studies of COVID-19 conducted in different countries enabled the identification of population groups that are most vulnerable to this infection, examination of the infection course, and development of preventive and treatment methods [4–7].

SARS-CoV-2 causes the development of acute infectious disease of the respiratory tract with typical catarrhal symptoms and can clinically occur as seasonal acute respiratory viral infections. Most patients with COVID-19 have mild or moderate symptoms; however, severe pneumonia develops in approximately 15% of patients, and acute respiratory distress syndrome and multiple organ failure are registered in 5% of cases [8–11].

In response to SARS-CoV-2 infection, protective reactions develop because of the activation of innate and acquired immunity aimed against the virus; however, the immunopathogenesis of COVID-19 is associated with an unbalanced immune response, leading to severe cases of respiratory distress syndrome and impaired lung function [11, 12]. The concept of protective reactions is not limited to the involvement of the cellular components of the immune response. Cytokines serve as an organizing system that forms and regulates the entire complex of protective reactions upon the introduction of pathogens, implementing the relationship between nonspecific protective responses and specific immunity within the immune system, acting in both directions. Some cytokines are constantly synthesized in small amounts, regulating various stages of normal hematopoiesis; however, most cytokines are not involved in the normal physiology of the body, and they are synthesized only for protective reactions. Low levels of cytokines are required for the correct formation of local inflammation, higher doses cause the development of a systemic inflammatory response; however, pathologically high levels lead to the development of the so-called cytokine storm and death.

An unbalanced immune response to the virus, accompanied by insufficient synthesis of interferon (IFN) at disease onset, followed by hyperproduction of pro-inflammatory cytokines, has been to cause severe inflammation in the lung tissue with the development of acute lung injury. In this regard, studying the cytokine profile of patients with COVID-19 in various clinical forms and asymptomatic (AS) carriers of SARS-CoV-2 was considered interesting and important.

This study aimed to analyze the cytokine link of immunity in patients with COVID-19 and the possibility of using these data to predict the risk of lung tissue damage.

MATERIALS AND METHODS

We examined 74 men aged 22–45 years diagnosed with COVID-19. The patients were distributed into four groups depending on the degree of lung tissue damage, where the AS group consisted of 19 patients with a positive test for polymerase chain reactions (PCR) to the ribonucleic acid of the virus without clinical signs of infection, CT-1 included 19 patients with 25% lung tissue damage according to computed tomography findings, CT-2 consisted of 23 patients with 50% lung tissue damage, and CT-3 included 13 patients with 75% lung tissue damage. Venous blood sampling for immunological studies was performed three times, that is, upon admission to the clinic (point 1, on average 1 week after the onset of clinical symptoms), then after 7 days (point 2), and before discharge (point 3, on average 3 weeks after the onset of clinical symptoms). The AS group was admitted to the clinic after receiving a positive PCR test and stayed there for an average of 1.5–2 weeks.

The levels of tumor necrosis factor (TNF), IFN-γ, interleukin (IL)-1, IL-2, IL-4, IL-6, IL-8, and IL-10 were determined by enzyme-linked immunosorbent assay using reagent kits from Vector Best.

Mathematical processing of the results was performed on a personal computer using the standard software package STATISTICA for Windows, version 10.0. To describe the data obtained, the minimum and maximum values of the indicator were used, and the median (*Me*) and the quartile range were calculated. Since the distribution of many indicators differed from the normal distribution, the significance of differences was assessed using the nonparametric Mann–Whitney test and Fisher's exact test.

RESULTS AND DISCUSSION

The results of the analysis of the main pro-inflammatory cytokines in the blood serum of patients with COVID-19 in various clinical forms are presented in Table 1.

According to its data, not only the median levels of IFN-γ in different groups did not exceed the proper values upon hospital admission but also upon personification in all patients examined, and the indicator level was within the reference values.

The highest individual values upon hospital admission were registered in CT-3 (7.10 pg/mL), which was two times lower than the upper limit of normal values. No statistically significant differences were found between the groups, and no significant changes in IFN-γ levels were noted during follow-up.

