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INTEGRATIVE INDICATORS OF ENDOGENOUS INTOXICATION, INFLAMMATORY ACTIVITY, AND SPECIFIC REACTIVITY IN PATIENTS WITH COVID-19

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The aim of the study is to identify changes in blood laboratory parameters, integrative indicators of endogenous intoxication, inflammation, and specific reactivity in patients with coronavirus disease.

Patients and methods. *The study included 77 patients with COVID-19, taking into account the inclusion and exclusion criteria. The comparison group consisted of 68 practically healthy people of the corresponding age. Laboratory blood tests were performed, on the basis of which integrative indicators of endogenous intoxication, inflammation and specific reactivity were calculated.*

Results. *The data of the general blood test showed no significant differences between the patients of the groups, the indicators remained within acceptable limits. A slight inflammatory reaction in patients with COVID-19, especially in the period from 3 to 6 months, is confirmed by an increase in the level of endogenous intoxication (LII, LSI, NLRI, HII) in the group of patients compared to healthy individuals. During the same period, there are signs of activation of the cellular immune system in response to the presence of latent bacterial infection or endogenous intoxication, which is confirmed by a decrease in inflammation activity (LGI, LESRI, CI). Reduced indices of nonspecific reactivity (RC, ILYM, AI) confirmed the activation of the cellular immune system, given the decrease in the number of lymphocytes relative to granulocytes. Changes in integrative indices did not depend on the presence of Long-COVID symptoms. In the period from 12 months after the coronavirus disease, the development of autoimmune processes is possible, since there was a tendency to decrease the indices of endogenous intoxication (NLRI, LSI) simultaneously with an increase in the indices of inflammatory activity (LGI, LESRI, TI) and indices of nonspecific reactivity (RC, Ilymph, AI).*

Key words*: Long-COVID; COVID-19; integrative indicators; endogenous intoxication; good health; inflammation.*

The consequences of the coronavirus disease caused by SARS-CoV2, or COVID-19, are currently one of the problems that can create an additional burden on the healthcare system and the economy of countries. These negative phenomena are associated with a decrease in performance due to a prolonged systemic inflammatory response and complications associated with it [1]. According to a number of studies, this systemic inflammation is associated with increased concentrations of proinflammatory cytokines, endothelial dysfunction, autoimmune component, and predominant damage to the cardiovascular, nervous, and endocrine systems [2-5]. The most severe complication associated with an inflammatory response is a multisystem inflammatory syndrome characterized by cardiovascular damage, conjunctivitis, encephalopathy, thrombocytopenia, and laboratory parameters indicating acute inflammation (increased levels of C-reactive protein, ferritin, procalcitonin, and interleukin-6) [6, 7]. According to various sources, this form of post-covid pathology occurs from 3.27 to 3.8 per 100,000 people [8, 9]. Other, less clinically significant, but more numerous symptoms are found in approximately 70 % of people who have had coronavirus disease [10]. An accessible method for determining the state of the immune system due to prolonged exposure to viral infection is to calculate integrative indicators of inflammation, endogenous intoxication, and specific reactivity [11, 12].

The aim of this study was to identify changes in blood laboratory parameters, integrative indicators of endogenous intoxication, inflammation activity, and specific reactivity in patients with coronavirus disease.

Patients and methods

We examined and interviewed 112 people who had contracted COVID-19 during the year and were treated at St. Panteleimon Clinical Hospital and the University Clinic of Sumy State University, and analyzed the outpatient records of these patients.

After applying the inclusion and exclusion criteria, 77 patients were included in the study group.

The comparison group included 68 people who are declarants of family doctors at the University Clinic of Sumy State University or who have undergone a medical examination there.

This study was conducted in accordance with the Declaration of Helsinki. Before participating in this study, each participant gave written informed consent to participate.

Criteria: inclusion – anamnestic (presence of coronavirus disease in the last year); laboratory (confirmation of coronavirus disease using PCR).

Exclusions: clinical and anamnestic (history of blood diseases or coagulation disorders that were associated with other causes, use of drugs that affect the coagulation function of the blood, the presence of acute diseases); laboratory (changes in clinical blood counts indicating an acute disease – leukocytosis, a significant shift in the leukocyte formula, acceleration of ESR).

