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Clinical and immunological characteristics of COVID-19 in patients with disease dynamics

Yana A. Safronova, Mariya A. Charkina, Aleksandr S. Pankov
Orenburg State Medical University (Orenburg, Russian Federation)

Abstract

Aim – to study the clinical and immunological indicators of COVID-19 convalescents 1 and 3 months after the disease in dynamics with the determination of predictors of the development of changes in the lungs.

Material and methods. The object of the study was 35 patients aged 22 to 75 years in the dynamics of COVID-19 disease, divided into two groups according to the identified clinical and immunological disorders. Markers of cellular (CD-3, CD-4, CD-8, CD-19) and humoral immunity, cytokines (IL-6,8, TGF-β, TNF-α), CEC were determined in all examined patients. Statistical processing of the obtained results was carried out using the Statistica 10.0 software suite.

Results. It was found that all the subjects retained clinical and immunological changes during the entire follow-up period, which indicates an ongoing disease. At the same time, significant differences in the severity of changes in individuals were revealed, taking into account age and the presence of chronic somatic pathology, expressed primarily in violation of the parameters of the T-system of immunity. In patients with the development of post-Covid changes in the lungs, characteristic immunological features were revealed, taking into account age.

Conclusions. A violation of the identified indicators of the immune system may indicate the persistence of the virus, which means a prolongation of a specific inflammatory response with the risk of extensive tissue damage. The tendency towards the formation of humoral immunity persists in both groups within three months after recovery. Humoral immunity was formed by the end of 1 month after the disease in both groups and continued to persist throughout the entire follow-up period. In the risk group for the development of pneumofibrosis in the outcome of a new coronavirus infection, the combination of IL-8 and TGF-β is the most optimal, despite their significant decrease in dynamics compared with the acute period.

Keywords: cellular immunity, humoral immunity, convalescents of COVID-19, catamnesis.

Conflict of interest: nothing to disclose.

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Information about authors
Yana A. Safronova – a postgraduate student of the Epidemiology and Infectious Diseases Department.
ORCID: https://orcid.org/0000-0003-3949-6851
E-mail: charkina.ya@yandex.ru
Mariya A. Charkina – a student of the Faculty of Medicine.
ORCID: https://orcid.org/0009-0002-2889-5582
E-mail: charkina.marya@gmail.com
Aleksandr S. Pankov – PhD, Associate professor, Head of the Epidemiology and Infectious Diseases Department, Director of the Research Center.
ORCID: https://orcid.org/0000-0003-4994-6633
E-mail: aspan751@mail.ru

Corresponding Author
Yana A. Safronova
Address: Orenburg State Medical University, 6 Sovetskaya st., Orenburg, Russia, 460014.
E-mail: charkina.ya@yandex.ru

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Клинико-иммунологическая характеристика COVID-19 у пациентов в динамике заболевания

Я.А. Сафронова, М.А. Чаркина, А.С. Паньков
Оренбургский государственный медицинский университет (Оренбург, Российская Федерация)

Аннотация

Цель – изучить клинико-иммунологические показатели реконвалесцентов COVID-19 через один и три месяца после перенесенного заболевания с определением предикторов развития изменений в легких.

Материал и методы. Объектом исследования были 35 пациентов в возрасте от 22 до 75 лет в динамике заболевания COVID-19, разделенные на две группы в соответствии с выявленными клинико-иммунологическими нарушениями. У всех обследованных были определены маркеры клеточного (CD-3, CD-4, CD-8, CD-19) и гуморального иммунитетов, цитокины (IL-6,8, TGF-β, TNF-α), ЦИК. Статистическая обработка полученных результатов была проведена с использованием компьютерной программы Statistica 10.0.

Результаты. Было установлено, что у всех обследуемых сохраняются клинико-иммунологические изменения в течение всего периода наблюдения, что свидетельствует о продолжающемся заболевании. При этом выявлены существенные отличия выраженности изменений у лиц с учетом возраста и наличия хронической соматической патологии, выражающиеся в первую очередь в нарушении параметров Т-системы иммунитета. У пациентов с развитием постковидных изменений в легких выявлены характерные иммунологические особенности с учетом возраста.

