CHANGES IN SOME IMMUNOLOGICAL PARAMETERS AFTER COVID-19: GENERAL TRENDS AND INDIVIDUAL CHARACTERISTICS

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The specifics of individual immune reactions after COVID-19 have not been studied sufficiently. This study aimed to describe the changes in indicators of cellular and humoral levels of immunity after COVID-19, and gage general trends and individual characteristics. We sampled blood of 125 unvaccinated COVID-19 patients (29 men and 96 women, median age 53 years) 1 to 4 months after recovery, and determined the relative content of T-lymphocytes ($CD3^+$), B-lymphocytes ($CD19^+$), and cells with late activation markers ($CD3^+HLA^-DR^+$) in them using flow cytometry. With the help of ELISA, we have registered the level of circulating immune complexes, which can be medium molecular weight (CICmed) and low molecular weight (CIClow), and the content of antibodies to SARS-CoV-2. In the mild course group, significant differences from the normal values ($p < 0.001$) were found for T cells (growth, 74.4 ± 1.2% vs. 68.6 ± 1.1%) and B cells (decline, 10.2 ± 0.7% vs. 13.9 ± 0.9%). In the moderately severe course and severe course groups, the level of $CD3^+HLA–DR^+$ lymphocytes was increased (7.7 ± 0.4% and 15.7 ± 2.5%, respectively, versus 3.9 ± 0.8% in the control group; $p < 0.01$). All the examined patients had high levels of CIClow (2.6-2.9-fold increase) and CICmed (1.6–1.8-fold increase). The protective level of antibodies to SARS-CoV-2 above 150 BAU/ml was registered in about 50% of the mild group participants, 75% of the moderately severe group members, and 100% of patients who had the disease in a severe form. We detected no connections between immune disorders and clinical features of the course of the disease and the period thereafter, with the exception of abdominal syndrome peculiar to the acute stage of the disease. The article also describes a clinical case of detection in the early post-COVID-19 period of a pathological clone characteristic of B cell chronic lymphocytic leukemia, and its subsequent disappearance and normalization of the immunophenotype as registered during a follow-up 1.5 years after recovery. The persistent immunological shifts should be taken into account when assessing the risks of reinfection and possible complications.

Keywords: COVID-19, T-lymphocytes, B-lymphocytes, circulating immune complexes, individual characteristics

Compliance with the ethical standards: the study was approved by the Ethics Committee of the Russian Hematology and Transfusiology Research Institute of the FMBA of Russia (Minutes #31 of July 20, 2023). All participants have voluntarily signed informed consent forms.

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ИЗМЕНЕНИЯ НЕКОТОРЫХ ИММУНОЛОГИЧЕСКИХ ПОКАЗАТЕЛЕЙ ПОСЛЕ ПЕРЕНЕСЕННОЙ ИНФЕКЦИИ COVID-19: ОБЩИЕ ТЕНДЕНЦИИ И ИНДИВИДУАЛЬНЫЕ ОСОБЕННОСТИ

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Особенности индивидуальных иммунных реакций после перенесенного COVID-19 недостаточно изучены. Целью работы было охарактеризовать изменения показателей клеточного и гуморального звеньев иммунитета после перенесенного COVID-19 с оценкой общих тенденций и индивидуальных особенностей. У 125 невакцинированных пациентов, перенесших COVID-19 (29 мужчин и 96 женщин, Me возраста — 53 года), через 1–4 месяца после выздоровления методом проточной цитометрии определяли относительное содержание Т-лимфоцитов ($CD3^+$), В-лимфоцитов ($CD19^+$), клеток с маркерами поздней активации ($CD3^+HLA^-DR^+$). Исследовали уровень циркулирующих иммунных комплексов — среднемолекулярных (ЦИКср) и низкомолекулярных (ЦИКн) и содержание антител к SARS-CoV-2 методом ИФА. Достоверные отличия от нормы ($p < 0,001$) выявлены для Т-клеток — повышение (74,4 ± 1,2% против 68,6 ± 1,1%) и В-клеток — снижение (10,2 ± 0,7% против 13,9 ± 0,9%) в группе с легким течением. В группах со среднетяжелым и тяжелым течением COVID-19 повышен уровень $CD3^+HLA^-DR^+$ лимфоцитов (7,7 ± 0,4% и 15,7 ± 2,5% соответственно, против 3,9 ± 0,8% в контроле; $p < 0,01$). У всех обследованных повышен уровень ЦИКн (в 2,6–2,9 раз) и ЦИКср (в 1,6–1,8 раз). Защитный уровень антител к SARS-CoV-2 выше 150 BAU/мл отмечен примерно у 50% обследованных с легкой формой инфекции, у 75% — со среднетяжелой формой и у 100% — с тяжелой. Связи между иммунными нарушениями и клиническими особенностями течения COVID-19 и постковидного периода не обнаружено, кроме наличия абдоминального синдрома в остром периоде болезни. Описан клинический случай выявления в раннем постковидном периоде патологического клона, характерного для В-клеточного хронического лимфолейкоза с последующим его исчезновением и нормализацией иммунофенотипа при повторном обследовании через 1,5 года. Сохраняющиеся иммунологические сдвиги необходимо учитывать для оценки рисков повторного заражения и развития возможных осложнений.