INF-γ is secreted by cells of both the innate (natural killer cells) and adaptive immune systems (T-helper lymphocytes of the first type). IFN-γ, secreted by killer cells, increases the expression of class II molecules

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Table 1. Blood serum levels of the main pro-inflammatory cytokines of patients with COVID-19 in various clinical forms

Parameter (reference values)	Group	Point 1		Point 2		Point 3	
		Me	quartile range, min–max	*Me*	quartile range, min–max	*Me*	quartile range, min–max
IFN-γ (0–15 pg/mL)	AS	0.00	0.00–3.32 0.00–3.60	0.00	0.00–2.48 0.00–2.49	0.63	0.00–3.74 0.00–3.99
	CT-1	0.00	0.00–0.00 0.00–0.00	0.63	0.00–1.75 0.00–2.66	0.02	0.00–0.36 0.00–3.61
	CT-2	0.62	0.00–2.14 0.00–6.76	0.00	0.00–1.55 0.00–3.28	0.00	0.00–0.32 0.00–2.72
	CT-3	0.00	0.00–0.50 0.00–7.10	0.00	0.00–0.30 0.00–3.67	0.00	0.00–0.45 0.00–0.99
TNF (0–6 pg/mL)	AS	2.47	1.11–3.36 0.78–3.50	2.70	1.79–2.83 1.65–3.37	2.26	1.69–3.43 0.32–3.75
	CT-1	2.23	1.81–2.73 1.40–3.19	2.38	1.81–2.85 0.59–4.43	2.77	1.96–2.90 1.82–4.59
	CT-2	2.73	1.81–3.72 0.65–5.23	2.50	1.64–3.16 0.93–7.29	3.13	2.41–4.56 1.85–6.59
	CT-3	2.17	1.65–2.99 1.14–6.67	2.39	2.22–3.84 0.84–5.16	2.59	1.86–3.21 1.39–4.32
IL-1 (0–11 pg/mL)	CT-1	3.79	1.51–5.26 0.27–6.38	1.28	0.50–2.77 0.00–5.24	2.53	1.26–3.52 0.0–5.16
	CT-2	1.84	0.04–4.41 0.00–9.69	1.07	0.29–2.43 0.00–4.48	0.62	0.36–1.81 0.00–47.78
	CT-3	0.76	0.00–2.25 0.00–3.40	1.09	0.63–2.27 0.10–3.70	1.50	0.22–3.44 0.00–8.57
IL-2 (0–10 pg/mL)	AS	1.36	0.00–1.65 0.00–1.78	0.18	0.15–0.78 0.14–0.83	1.00	0.58–1.33 0.37–1.78
	CT-1	1.23	0.00–1.65 0.00–1.76	0.87	0.51–1.18 0.34–1.51	0.69	0.33–0.90 0.00–1.54
	CT-2	1.27	0.25–1.62 0.00–2.84	0.61	0.55–1.15 0.00–2.04	1.05	0.46–1.70 0.00–2.06
	CT-3	0.91	0.68–1.80 0.20–2.11	0.26	0.00–0.46 0.00–0.80	0.25	0.00–1.02 0.00–1.54
IL-6 (0–10 pg/mL)	AS	1.68	1.07–3.44 0.00–6.08	1.39	0.00–2.29 0.00–3.51	2.06	1.68–2.66 1.33–4.89
	CT-1	2.59	0.68–6.27 0.00–353.00	2.36	0.77–4.47 0.24–5.51	1.21	0.78–1.29 0.00–3.97
	CT-2	4.03	1.44–7.44 0.00–27.92	1.88	0.67–4.67 0.00–43.98	1.62	1.16–3.70 0.06–59.60
	CT-3	5.63	1.09–7.78 0.50–482.00	2.39	1.36–19.8 0.64–458.26	1.68	1.45–1.98 0.85–408.50
IL-8 (0–10 pg/mL)	AS	4.89	3.45–8.83 1.84–65.89	4.00	3.38–5.72 2.49–269.00	4.66 ± 5.55	3.28–12.40 2.97–16.87
	CT-1	9.49	3.79–28.07 1.18–385.21	7.99	4.51–13.93 1.86–240.40	6.76	5.97–22.48 0.99–129.10
	CT-2	16.51	9.89–85.82 0.51–466.39	12.47	8.05–34.33 2.15–89.27	13.91	7.53–31.71 3.57–493.90
	CT-3	11.74	6.78–17.35 5.41–42.04	17.89	9.58–35.28 2.71–41.78	18.74	7.68–59.43 2.76–453.70

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of the major histocompatibility complex on the cell surface, and enhances phagocytosis and destruction mechanisms.

When the virus replicates in cells, IFN production increases, which has varying effects on IFN-γ synthesis and causes the cessation of protein synthesis in infected cells, thereby preventing the production of viral proteins. IFN-γ, which is produced by T-helper lymphocytes of the first type, is involved in the activation of cytotoxic T-cells and macrophages, playing an important role in the immune response to a viral infection.

A similar presentation was noted when analyzing the level of TNF, one of the important factors of antiviral protection. The median TNF values upon hospital admission were within the normal range. Individual values of the indicator exceeded insignificantly the reference values only in one patient from CT-3 (6.67 pg/mL). No statistically significant differences were found between the groups, and no significant changes in TNF levels were noted during follow-up.