Выводы. Нарушение выявленных показателей иммунной системы может свидетельствовать о персистенции вируса, а значит, о пролонгации специфического воспалительного ответа с риском обширного повреждения ткани. В течение трех месяцев после выздоровления в обеих группах сохранялась тенденция к формированию гуморального иммунитета. Гуморальный иммунитет сформировался к концу первого месяца после перенесенного заболевания в обеих группах и сохранился в течение всего периода наблюдения. В группе риска развития пневмофиброза в исходе новой коронавирусной инфекции наиболее оптимальным является сочетание IL-8 и TGF-β, несмотря на достоверное уменьшение их в динамике по сравнению с острым периодом.

Ключевые слова: клеточный иммунитет, гуморальный иммунитет, реконвалесценты COVID-19, катамнез.

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Сведения об авторах
Сафронова Я.А.– аспирант кафедры эпидемиологии и инфекционных болезней.
ORCID: https://orcid.org/0000-0003-3949-6851
E-mail: charkina.ya@yandex.ru
Чаркина М.А.– студентка лечебного факультета.
ORCID: https://orcid.org/0009-0002-2889-5582
E-mail: charkina.marya@gmail.com
Паньков А.С. – д-р мед. наук, доцент, заведующий кафедрой эпидемиологии и инфекционных болезней, директор НИЦ.
ORCID: https://orcid.org/0000-0003-4994-6633
E-mail: aspan751@mail.ru

Список сокращений
ЦИК – циркулирующие иммунные комплексы; ФП – фагоцитарный показатель; КТ – компьютерная томография; ССЗ – сердечно-сосудистое заболевание; СД – сахарный диабет.

Автор для переписки
Сафронова Яна Александровна
Адрес: Оренбургский государственный медицинский университет, ул. Советская, 6, г. Оренбург, Россия, 460014.
E-mail: charkina.ya@yandex.ru

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INTRODUCTION

Despite the fact that in May 2023, WHO declared the end of the COVID-19 pandemic, data on the persistence of symptoms in convalescents that significantly reduce the quality of life, continue to emerge. The main complaints are fatigue, shortness of breath, muscle weakness, impaired concentration, impaired sense of smell, and lack of sleep [1]. The high prevalence of respiratory failure in the outcome of the new coronavirus infection, the need for artificial ventilation in patients with severe disease contribute to the development of remote pulmonary complications, primarily pulmonary fibrosis [2]. The pathogenesis of COVID-19 is based on pathoimmunological mechanisms with a damaging effect on organs and tissues.

The diversity of clinical manifestations of the course of infection in the follow-up determines the interest in studying clinical and immunological changes in dynamics in COVID-19 convalescents of different age. The pathogenesis of multiple organ damage in COVID-19 is diverse and is associated, firstly, with the direct cytopathic effect of the virus on tropic cells, secondly, with the damaging effect of cytokines, and thirdly, with a violation of the hemostasis system due to damage to the endothelium with the development of thrombosis.

The issue of the development of remote changes in a past infection, as well as proinflammatory mechanisms of prolongation of changes in the lungs, has interested scientists for quite some time. The aspects of formation of pulmonary fibrosis as a result of viral infections have been studied most thoroughly using MERS-CoV, SARS-CoV influenza as an example [3, 4, 2, 5–7]. Thus, in the influenza caused by the H1N1 virus, the development of fibrosis is of a multi-factor nature: aggressive fibroblastic activity that occurs in response to massive damage to lung tissue and hypoxia, high level of TNF-α correlating with the duration of hypoxia, and the role of TGF-β, independent from other factors, in the stimulation of fibroblast proliferation and subsequent growth of connecting tissue [3, 8, 9].

Based on the data from a retrospective analysis of foreign colleagues, Russian scientists identified the pathogenetic mechanisms of the lung fibrosis induced by SARS-CoV-2 [1–3]. Important roles were identified in the tumor necrosis factor α, transforming factor β, interleukin-6, which is confirmed by the increase of the said factors in the COVID-19 patients' serum. The literature describes cases of detection of fibrogenesis biomarkers in bronchoalveolar lavage (BAL) 24 hours after the development of ARDS [1, 2]. Data on the assessment of biomarkers in blood serum in comparison with radiological data in dynamics in convalescents are not provided.