Ключевые слова: COVID-19, Т-лимфоциты, В-лимфоциты, иммуноглобулины, циркулирующие иммунные комплексы, индивидуальные особенности

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Since the emergence of SARS-CoV-2, there has been accumulated a significant amount of data about risk factors that can make the course of the disease severe, as well as about characteristics of the post-COVID period. The mechanisms of damage to cells and tissues caused by the virus and those behind the development of specific immunity were investigated in sufficient detail. However, several studies suggest that there is an individual immune response to the disease, unrelated to age or gender. The currently unanswered questions pertain to the role of individual immune factors in COVID-19 cases and the specifics of individual reactions in various groups of patients, including in the post-COVID period; the urgency of these questions stems from the fact that the effectiveness of protection against reinfection largely depends on the ability

to preserve immune memory after exposure to the virus. Humoral response has been considered in a sufficient number of publications, unlike the state of T-cell immunity, although it plays an important role in the development of adaptive immunity, and the synthesis of specific immunoglobulins is not a reliable indication of a formed protective immune response [1–4]. Moreover, some papers report that the amount of protective antibodies to SARS-CoV-2 is not a factor that significantly affects the risk of developing the post-COVID syndrome [5].

The term "long COVID" has been widely used since 2020; it unites various symptoms that persist or manifest several weeks or months after SARS-CoV-2 contraction. ICD-10 was extended with a new code, U09.9, post-COVID-19 condition. The symptoms of the post-COVID syndrome may be manifesting for three or more months after the acute stage of COVID-19 [6, 7]. However, persisting immune imbalance can be diagnosed even when there are no clinical signs of the said symptoms. Presence of the anti-infection protection markers for 4–6 months or more after vaccination or a past disease does not always shield against reinfection, especially since even such a significant indicator as the amount of specific antibodies is not the only factor determining the body's neutralizing capacity [8]. In addition, immune response disruptions may predispose people with a history of COVID-19 to secondary bacterial and fungal infections [9].

Papers covering the respective issues note a number of general trends, including altered composition of the circulating immune cells (more activated T lymphocytes, short-lived highly differentiated $CD8^+$T lymphocytes, and proinflammatory T helper cells), which was accompanied by a change in the proportion of anti-inflammatory regulatory T cells and their malfunctioning, along with a growing amount of NK cells ($CD16^+/CD56^+$) [10–13]. Another common feature was an increased level of IgA in plasma and the number of circulating immune complexes [2]. At the same time, many researchers note high variability of the immune response to SARS-Cov-2 [2, 12, 13], with attempts to identify patterns thereof and regularities in the development of immune memory associated with the virus remaining largely unsuccessful so far.

Thus, it is necessary to continue studying the state of the immune system after exposure to SARS-CoV-2.

This study aims to describe the changes in some indicators of immunity to COVID-19 (cellular and humoral levels) and assess general trends and individual characteristics.

METHODS

Patients that recovered from COVID-19 1 to 4 months before the start of the study could participate therein. The exclusion criteria were a chronic somatic pathology (including diseases of the respiratory and cardiovascular systems, diabetes mellitus, confirmed immunodeficiency, etc.), and a positive SARS-CoV-2 PCR test result. The study included 125 unvaccinated patients who had had COVID-19 in 2020-2021, including 29 men and 96 women, aged 25-83 years (median — 53 years); on average, they recovered from the disease 2.6 months ago (median — 2 months). Additionally, we re-examined a group of 14 patients (2 men, 12 women) that recovered from COVID-19 6-8 months ago. As for the severity of COVID-19, 61 participant had a mild form of the disease, 55 moderate, and 9 — severe. The degree was determined based on the criteria established by the current revision of the Guidelines for the Prevention, Diagnosis and Treatment of COVID-19, factoring in fever, shortness of breath, blood saturation, serum C-reactive protein levels, and CT data. The respective information was collected from the medical records provided by the examined individuals. Before taking a blood sample for the study, we asked the participants whether they had clinical symptoms peculiar to the post-COVID period, such as impaired sense of smell and taste, abdominal syndrome, skin syndrome (dryness and peeling of the skin).