Participants in both groups underwent a complete blood count. Taking into account its results, integrative indicators of endogenous intoxication, inflammation activity, and specific reactivity were calculated to determine the relevant pathophysiological mechanisms that are the basis of Long-COVID [11, 12].

The following indices of endogenous intoxication were determined: leukocyte intoxication index (LII), hematological index of intoxication (HII), leukocyte shift index (LSI), intoxication index (II), neutrophil reactive response (NRR), neutrophil-lymphocyte ratio index (NLRI).

Indices of inflammation activity – lymphocyte-granulocyte index (LGI), leukocyte – erythrocyte sedimentation rate index (LESRI), total index (TI).

Indices of nonspecific reactivity – resistance coefficient (RC), immunoreactivity index (IRI), neutrophil-monocyte ratio index (NRMI), lymphocyte-monocyte ratio index (LMRI), lymphocyte index (ILYM), eosinophil-lymphocyte ratio index (ELRI), allergy index (AI), nuclear index (NI).

The Shapiro-Wilk method was used to check the normality of the distribution of the study groups, comparison and comparability. If the groups were normally distributed, the comparison of indicators was carried out using the Student's t test, otherwise, the nonparametric Mann-Whitney U test was used. The critical significance level for testing statistical hypotheses in this study was 0.05. The Stata/SE 18 software package, which is licensed for use at Sumy State University, was used for statistical calculations.

Results

The average age of the subjects was 45.0 (34.8-52.0) years. There were 1.2 times more women than men (54.5 % and 45.5 %, respectively). The average age of the participants in the comparison group was 42.0 (34.0-50.0) years, and women also prevailed 1.2 times more than men (54.4 % and 45.6 %, respectively). The groups were comparable.

The age distribution in the groups was dominated by people aged 41 to 60. The main group was slightly dominated by people aged 51-60 (1.4 times), and the comparison group by people aged 41-50 (1.2 times). The proportion of reconvalescents and comparison group members aged 20 to 40 was the same (see Fig. 1).

The subjects were divided into 4 subgroups according to the duration of coronavirus disease: up to 3 months

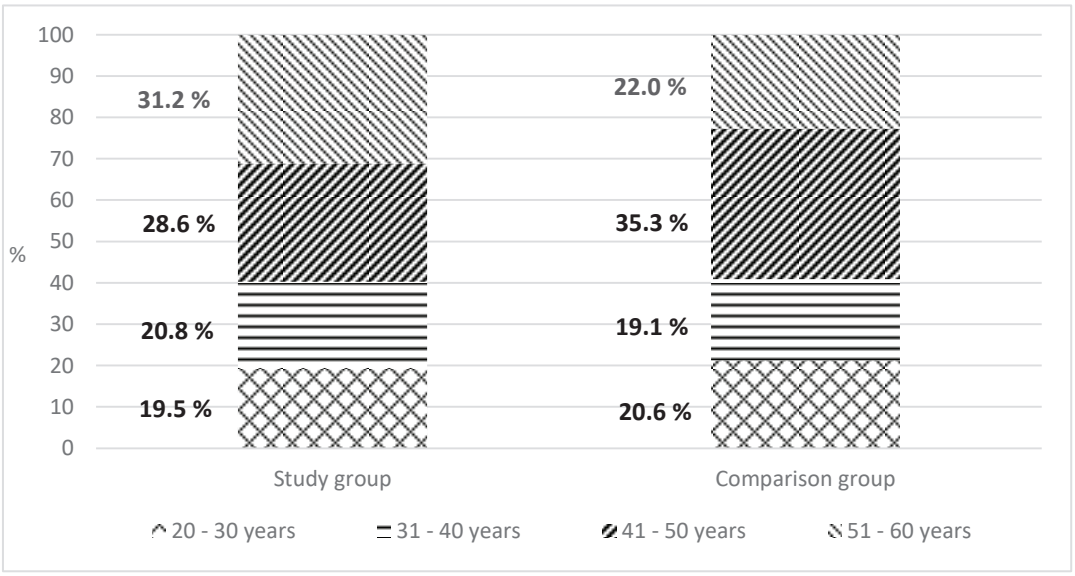

Fig. 1. Distribution of people in groups by age.