The importance and clinical significance of immunological aspects of development of lifelong complications of the disease in the form of fibrosis have been studied for years [2, 3]. Understanding the mechanisms involved in the development of long-term sequelae of SARS-CoV-2 infection necessitates monitoring patients beyond the acute stage of SARS-CoV-2 infection.

AIM

To study the clinical and immunological parameters of COVID-19 convalescents one month and three months after the disease with the identification of predictors of the development of changes in the lungs.

MATERIAL AND METHODS

The study was performed in the scientific research center of the Orenburg State Medical University (OSMU). *Inclusion criteria:* positive PCR result from the nasopharynx for the presence of SARS-CoV-2, bilateral viral pneumonia according to the results of computed tomography of the chest organs. All patients signed informed voluntary consent for the processing of personal data and medical intervention upon hospitalization.

Thirty-five (35) convalescents aged 22 to 75 years were examined in the dynamics of the COVID-19 disease (one and three months after recovery). During the examination, patients were divided into two groups in accordance with the identified clinical and immunological disorders. The first group included young and adult individuals (n=20); the second, elderly and senior individuals (n=15). As the control, the standard values of immunological indicators developed in the OSMU problem laboratory for studying the mechanisms of natural immunity were used.

In all of the examined individuals, markers of cellular immunity were identified (CD-3, CD-4, CD-8, CD-19) by immunofluorescence using monoclonal antibodies from "Sorbent" (Moscow); phagocytic index and phagocytic index in relation to St. aureus, metabolic activity of segmented neutrophils in spontaneous and induced reaction with nitroblue tetrazolium dye (NBT test); levels of A, M, G immunoglobulins in the immunodiffusion reaction, as well as content of circulating immune complexes (CIC) in a precipitation reaction with polyethyleneglycol, cytokines IL-6, IL-8, TGF-β, TNF-α by enzyme immunoassay (EIA) using test systems from "Vector Best". To identify a possible relationship between qualitative characteristics, the Pearson coefficient

Characteristic		Total sample	Young and adult age (n=20)	Senior and old age (n=15)
Age		52,4±17,6	53,7±13,5	76,2±13,8
Sex	Male	23 (65,7%)	**13 (65%)**	**10 (66,7%)**
	Female	12 (34,3%)	7 (35%)	5 (33%)
CVD		5 (14%)	4 (20%)	**1 (6,7%)**
Respiratory system		3 (8,5%)	1 (2%)	2 (13,3%)
Diabetes mellitus		4 (11,4%)	2 (10%)	**2 (13,3%)**
Obesity		4 (11,4%)	2 (10%)	2 (13,3%)
Multiple sclerosis		2 (5,7%)	2 (10%)	0
Mixed nosology		10 (28,5%)	2 (10%)	8 (53%)
Severe degree of COVID-19		12 (34,3%)	5 (25%)	7 (46,7%)
Disease duration before hospitalization, M±SD		6,3±1,7	7,8±2,2	8,5±2,15
Duration of hospitalization, M±SD		13,56±3,44	12,47±4,03	23,71±11,2

Table 1. *General characteristics of the studied groups of patients*

Таблица 1. *Общая характеристика исследуемых групп пациентов*

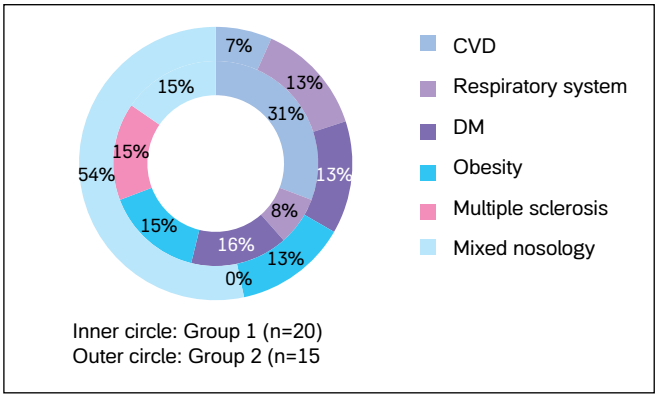

Figure 1. *Characteristics of the sample, taking into account the comorbid background.*