To identify lymphocyte subpopulations, we used a Navios EX Flow Cytometer (Beckman Coulter; USA) and the following panel of monoclonal antibodies (Beckman Coulter; USA): CD3-FITC, CD8-PE, CD19-ECD, CD16-Pc5.5, CD56-Pc7, CD4-APC, CD25-A700, HLA-DR-PB, CD45-KO. The lymphocytic region was isolated according to the parameters of direct and lateral light scattering with CD45 gating. The level of total serum G, A and M immunoglobulins was determined by turbidimetry in a Vitalon 400 automatic biochemical analyzer (Human set of reagents; Germany). To establish the content of circulating immune complexes (CIC) of low (CICIow) and medium (CICmed) molecular weight, we measured optical density of the samples after deposition with polyethylene glycol in various concentrations, comparing with the control samples that did not contain the studied sera. The results were expressed in conventional units (CU) [14]. The content of class G antibodies to SARS-CoV-2 was determined by ELISA using the SARS-CoV-2-IgG quantitative IFA-BEST test systems (VECTOR-BEST; Russia); the results were given in BAU (binding antibody units) per 1 ml. The threshold value agreed as providing a full-fledged antiviral protection against COVID-19 is 150 BAU/ml; all samples that reached that figure proved to neutralize the virus in laboratory studies [15].

The control group consisted of 35 donors without a history of COVID-19. For statistical processing of the results, we used the Statistica 10.0 software package (StatSoft Inc.; USA). The intergroup comparison was done with the help of the nonparametric Mann-Whitney test. The differences were considered statistically significant at $p < 0.05$.

RESULTS

After COVID-19, all participants had certain parameters of cellular immunity, the level of class A immunoglobulins, and CIC different from those registered in the control group, which signals an imbalance in the immune system.

As for the specific subpopulations of lymphocytes, the significant deviations were peculiar to T lymphocytes ($CD3^+$) and B lymphocytes ($CD19^+$) only in the mild course group, where their relative content was higher and lower than in the control group, respectively (Table 1). We did not register such differences in the moderate and severe course groups; there, the increased indicator was the relative content of T lymphocytes with markers of late activation ($CD3^+HLA\text{-}DR^+$).

Overall, in the mild course group, the values fluctuated within a significantly wide range, with the level of $CD3^+$ lymphocytes increased about 4 times more often than decreased, and that of $CD19^+$ lymphocytes, on the contrary, decreased 12 times more often than increased (Table 2). Similar patterns were observed in the moderate course group: elevated $CD3^+$ lymphocyte levels were 1.9 times more common than decreased, and $CD19^+$ lymphocyte levels were 2.2 times more likely to be reduced than elevated. In the severe course group, on the contrary, lower levels of $CD3^+$ lymphocyte were registered 2 times more often than higher, and higher $CD19^+$ levels — 2.2 times more often than lower.

By the level of immunoglobulins G and M, the groups did not differ significantly. In all groups, we registered a drop in the serum concentration of immunoglobulin A, with difference, compared to the control group, significant in the mild and

Table 1. Post-COVID cellular immunity indicators, groups by disease course severity

Indicator / Group	$CD3^+$ (%)	$CD3^+CD4^+$ (%)	$CD3^+CD8^+$ (%)	$CD3^+HLA^-DR^+$ (%)	$CD3^-CD16^+/CD56^+$ (%)	$CD19^+$ (%)
Mild *n* = 61 (I)	74.4 ± 1.2	45.4 ± 1.2	26.3 ± 1.1	4.2 ± 0.2	12.5 ± 0.8	10.2 ± 0.7
Moderate *n* = 55 (II)	69.7 ± 1.7	45.7 ± 1.6	23.1 ± 1.4	7.7 ± 0.4	12.9 ± 1.0	13.3 ± 1.2
Severe *n* = 9 (III)	69.5 ± 4.5	43.8 ± 4.0	23.6 ± 3.9	15.7 ± 2.5	13.3 ± 1.6	13.3 ± 2.8
Control *n* = 35 (IV)	68.6 ± 1.1	42.6 ± 1.1	24.0 ± 0.9	3.9 ± 0.8	12.4 ± 1.0	13.9 ± 0.9
$p_{I–IV}$ $p_{II–IV}$ $p_{III–IV}$	< 0.001 – –	– – –	– – –	– < 0.01 < 0.01	– – –	< 0.001 – –