(subgroup A), 3-6 months (B), 6-12 months (C), 12 months and more (D).

Symptoms that are signs of Long COVID were observed in 65 subjects (84.4 %). Women were 1.2 times more prevalent among them (36, 55.4 % women; 29, 44.6 % men). The main complaints (as a % of the total number of subjects) were weakness – 36 (46.8 %), headache – 22 (28.6 %), mood disorders – 32 (41.6 %), anxiety – 34 (44.2 %), shortness of breath – 18 (23.4 %), palpitations at rest – 18 (23.4 %), and dizziness – 13 (16.7 %).

Complete blood counts were within normal limits in both groups, but some of them were significantly different. The number of leukocytes in the study group was 1.1 times higher (p=0.009), segmented leukocytes were similarly 1.1 times higher than in the comparison group (p=0.010), and the level of red blood cells was also 1.1 times higher (p=0.017) (see Table 1). The highest leukocyte count was in subgroup B – 6.5×10^9 (5.3-7.1), the lowest – in subgroup C – 5.4×10^9/L (4.7-6.3). The proportion of segmented neutrophils was the highest in subgroup B – 60 % (56-63), the lowest in subgroup D – 51 % (46-57). The number of red blood cells prevailed in subgroup A – 4.9×10^{12} (4.7-5.6), and was determined at the lowest level in subgroup C – 4.3×10^{12}/L (4.2-4.4).

Table 1

Changes in clinical blood tests in the study group, median (25th percentile – 75th percentile)

Indicator	Group		p
	Comparison	Study	
White blood cells (WBC, 1×10^9)	5.6 (4.8-6.3)	6.3 (5.2-7.1)	0.009
Platelets (PLT, 1×10^9)	252 (212-274)	250 (210-282)	0.957
Rods (%)	3.0 (2.0-4.0)	3.0 (2.0-5.0)	0.323
Segmented (%)	55 (51-58)	59 (54-62)	0.010
Eosinophils (%)	2 (1-3)	2.0 (1-2)	0.081
Monocytes (%)	7 (5-9)	7 (5-8)	0.753
Lymphocytes (%)	32 (29-35)	31 (24-34)	0.023
Red blood cells (RBC, 1×10^{12})	4.4 (4.3-4.8)	4.7 (4.4-5.0)	0.017
Hemoglobin (HGB, g/l)	131 (123-136)	132 (126-143)	0.119
Hematocrit (HCT, %)	40.1 (37.9-42.3)	40.6 (38.6-44.2)	0.053
Mean corpuscular volume (MCV, fL)	91.0 (85.1-95.4)	87.6 (82.3-92.0)	0.098
Mean corpuscular hemoglobin (MCH, pg)	29.5 (27.7-30.5)	28.4 (27.5-29.7)	0.152
Mean corpuscular hemoglobin concentration (MCHC, g/l)	325 (317-332)	323 (316-329)	0.251
ESR (mm/h)	7 (4-8)	7 (5-10)	0.234

Note: p is the significance level when assessing the difference with the comparison group.

The indices of nonspecific reactivity did not have a significant difference between the study and comparison groups, except for three indicators – AI, ILYM and RC. In general, AI had a slight difference (1.02 times lower among convalescents; p=0.037). At the same time, this index was 1.1 times lower in subgroup B (p=0.000) and 1.1 times higher in subgroup D (p=0.037). The RC was 1.2 times lower in the study group as a whole (p=0.039). Similarly, it was 1.2 times lower in subgroup B (p=0.000), but in subgroup D this indicator was 1.2 times higher (p=0.024). In general, the ILYM was similar in both groups, but significantly lower by 1.3 times in subgroup B (p=0.000) and 1.4 times higher in subgroup D (p=0.025).