In addition to IFN-γ and TNF, this study examined the levels of the pro-inflammatory cytokines IL-1, IL-2, IL-6, and IL-8.

When analyzing the serum level of IL-1 upon hospital admission, both median and individual IL-1 values were within the reference values. In the AS group, this indicator was not determined. In CT-3, the level of IL-1 was the lowest and differed significantly ($p = 0.007$) from the level noted in CT-1. Statistical analysis revealed that an IL-1 value <3.58 pg/mL ($p = 0.004$) was a significant risk factor for severe disease.

Over time, insignificant multidirectional fluctuations in IL-1 levels were noted; as a result, upon hospital discharge, the differences ceased to be significant. The highest value of IL-1 (significantly exceeding the normal level) of 47.78 pg/mL was recorded in CT-2 at hospital discharge.

IL-2 plays a decisive role in the next stage of immune response development. It is produced by activated T-lymphocytes and stimulates the division and growth of T- and B-lymphocytes, natural killers, and monocytes. In this study, the median IL-2 level upon hospital admission in all groups was near the lower limit of the reference values. No significant changes were found over time, and at hospital discharge, IL-2 levels remained quite low in all groups; no values exceeded the threshold of normal values.

The level of IL-6 should be discussed in more detail. The mortality rate in COVID-19 is associated primarily with an avalanche-like increase in this pro-inflammatory cytokine that coordinates the immune response. In this study, no lethal outcomes and cases of the so-called cytokine storm were recorded. Despite the high levels of IL-6 in some patients upon hospital admission (even in CT-3), the median IL-6 values were within normal limits, although with a wide range of indicators, amounting to 5.63 with a quartile range of 1.09–7.78 pg/mL. Despite the normal median values, IL-6 levels upon hospital admission corresponded to the severity of the disease's clinical signs; however, a statistically significant difference was noted only between the level of IL-6 in the AS and CT-2 groups ($p = 0.046$). In the AS group, not a single patient had an IL-6 level above the normal values; in the comparison groups, high IL-6 levels were noted in 15%–17% of the patients examined. Only two patients had IL-6 levels that exceeded the normal threshold many times over, as 353.87 pg/mL was registered in one patient from CT-1, and one patient from CT-3 had a level of 482.25 pg/mL. During treatment, IL-6 levels decreased insignificantly; however, upon hospital discharge with a significant improvement, it remained extremely high (408.46 pg/mL).

When analyzing IL-8 levels, the following data were obtained. In the AS group, the median IL-8 level upon hospital admission was within the normal range (4.89, quartile range 3.45–8.83 pg/mL); however, 20% of the examined patients in this group had high IL-8 levels (14.02–65.89 pg/mL). In CT-1, half of the examined patients had high IL-8 levels (including multiple times, 10.55–385.21 pg/mL), and the median level was at the upper limit of the reference interval, with 9.49 (quartile range 3.79–28.07) pg/mL. In CT-2 and CT-3, the median level of IL-8 was high, and a high IL-8 level (10.52–466.39 pg/mL) was noted in 74% of the patients in CT-2 and 64% in CT-3 (the excess was the smallest, 10.62–42.04 pg/mL). Differences were significant between the AS group and CT-2 ($p = 0.004$) and CT-3 ($p = 0.014$). With follow-up over time, the noted situation did not change significantly. IL-8 levels in CT-2 and CT-3 remained high at hospital discharge. The statistical significance of the differences persisted in the AS group when compared with CT-2 ($p = 0.015$) and CT-3 ($p = 0.029$).

We also conducted an analysis over time of anti-inflammatory cytokines, namely, IL-4 and IL-10, in the blood serum of patients with COVID-19 in various clinical forms. IL-4 is produced by T-helper lymphocytes of the second type; it is a factor in the differentiation of T- and B-cells and limits the synthesis by macrophages of pro-inflammatory IL-1, IL-6, IL-8, and TNF, the formation of highly active metabolites of oxygen and nitrogen. IL-10 is produced by T-helper lymphocytes of the first and second types, monocytes, macrophages, and cytotoxic cells, and has a wide spectrum of action, with a pronounced immunosuppressive effect. In its inhibitory effect on cellular immunity, IL-10 is synergistic with IL-4, can suppress immune inflammation, and is the most important regulator of cytokines, which largely determines the direction of immune responses. The study results are shown in Table 2. Accordingly, the median level of anti-inflammatory cytokines was within normal limits.