severe course groups: 2.3 ± 0.1 g/l ($p < 0.01$) and 2.0 ± 0.4 g/l ($p < 0.05$), respectively, versus 2.8 ± 0.1 g/l in the control samples.

In addition, all participants who recovered from COVID-19 had the level of circulating immune complexes increased, which is a noteworthy finding (Table 3).

In 39 individuals (30.5% of all the participants, 30.3% of participating females and 31% of participating males), we have registered an especially significant rise of the level of ClClow: above 400 CU. Many of them (23 persons, 40.4% of the moderate course group) had COVID-19 in a moderately severe form. As for the age, the subgroup of individuals with the highest CIC values did not differ significantly from the entire sample of participants: the median age in the former was 56 years (29 through 83), in the latter — 53.

Level of G class antibodies to SARS-CoV-2: in the mild course group, 51.5% of the patient had it above 150 BAU/ml, in the moderate course group — 75.8%, in the severe course group — 100%.

In the group of 14 people who were re-examined at a later period (6–8 months after recovery), 8 persons (57%) exhibited persistence of pronounced abnormalities. The most common of them was a significantly elevated (>300 CU) level of ClClow, registered in 7 participants, five of whom had COVID-19 in a mild form, and 2 in a moderately severe form. Two individuals had a high content of T cells with markers of late activation ($CD3^+HLA\text{-}DR^+$): >7% versus normal 3.9 ± 0.8%. In another 2, we registered a significant disruption of the $CD4^+/CD8^+$ ratio, and a high amount of $CD4^+$ cells (T helpers). One patient had the IgA level at 4 g/l while the normal value is 2.8 ± 0.1 g/l.

Thus, while we did register immunity abnormalities common for most COVID-19 survivors, some of the examined had rather rare disruptions.

According to the clinical records, during the disease and thereafter, about half of the patients (46.9%) suffered significant smell and taste impairments, a fourth (26.6%) had abdominal symptoms (pain, dyspeptic disorders), and over a third (39.8%) of the entire sample reported skin dryness and peeling. In most participants, the said symptoms were concomitant to each other. Considering the degree of ClClow elevation, it is feasible to distinguish between patients who had the respective value at above 400 CU and below this figure (Table 4). These cohorts did not differ significantly from in terms of the frequency of manifestation of the abovementioned symptoms, with the exception of the abdominal syndrome, which was registered in patients with the ClClow level above 400 CU twice as often.

As for the changes in cellular immunity, we failed to identify clear patterns and associations with the clinical records. Nevertheless, there were some noteworthy features registered in individual COVID-19 patients. Against the background of reduced relative content of $CD3^+$ lymphocytes and increased content of $CD19^+$ lymphocytes, which was observed in 4 patients, 3 of them (aged 62–65 years) complained of severe skin dryness and peeling, and two had pronounced alopecia. Among younger participants, there was a 44-year-old man with significantly (up to 49.1%) low amount of $CD3^+$ lymphocytes and high levels of ClCmed and ClClow (102 CU and 520 CU, respectively); for a long time, he reported numbness of fingers and legs and headaches along with pronounced weakness and cognitive impairment, which can be interpreted as as post-COVID neurological disorders. Another patient, a female 40 years old, had the low level of $CD3^+$ lymphocytes as the only abnormality; she reported severe abdominal pain and prolonged dyspeptic disorders during the disease and thereafter. The latter case, however, can also be associated with antibiotic therapy and dysbiosis.

Below is the description of a case of detection of a pathological clone in the post-COVID period.