Рисунок 1. *Характеристика выборки с учетом коморбидного фона.*

Immune status values in convalescents		After one month Me [Q_{25}; Q_{75}]		After three months Me [Q_{25}; Q_{75}]	
		Group 1 (n=25)	Group 2 (n=19)	Group 1 (n=25)	Group 2 (n=19)
Leukocytes, 10^9/л		**4,1**	7,9	7,1	5,6
Lymphocytes	%	**25,6** [24,25; 27,25]	10,4 [9,1; 14,3]	35,4 [27; 41]	24,1 [19,8; 29,7]
	10^9/л	**1,09 [1,25; 1,37]↓**	0,81 [0,61; 1,45]	2,4 [1,96; 3,034]	1,97 [1,86; 2,091]
CD-3	%	**52 [46,25; 57,25]↓**	**44 [39; 54]**	**56 [50; 60]**	**47 [46;51]↓**
	10^9/л	**0,46 [0,62;0,72]↓**	**0,511 [0,166; 0,751]**	1,344 [0,98; 1,608]	0,943 [0,82; 0,95]
CD-4	%	**36 [35; 37,5]**	**30 [26; 41]↓**	48 [42; 53]	**33,6 [30;41]↓**
	10^9/л	**0,37 [0,19; 0,49]**	**0,23 [0,16; 0,41]↓**	1,152 [0,769; 1,305]	**0,219 [0,12; 0,68]↓**
CD-8	%	**25 [18; 30]**	32 [25; 34]	30 [23;31]	**21,6 [20,2; 26,3]**
	10^9/л	**0,297 [0,18;0,67]**	**0,29 [0,19; 0,47]**	0,72 [0,52; 0,758]↑	0,386 [0,23;0,51]
CD-19	%	14 [10; 17]	15 [12; 21]	16 [12; 23]	21,4 [20;24]↑
	10^9/л	**0,129 [0,13; 0,19]**	**0,15 [0,11; 0,21]**	0,379 [0,359; 0,48]	0,414 [0,37; 0,49]
PC, %		**49,5 [33,5; 66,75]**	**33 [28,7; 42,9]**	**39 [33; 50]**	**38,2 [35; 41]**
PI, conv. Units		**5,65 [4,525; 6,4]**	**3,8 [3,5; 3,9]**	**3,9 [3,7; 4,2]**	4,34 [3,9; 4,4]
Spontaneous NBT, %		**3,62 [3; 4,35]↓**	**1,2 [0,7; 2,3]**	**1,0 [0,7; 1,3]**	**2,72 [1; 4,3]↓**
Stimulated NBT, %		**27,8 [15; 46,28]↓**	44,2 [37,8; 45,4]	35,7 [34,7; 43,7]	35,14 [25,7; 47,3]
CIC, U		**144 [154;169,5]↑**	**178 [67; 393]**	**113 [96; 227]**	**233,2 [175;193]↑**
IgA, g/l		2,4 [2,13; 3,125]	2,53 [2,15; 3,03]	2,84 [2,23; 4,46]	**3,51 [2,57;4,22]**
IgM, g/l		**0,8 [0,6; 1,05]↓**	1,31 [1,13; 1,31]	1,31 [1,31; 1,76]	**0,84 [0,6;1,2]↓**
IgG, g/l		10,2 [6,8; 13,34]	10,56 [8,94; 10,68]	11,52 [6,91; 13,81]	10 [6,79; 13,81]
IgM specific to SARS-CoV-2		0,95 [1; 1,3]	4,71 [3,15; 10,73]	3,86 [1,77; 4,42]	1,64 [1,2; 1,97]
IgG specific to SARS-CoV-2		18,9 [15,6; 20]	16,9 [14,92; 18,67]	15,90 [11,92; 20,17]	16,65 [15; 17]

Note: values in bold are credibly ($p<0.05$) different from normative values.

Table 2. *Indicators of immune status in COVID-19 convalescents in the catamnesis*

Таблица 2. *Показатели иммунного статуса у реконвалесцентов COVID-19 в катамнезе*

was determined; between quantitative and qualitative characteristics, the methods of group and one-factor variance analysis with the determination of the F-test, the Kruskal-Wallis test was used. Methods of multivariate statistics were used, namely descriptive statistics. Statistical processing of the obtained results was carried out using Statistica 10.0 software suite.