LESRI was 1.3 times higher among the subjects (p=0.033), with a 1.7-fold increase in subgroup D (p=0.017). The level of this indicator in convalescents with Long-COVID symptoms and those without them was the same. LGI was 1.1 times higher in the comparison group (p=0.020) and 1.2 times lower in subgroup B (p=0.000), but at the same time, it was 1.1 times higher in subgroup D (p=0.041). Overall, there was no significant difference between the study and comparison groups, but in subgroup B it was 1.1 times lower (p=0.001), and in subgroup D it was 1.2 times higher (p=0.015).

Indicators of endogenous intoxication indices had a significant difference, with the exception of NRR. Thus, LII was generally 1.4 times higher in the study group (p=0.011). At the same time, in subgroup B, the advantage was even greater (1.6 times; p=0.002). A similar picture was observed with the LSI, where this index was 1.1 times higher in

general (p=0.006), in subgroup B – 1.3 times (p=0.000), and in subgroup D a decrease of 1.2 times (p=0.026) was observed. The difference was more pronounced in the NLRI, which was 1.2-fold higher in the overall group of recuperates (p=0.002) and 1.5-fold higher in subgroup B (p=0.000). II did not differ between the groups in general, with a 1.5-fold increase in subgroups B and D (p=0.002 and p=0.027, respectively). Similarly to the LII, the HII was 1.4 times higher in the study group as a whole (p=0.005), and in subgroup B – 1.6 times higher (p=0.001) (see Table 2). The rates of endogenous intoxication in individuals with Long-COVID symptoms and those without were similar or higher in symptomatic recovered patients, but not more than 1.5 times.

Table 2

Characteristics of integrative indicators in the study group and comparison group, median (25th percentile – 75th percentile)

Indicator	Group					
	Comparison n=68	Study				
		General n=77	Subgroup A n=13	Subgroup B n=50	Subgroup C n=6	Subgroup D n=8
1	2	3	4	5	6	7
Indices of endogenous intoxication						
LII	0.5 (0.4-0.7)	0.7* (0.5-0.8) p=0.011	0.6 (0.5-0.6) p_1=0.907	0.8* (0.5-1.0) p_2=0.002	0.5 (0.4-0.7) p_3=0.904	0.6 (0.5-0.7) p_4=0.918
LSI	1.5 (1.4-1.7)	1.7* (1.4-2.0) p=0.006	1.5 (1.0-1.7) p_1=0.776	1.9* (1.6-2.2) p_2=0.000	1.5 (1.3-2.1) p_3=0.881	1.3* (1.1-1.4) p_4=0.026
NLRI	1.5 (1.4-1.8)	1.8* (1.5-2.1) p=0.002	1.9 (1.1-2.2) p_1=0.969	2.3* (1.9-2.9) p_2=0.000	1.9 (1.6-2.8) p_3=0.662	1.5* (1.3-1.8) p_4=0.034
II	0.2 (0.1-0.3)	0.2* (0.2-0.4) p=0.001	0.2 (0.1-0.3) p_1=0.335	0.3* (0.2-0.5) p_2=0.002	0.2 (0.2-0.4) p_3=0.241	0.3* (0.3-0.4) p_4=0.027
NRR	7.4 (5.4-11.1)	8.1 (4.0-14.6) p=0.780	5.7 (5.0-13.8) p_1=0.335	5.1 (3.1-8.4) p_2=0.346	9.3 (4.5-14.6) p_3=0.132	4.2 (2.6-11.1) p_4=0.178
HII	0.5 (0.4-0.7)	0.7* (0.5-0.8) p=0.005	0.6 (0.5-0.6) p_1=0.938	0.8* (0.5-1.0) p_2=0.001	0.5 (0.5-0.7) p_3=0.896	0.6 (0.5-0.7) p_4=0.638
Indices of inflammatory activity						
LGI	4.7 (4.1-5.4)	4.4* (3.2-5.2) p=0.020	4.5 (3.8-7.7) p_1=0.938	4.0* (3.1-4.6) p_2=0.000	4.4 (3.0-5.4) p_3=0.519	5.4* (4.9-6.7) p_4=0.041
LESRI	0.3 (0.2-0.5)	0.4* (0.3-0.6) p=0.033	0.4 (0.2-0.4) p_1=0.713	0.4 (0.3-0.6) p_2=0.120	0.5 (0.3-0.9) p_3=0.092	0.5* (0.5-0.8) p_4=0.017
TI	5.1 (4.4-5.7)	4.8 (3.8-5.8) p=0.063	4.8 (4.2-7.9) p_1=0.979	4.5* (3.6-5.3) p_2=0.001	5.2 (4.1-5.8) p_3=0.921	6.2* (5.6-7.2) p_4=0.015
Indices of nonspecific reactivity						
RC	0.6 (0.5-0.7)	0.5* (0.4-0.6) p=0.029	0.5 (0.5-0.9) p_1=0.968	0.5* (0.4-0.6) p_2=0.000	0.6 (0.4-0.8) p_3=0.699	0.7* (0.6-0.9) p_4=0.024