Patient A., 64 years old. No significant chronic diseases in the history. Moderate manifestations of biliary dyskinesia and initial manifestations of hypertension. Survived moderately severe COVID-19 in August 2021. First examination a month after the infection. Features of the post-COVID period: prolonged general weakness, pronounced alopecia, and moderately impaired sense of taste. At the time of examination, key hemogram indicators normal. Amount of leukocytes — 5.5 × 10^9/l, absolute number of lymphocytes — at the lower limit of the normal range (1.3 × 10^9/l). At the initial examination, flow cytometry revealed several deviations beyond healthy ranges of the respective indicators. The content of B cells ($CD19^+$) was up to 57.3%, which disturbed the subpopulation

Table 2. Post-COVID abnormalities in the $CD3^+$ and $CD19^+$ counts (peripheral blood), % of the examined

Indicator / Group	$CD3^+$ level			$CD19^+$ level		
	Increased	Decreased	Normal	Increased	v	Normal
Mild	50%	12%	38%	6%	74%	20%
Moderate	38%	20%	42%	22%	49%	29%
Severe	22%	44%	34%	56%	22%	22%

Table 3. Content of CIC in COVID-19 patients, depending on the severity of the disease

	CICmed (CU)	CICIow (CU)
Mild *n* = 61 (I)	53.9 ± 3.1	331.1 ± 12.7
Moderate *n* = 55 (II)	61.8± 3.8	362.8 ± 18.0
Severe *n* = 9 (III)	63.6 ± 7.0	325.4 ± 22.5
Control *n* = 35 (IV)	34.1 ± 3.6	122.5 ± 11.9
$p_{I–IV}$ $p_{II–IV}$ $p_{III–IV}$	$p < 0.001$ $p < 0.001$ $p < 0.001$	$p < 0.001$ $p < 0.001$ $p < 0.001$

composition of lymphocytes; the immunophenotype of B cells was pathological, as in a chronic lymphocytic leukemia (CLL): $CD19^+CD20^+lowCD22^+lowCD5^+CD23+CD43^+CD200^+$ (Figure 1).

At the level of humoral immunity, the changes were similar to those common in the group, with the only noteworthy exception of a higher IgA value, which still remained within the normal range.

Presence of a pathological clone characteristic of B-CLL was confirmed on a fresh sample of peripheral blood, but there were no signs of lymphadenopathy, morphologically altered lymphocytes in clinical blood tests. Nevertheless, accidental detection of chronic lymphocytic leukemia in the initial stage (CLL stage 0) was considered. The plan was to continue monitoring and conduct an additional examination for clonality.

A year after recovery from COVID-19, the patient's general well-being returned to normal. She did not seek medical assistance, nor had any medical interventions, with the exception of a 1.5-month course of multivitamins. A second examination conducted in April 2023 has shown that the relative content of mature T lymphocytes ($CD3^+$), NK cells ($CD3–CD16^+CD56^+$) returned to the normal ranges. Higher amount of T helpers ($CD3^+CD4^+$) caused an imbalance in the content of the main subpopulations of effector cells. Mature B cells were polyclonal, with a normal $CD19^+$ $CD20^+$ $CD22^+$ $CD79b^+$ IgM^+ phenotype, and accounted for about 8.0% of the total pool of lymphocytes ($CD45^+$). No pathological clone of B lymphocytes with a B-CLL phenotype has been identified. To date (April 2024), the patient's condition remains satisfactory, with no pathological symptoms manifesting.

Figure 1 shows the results of the study of individual subpopulations of lymphocytes.

Thus, monitoring of the patient's condition over time yielded no data confirming presence of a chronic lymphoproliferative disease. The disturbance of the subpopulation composition of lymphocytes was regarded as reactive changes against the background of activation of the B-cell immunity in response to COVID-19.

DISCUSSION

Since the emergence of SARS-CoV-2, there has been collected a significant amount of data about the specifics of development of immune response upon exposure thereto. The said data indicate that there are both common trends and individual reactions, as well as dysfunctional immune response in some patients [12, 13, 16]. The wide range of values of immunological parameters registered in COVID-19 survivors can be attributed to many factors, from innate features of the immune system to dysbiosis and comorbidities [17, 18].

The importance of assessment of persisting immune disorders stems from the need to fully understand the patterns of formation of a full-fledged antiviral immunity, which relies on coordinated cooperation between the cellular and humoral levels of immunity. There is also evidence that COVID-19, triggering dysregulation of the immune system, can promote development of autoimmune diseases [16, 19, 20].

The long recovery of immunity indicators after COVID-19 can be explained by the "squeezed" condition of the immune system after a severe course of the disease, and SARS-CoV-2's ability to suppress development of the adaptive immune response, influence the number and functional activity of lymphocytes, the effectors of cellular immunity, and consequently hinder lymphopoiesis, apoptosis, and causing exhaustion of these cells [1].