RESULTS

The results obtained are shown in **Tables 1–3**. The average age of the patients in the first group was 53.7±13.5 years; the patients were predominantly male, 60% (15 patients). In the second group, the average age was 76.2±13.8 years; the patients were also predominantly male, 63.2% (12 patients). The predominance of males in the study group is associated with gender-specific features of the epidemiology of acute viral infections [10–12].

The analysis of the comorbid background revealed that young and adult patients had cardiovascular diseases (CVDs) most frequently (**Fig. 1**). Senior and old individuals had conditions of mixed nosology (diabetes mellitus, obesity, CVDs, diseases of the respiratory system). The most statistically significant ($p<0.05$) were the cardiovascular diseases in both age groups, as well as diabetes mellitus in senior and old age.

Among the patients with severe forms of the disease, senior and old patients were 58% (7 patients) from the total number of examined individuals (**Fig. 2**). The comorbid background, and the duration of the disease before hospitalization had statistical significance on the progression of the disease severity, which conforms with the data from the literature [10, 11, 13].

	After 1 month		After 3 months		Norm
	Group 1	Group 2	Group 1	Group 2	
IL-6	8,6	**53,16**	3,3	**33,72**	Не > 10 пг/мл
IL-8	7,3	8,34	**13,4**	**11,49**	Не > 10 пг/мл
TNF-α	5,1	4,36	3,7	6,1	Не > 6 пг/мл
TGF-β	6,43	18,72	22,3	11,88	Не >38 нг/мл

Table 3. *Assessment of cytokines in the blood of COVID-19 convalescents in dynamics*

Таблица 3. *Оценка цитокинов в крови у реконвалесцентов COVID-19 в динамике*

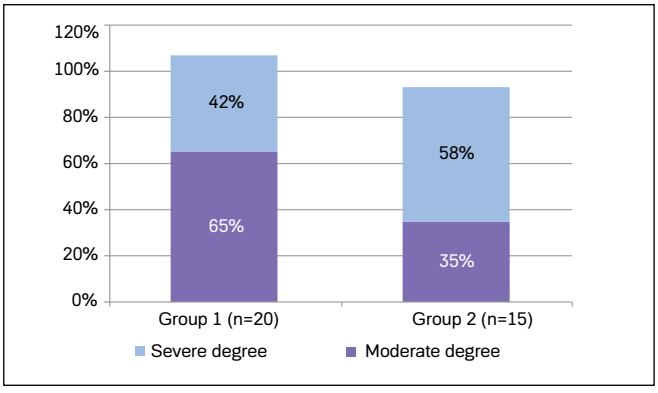

Figure 2. *Characteristics of the sample, taking into account the degrees of severity.*
Рисунок 2. *Характеристика выборки с учетом степеней тяжести.*

The values in bold have a credible difference from normative values ($p<0.05$). These include values of T-cellular immunity CD-3, CD-4, cytotoxic lymphocytes CD-8, phagocytic value, phagocytic index, IgA, amount of CIC, nitro-blue tetrazolium reduction test.

In both groups, absolute and relative lymphopenia was identified (CD-3, CD-4) one month after recovery. In the patients of the second group, the changes in CD-3 and CD-4 persisted for three subsequent months.

The evaluation of the CD-8 level revealed minor differences in both groups one month after the recovery. Three months after the recovery, there was a tendency towards decreasing of the CD-8 level as compared to the control values in the older patient group.

In patients of both groups, the IgA level had boundary values one month after the recovery, while the distribution of IgM and IgG was normal. In older patients, an increase of the IgA was identified three months after the recovery with normal values of IgM and IgG. The amount of specific IgM and IgG against SARS-CoV-2 in both groups was sufficient throughout the entire follow-up period.

The level of CIC was elevated in both groups one month after the recovery and in the follow-up.

Minor differences were seen in the assessment of phagocyte values in both groups; they were observed to decrease with the phagocyte index remaining stable, and the results of the spontaneous NBT test were lower one month after the discharge. In the second group of patients, the changes persisted.