Continuation of the Table 2

1	2	3	4	5	6	7
IRI	4.8 (3.9-6.5)	4.7 (3.4-5.9) p=0.113	3.9 (3.6-5.9) p_1=0.118	4.9 (3.4-5.9) p_2=0.284	3.5 (2.6-4.7) p_3=0.115	4.6 (4.3-6.1) p_4=0.933
ILYM	0.5 (0.5-0.6)	0.5* (0.4-0.6) p=0.012	0.5 (0.5-0.9) p_1=0.931	0.4* (0.4-0.5) p_2=0.000	0.6 (0.4-0.7) p_3=0.683	0.7* (0.6-0.8) p_4=0.025
NRMI	8.2 (6.3-11.8)	8.9 (7.0-11.8) p=0.656	7.1 (6.6-8.9) p_1=0.132	10.8 (8.0-12.2) p_2=0.090	7.0 (7.0-7.2) p_3=0.476	7.1 (5.9-8.0) p_4=0.361
LRMI	4.6 (3.5-6.1)	4.5 (3.2-5.6) p=0.163	3.7 (3.3-5.6) p_1=0.151	4.7 (3.1-5.6) p_2=0.347	3.2 (2.3-4.5) p_3=0.122	4.5 (4.1-5.9) p_4=0.793
ELRI	0.1 (0.0-0.1)	0.1 (0.0-0.1) p=0.653	0.1 (0.0-0.1) p_1=0.773	0.1 (0.0-0.1) p_2=0.421	0.1 (0.0-0.1) p_3=0.510	0.0
AI	32.3 (29.6-35.8)	31.1* (24.5-34.6) p=0.037	31.5 (28.2-43.8) p_1=0.995	28.8* (24.2-32.0) p_2=0.000	30.9 (23.6-38.7) p_3=0.656	35.5* (33.1-40.6) p_4=0.037
NI	0.1 (0.0-0.1)	0.1 (0.0-0.1) p=0.980	0.1 (0.0-0.1) p_1=0.816	0.1 (0.0-0.1) p_2=0.884	0.1 (0.0-0.1) p_3=0.660	0.1 (0.0-0.1) p_4=0.782

Notes. Levels of significance when assessing the difference relative to the comparison group: p – in general among the subjects; p_1 – in subgroup A; p_2 – in subgroup B; p_3 – in subgroup C; p_4 – in subgroup D. * – indicates significant changes.

Discussion

The results of the study indicate an inflammatory response and endogenous intoxication after COVID-19. The complete blood count remains within normal limits even in the presence of Long-COVID symptoms. At the same time, the total number of leukocytes and segmented leukocytes in the study group is significantly higher, which may be a consequence of the immune response to the latent bacterial infection that accompanies COVID-19 as a mix infection. Significant changes in integrative indices were observed in convalescents who had been ill with coronavirus disease for 3-6 and more than 12 months before the study. The absence of a significant difference in the period up to 3 months is probably due to immunosuppression due to the use of glucocorticoids during the treatment of acute coronavirus disease against the background of decreased immune function, which is a pathogenetic component of COVID-19 [2], which led to an unexpressed reaction to the restoration of immune system function. Within 6-12 months, there was probably a gradual recovery of tissues with the simultaneous formation of an autoimmune response, the manifestations of which became noticeable after 12 months.