As shown by the case reported above, post-COVID, the components of immunity can undergo unusual transformations, including production of cells with characteristics of pathological clones. Such developments necessitate prolonged monitoring of patients after recovery and point to the virus' capability to predispose to hematopoiesis disorders associated the disturbances of the immune system's balance.

It is believed that, post-COVID, a high titer of neutralizing antibodies for a period of 6 months or more and prolonged persistence of SARS-CoV-2 Spike and RBD IgG mean the virus remains in the body/microbiota of the patient, which can naturally affect the state of the immune system. The persistence of viral antigens causing immuno-mediated damage contributes to the polyclonal activation of immunocompetent cells, and the long-term growth of the number of CIC and activated T lymphocytes (described in the literature and noted in our study) is considered a sign of insufficiently effective elimination of the pathogen [20, 21]. Obviously, rehabilitation measures should factor in such a probability.

Thus, the literature data and the results of our study suggest some general trends in post-COVID changes of cellular and humoral components of immunity. At the same time, there are individual patients with unusual abnormalities of immunological parameters. Some of these abnormalities can be associated with the patients' age and severity of the disease, but some remain unclear in terms of their role and meaning. Apparently,

Table 4. Frequency of occurrence of certain symptoms in COVID-19 survivors depending on the level of CICIow

CICIow value	Abdominal syndrome	Impaired taste and sense of smell	Skin disorders
< 400 CU (*n* = 89)	20.20%	46.10%	39.30%
> 400 CU (*n* = 39)	41%	48.70%	41%