Table 2. Blood serum levels of the main anti-inflammatory cytokines in patients with COVID-19 in various clinical forms

Parameter (reference values)	Group	Point 1		Point 2		Point 3	
		Me	quartile range, min–max	*Me*	quartile range, min–max	*Me*	quartile range, min–max
IL-4 (0–4 pg/mL)	AS	0.79	0.24–1.69 0.00–2.28	0.43	00.00–1.03 0.00–1.20	1.27	0.81–2.48 0.41–3.62
	CT-1	1.09	0.22–2.17 0.00–2.59	1.16	0.89–5.40 0.66–9.61	2.42	0.52–4.60 0.30–5.11
	CT-2	1.65	0.29–3.29 0.00–5.89	1.26	0.66–3.99 0.00–5.75	1.10	0.00–2.17 0.00–7.90
	CT-3	0.95	0.70–1.17 0.63–1.44	0.32	0.00–1.46 0.00–1.86	1.20	0.31–2.07 0.00–3.72
IL-10 (0–31 pg/mL)	AS	2.21	0.97–3.60 0.96–4.35	1.47	0.71–2.84 0.17–3.11	0.84	0.11–2.88 0.00–4.05
	CT-1	4.23	3.75–5.68 1.21–7.32	3.90	3.43–4.81 1.94–5.95	5.11	3.44–6.34 3.15–7.54
	CT-2	6.46	4.05–8.02 1.18–13.26	4.35	3.18–7.99 1.36–12.89	3.55	2.26–4.75 1.03–10.74
	CT-3	6.55	3.61–14.41 0.00–22.88	6.03	5.21–10.56 2.17–24.35	5.49	3.56–6.42 2.51–9.73

A high IL-4 level (5.35 and 5.89 pg/mL) upon hospital admission was noted only in two patients from CT-2, and in one of them, the high level persisted until hospital discharge. However, no statistically significant differences were registered between the groups. When followed up over time, no significant fluctuations in the IL-4 levels were noted.

The median IL-10 level upon hospital admission was also within the proper range but was significantly higher in groups with clinically significant disease signs. The statistical significance of the differences between the group of AS patients and groups with clinically significant disease signs was $p = 0.046$, $p = 0.008$, and $p = 0.025$ compared with CT-1, CT-2, and CT-3, respectively.

CONCLUSION

All the examined groups had low levels of pro-inflammatory cytokines TNF and IFN-γ, leading to the implementation of antiviral immunity in the classical immune response, as well as low levels of IL-1, which modulate the activity of neutrophils, and IL-2, which provokes the clonal expansion of adaptive immunity cells. During the entire follow-up period, the level of the pro-inflammatory cytokine IL-6, which is considered one of the leading ones in the pathogenesis of severe COVID-19, was within the normal range in all groups, with multiple increases in some patients. No statistically significant difference was detected between the groups. Such results, in our opinion, are attributed to the cohort examined. Our studies of the cytokine profile were performed in young military men who were not included in the risk group for the development of severe disease. None of the participants had aggravating diseases such as obesity, diabetes mellitus, and chronic heart and respiratory diseases. Even in CT-3, no patients had clinically severe COVID-19. This once again confirms both the individuality of each living organism and the role of the general state of immunity in the ability to resist infection.

Groups with 50% and 75% damage to the lung tissue had high IL-8 levels, which forms a concentration gradient to attract activated neutrophils. The IL-8 level in these groups was higher than normal, and the differences when compared with the level in the AS group were significant.

Notably, IL-1 level <3.58 pg/mL is a significant risk factor for severe disease. All groups had a low level of anti-inflammatory cytokines IL-4 and IL-10, whereas no significant difference was found between the groups.

Thus, our data may indicate that in the cohort examined, against pronounced clinical disease signs, no significant activation of the cytokine link of adaptive antiviral immunity was detected. Serum levels of pro-inflammatory and anti-inflammatory cytokines were within normal limits, showing no significant intergroup differences. When comparing the data obtained, the degree of lung tissue damage correlated positively with the level of pro-inflammatory cytokines IL-6 (0.169), IL-2 (0.241), and IL-8 (0.228). Negative significant correlations were found between the degree of lung tissue damage and levels of pro-inflammatory cytokine IL-1 (–0.459) in the blood serum. An increase in IL-8 levels in groups with clinically pronounced signs of infection indicates indirectly the activation of indicators characterizing innate immunity.

ADDITIONAL INFORMATION

Conflict of interest. The authors declare no conflict of interest.

Ethical considerations. The study was approved by the local ethics committee of the S.M. Kirov Military Medical Academy (minutes dated 05/07/2020).

Author contributions. All authors made a significant contribution to the study and preparation of the article, read and approved the final version before its publication.

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