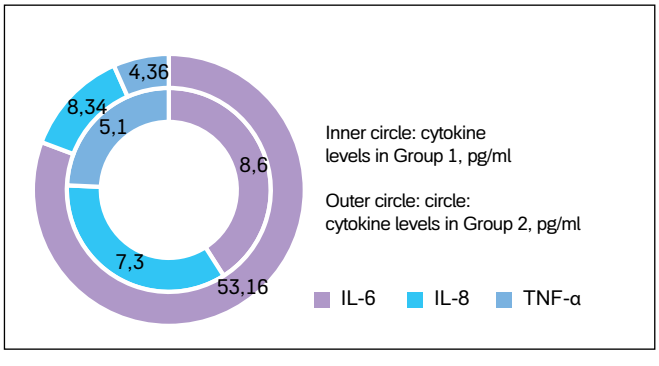

Figure 3. *Cytokine changes after 1 month in convalescents.*
Рисунок 3. *Изменение цитокинов через 1 месяц у реконвалесцентов.*

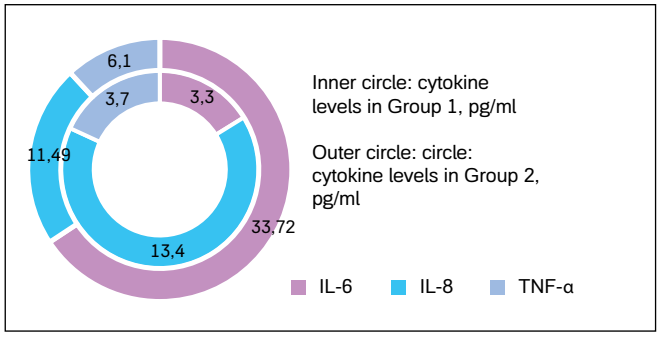

Figure 4. *Cytokine changes after 3 months in convalescents.*
Рисунок 4. *Изменение цитокинов через 3 месяца у реконвалесцентов.*

The analysis of the cytokines revealed various changes (**Fig. 3, 4**). In the first group, the changes only appeared three months after the recovery (increase of the IL-8). In the patients of the second group, the increase of the IL-6 was seen one month past the infection despite the implementation of targeted therapy. In three months, an increase of the IL-8 and TGF-β was observed (**Fig. 5**).

DISCUSSION

Our study established that clinical and immunological changes persist throughout the entire duration of the disease in all examined individuals; this indicates that the disease was in progress. The revealed significant differences in the degree of changes in clinical and immunological parameters in individuals, taking into account age and the presence of chronic somatic pathology, are expressed primarily in the violation of the parameters of the T-system of immunity. These circumstances are novel and require discussion [14, 15]. An important problem is the assessment of risks of development of a severe course of the disease, as well as influence of various factors and development of adverse outcomes [16, 2, 17]. The fact that the convalescents still demonstrated symptoms of COVID-19 for more than 21 days confirms importance of studying the changes in the immunity after the disease [12, 16, 18, 19].

According to literature data, the leading role in the formation of immunity is assigned to CD4+ T-cells due to the neutralization of antibodies and the emigration of lymphocytes into the lung tissue [20, 4]. The functional lowering of the level of cytotoxic CD8+ lymphocytes

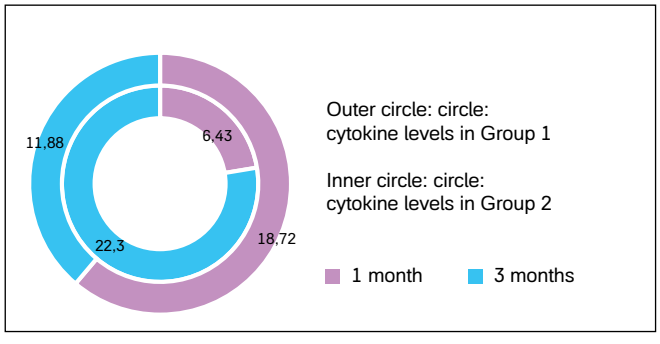

Figure 5. *Change in cytokine TGF-β after 1, 3 months in convalescents, ng/ml.*
Рисунок 5. *Изменение цитокина TGF-β через 1, 3 месяца у реконвалесцентов, нг/мл.*

correlates with the progression of the disease, and vice versa [5, 7]. Disruption in several components of the immune system may indicate the persistent nature of the virus, and, respectively, the persistence of the specific inflammatory response and severe tissue injury.