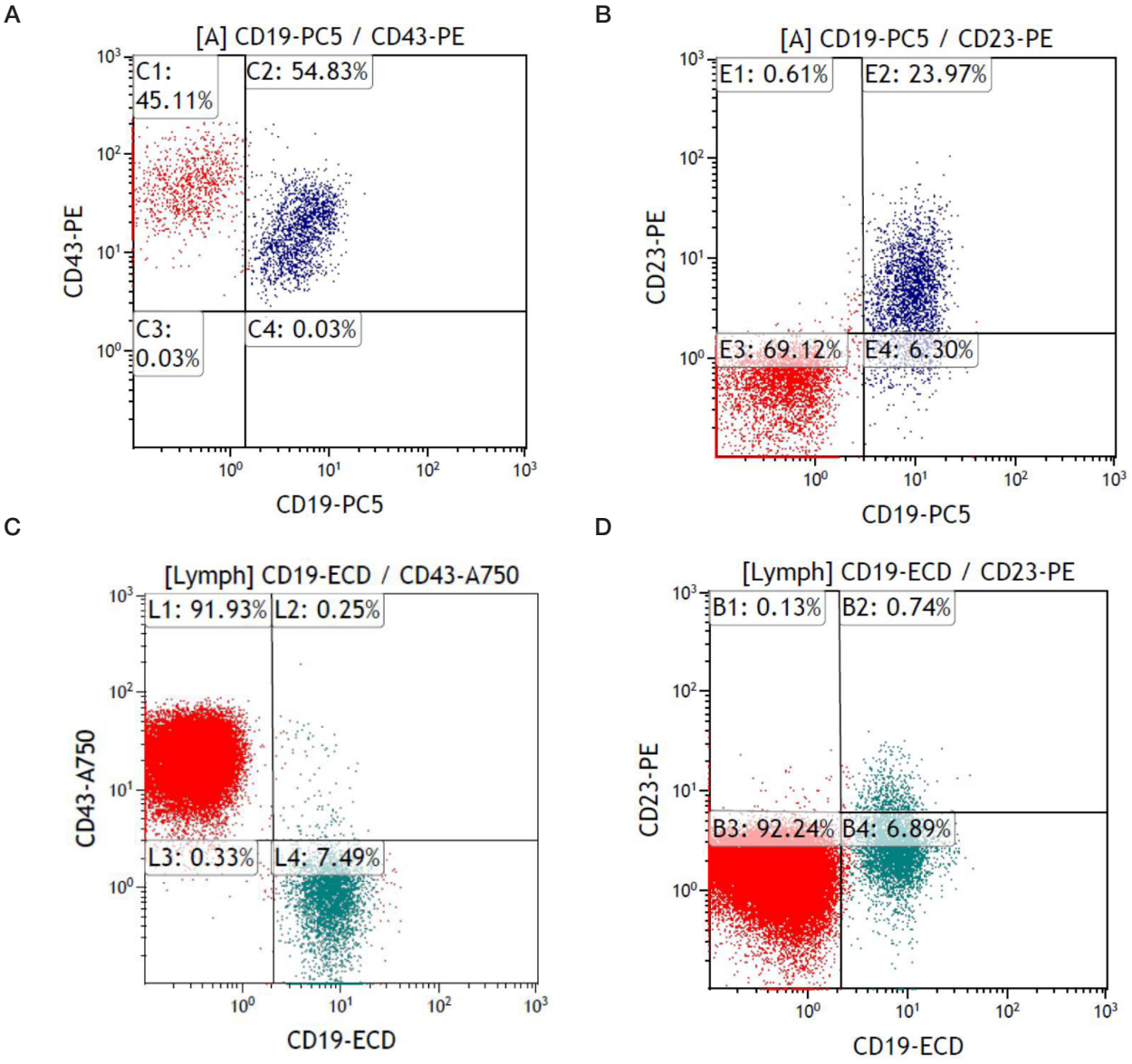

Fig. Immunophenotypic study results, patient A. Device used for the study: Navios EX 10 Colors (Beckman Coulter; USA). The lymphocytic pool was isolated by the parameters of direct and lateral light scattering with CD45 gating. A, B. Results of the study of August 2021. For these histograms, a 5 color panel was used: 1) CD20–FITC+CD23–PE+CD45–ECD+CD19–Pc5+CD5–Pc7 and 2) CD22–FITC+CD43-PE+CD19–Pc5+CD45–Pc7. C, D. Results of the study of April 2023. For these histograms, a 10 color panel was used: FMC7–FITC+CD23–PE+CD19–ECD+CD79b–Pc5.5+CD200–Pc7+CD43–A750+CD38–A700+IgM–PB+CD45–KO. X-axis: CD19+ (%), Y-axis: A and C — CD43+ (%), B and D — CD23+ (%). The upper right quadrants of all the histograms (C2 (A), E2 (B), L2(C) and B2 (D)) show the region where the clone of pathological cells characteristic of B-CLL should be located

special long-term monitoring is required for those who have persisting COVID-associated changes of late activation T cells, class A immunoglobulins, and low molecular weight CIC, since they play an essential role in the development of infectious-inflammatory and autoimmune reactions [20, 22].

It is important to take into account the ongoing immunological shifts when assessing the risks of reinfection and considering revaccination. Continued monitoring and examinations are required to better understand the features of changes in the immune profile caused by SARS-CoV-2. In addition, it is necessary to further study the state of the regulatory mechanisms of immunity in patients after COVID-19, and to develop informative prognostic criteria for assessing the post-COVID condition. Currently, it is not possible to fully assess individual risks without conducting a large-scale multifactorial analysis in groups of individuals who are homogeneous in terms of baseline data, age, strain of the pathogen, and severity of the disease. The new data will allow personalization of the revaccination schedules and development of rational immunocorrection programs that will help increase resistance to repeated infections.

CONCLUSIONS

Regardless of the severity of the course, all COVID-19 survivors had their immune systems imbalanced, and this status did not change for a long time in many of them. Those who have the disease in a mild form typically have high relative content of $CD3^+$ T cells and low amount of B cells ($CD19^+$), as well as low level of serum IgA. Almost half of the individuals in this group had a low level of protective antibodies to SARS-CoV-2 (<150 BAU/ml). In the severe course group, compared to other groups, the level of $CD19^+$ cells was often higher, and the drop of the level of IgA most pronounced. Moreover, all members of this group had the amount of antibodies above the protective threshold. In the moderately severe course group, some abnormalities were similar to those registered for the mild form of the disease (high content of $CD3^+$ cells, low amount of

CD19+ cells), but less pronounced; a less common effect was a drop of the level of protective antibodies, and the growth of IgA was unreliable. Along with general trends, some individuals exhibited uncommon immunity deviations, including a patient with a pathological clone characteristic of B-CLL registered a month after recovery, which spontaneously disappeared later on. The genesis of such disorders is currently not entirely clear, and COVID-19 survivors, obviously, need long-term monitoring and repeated examinations, which would enable not only treatment of the post-COVID syndrome but also further study and comprehensive assessment of the associated immune imbalance.

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