Our research also correlates the abnormal quantities of CD-3 and CD-4 cells in patients with the development of severe forms of the disease regardless of the initial moderate progression. The time required for the normal levels of the immunity depends on the age. Additionally, the quantitative change in the cytotoxic CD-8 lymphocytes in the patients of Group 2 three months after the disease creates the conditions for exacerbation of chronic infections, risk of development of other acute infections, but still is not sufficient for the development of autoimmune reactions. It is necessary to study the immune parameters in the follow-up in order to understand of mechanisms of deferred changes in the convalescents' organism [12, 16, 19].

As a rule, humoral and cellular immunity should be formed in patients who have had a new coronavirus infection, but the response of antibodies and specific CD8+ T-lymphocytes develops independently of each other and is determined by genetic factors [21, 19]. Within three months after the disease, the examined groups retained the capability for a specific humoral response with respect to the normal levels of cytotoxic lymphocytes [14, 5].

The elevated amounts of CIC in both groups in the follow-up may be related to exacerbation of chronic diseases and advances a high risk of development of auto-allergic reactions [11, 20, 4].

A relevant intra-vital outcome of COVID-19 that affects the patient's quality of life is the development of pneumofibrosis [13, 17, 22]. The literature describes at least two mechanisms of development of pneumofibrosis under the new coronavirus infection. Firstly, the capability of SARS-CoV-2 to induce the decrease of ACE-2 clearance in the lungs resulting in a disruption of TGF-β and CTGF regulation [3, 5, 15]. Secondly, the direct cytopathic action of TNF-α on the capillary endothelium of alveolar wall, the proinflammatory action being supported by IL-6, IL-8, IL-18 [3, 10]. The damage of the basement membranes seen in the new coronavirus infection promotes a progressive growth of fibroblastic tissue. The prognostic significance of these factors remains poorly understood and relevant for understanding the risks of developing long-term consequences of the disease.

The identified changes of the cytokines (IL-6, IL-8, TNF-α, TGF-β) in convalescents of COVID-19 were analyzed with respect to development of post-COVID changes in the lungs using the method of CT of the lungs [10, 5]. The increase of the IL-8 and TGF-β, when compared to the X-ray pattern of the pneumofibrosis in the convalescents confirms the correlation of the indicators. The absence of pneumofibrosis on CT may indicate an existing high predisposition to the development of pneumofibrosis with characteristic blood changes in the presence of any trigger (viruses of influenza, SARS-CoV-2, and other ARDs) [3, 13, 17]. In a similar study, the characteristics of immunity of patients with co-infection of influenza and COVID-19 in the acute stage of the disease when assessing the cytokines, saw normal values of IL-6, IL-8, TGF-β, TNF-α, which indicates a low risk of development of lung fibrosis [12].

CONCLUSIONS

1. The persistence of clinical and immunological changes in the body of convalescents indicates the persistence of the SARS-CoV-2 virus, and an increase in the level of CIC indicates the prolongation of the damaging effect of the virus on the body of the recovered individual.

2. The pronounced disruptions caused decrease in the levels of CD-3, CD-4. Statistically significant changes were identified in the group of senior patients due to preservation of absolute and relative lymphopenia throughout the period of observation.

3. In the risk group of pneumofibrosis development, the most optimal is the combined increase in the levels of IL-8 and TGF-β. The absence of pneumofibrosis on CT with an immunological pattern of the blood may indicate a high predisposition of this group of patients towards development of pneumofibrosis.

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Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. Ya.A. Safronova – research concept and design, material collection and processing, statistical data processing, text writing, editing. M.A. Charkina – material collection and processing, text writing. A.S. Pankov – editing, approval of the final version of the article. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Я.А. Сафронова – концепция и дизайн исследования, сбор и обработка материала, статистическая обработка данных, написание текста, редактирование. М.А. Чаркина – сбор и обработка материала, написание текста. А.С. Паньков – редактирование, утверждение окончательного варианта статьи. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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