A decrease in LGI and an increase in LESRI among convalescents relative to the comparison group within 3-6 months after COVID-19 indicates the activity of the cellular immune system in response to endogenous intoxication. An increase in endogenous intoxication indicators during this period, in particular LII and HII, may indicate an ongoing inflammatory process with activation of tissue breakdown processes. The increase in the LSI and NLRI was probably a response to the stimulation of leukopoiesis due to increased levels of endotoxins, which also indicates systemic cell damage. The decrease in nonspecific reactivity indices in the period of 3-6 months, such as RC, ILYM and AI, complement this picture, as their decrease in the group of subjects reflects the predominance of granulocyte activity in the immune system response to latent bacterial infection and endotoxins [13, 14].

In the period from 12 months after coronavirus disease, endogenous intoxication indices (LSI, NLRI), on the contrary, tend to decrease, and indices of inflammatory activity (LGI, LESRI, TI) and nonspecific reactivity (RC, ILYM, and AI) tend to increase, which may indicate an increase in the levels of proinflammatory cytokines such as IL-1α, IL-6, IFN-γ and the development of autoimmune reactions [13, 14].

According to various sources, the peak of clinical signs of Long-COVID is observed within 6-12 months after the

disease [15, 16]. The most significant changes in integrative indicators are observed mainly in patients who had the disease in the period of 3-6 and 12 months, which confirms the results of these studies.

To clarify the relationship between changes in integrative indicators and clinical signs in the relevant periods, additional clinical and laboratory studies are needed to determine the levels of inflammatory mediators, coagulation function and indicators of endothelial function, such as endothelin-1.

Conclusions

The data of the complete blood count showed no significant differences between the patients of the groups, the indicators remained within acceptable limits.

The inflammatory response in patients with COVID-19, especially in the period from 3 to 6 months, is confirmed by an increase in the level of endogenous intoxication (LII, LSI, NLRI, HII) in the group of subjects compared to relatively healthy individuals.

There are signs of activation of the cellular immune system in response to the presence of latent bacterial infection or endogenous intoxication in the period from 3 to 6 months after an acute illness, which is confirmed by a decrease in inflammatory activity (LGI, LESRI, TI).

A decrease in the indices of nonspecific reactivity (ILYM, AI) confirmed the activation of the cellular immunity, given the decrease in the number of lymphocytes relative to granulocytes.

In the period from 12 months after coronavirus disease, autoimmune processes may develop, as there was a tendency to decrease the indices of endogenous intoxication (LSI, NLRI) simultaneously with an increase in the indices of inflammation activity (LGI, LESRI, TI) and indices of nonspecific reactivity RC, ILYM, AI).

Changes in integrative indicators did not depend on the severity of Long-COVID symptoms.

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ІНТЕГРАТИВНІ ПОКАЗНИКИ ЕНДОГЕННОЇ ІНТОКСИКАЦІЇ, АКТИВНОСТІ ЗАПАЛЕННЯ ТА СПЕЦИФІЧНОЇ РЕАКТИВНОСТІ У ПАЦІЄНТІВ, ЯКІ ПЕРЕНЕСЛИ COVID-19

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РЕЗЮМЕ. Мета дослідження – виявлення змін лабораторних показників крові, інтегративних показників ендогенної інтоксикації, активності запалення, специфічної реактивності у пацієнтів, які перехворіли на коронавірусну хворобу.

Пацієнти і методи. *Здійснено обстеження осіб, які перехворіли на COVID-19. З урахуванням критеріїв включення та виключення були залучені до групи дослідження 77 осіб. Групу порівняння склали 68 практично здорових людей відповідного віку. Здійснені лабораторні дослідження крові, на підставі яких розраховані інтегративні показники ендогенної інтоксикації, активності запалення та специфічної реактивності.*

Результати. *Дані загального аналізу крові свідчили про відсутність значущих розбіжностей між пацієнтами груп, показники залишались у межах прийнятних норм. Незначна запальна реакція в осіб, які перехворіли на COVID-19, особливо в період від 3 до 6 місяців підтверджується підвищенням рівня показників ендогенної інтоксикації (ЛІІ, ІЗЛК, ІСНЛ, ГПІ) у групі досліджуваних відносно здорових осіб. У цей же період є ознаки активації клітинної ланки імунітету у відповідь на наявність прихованої бактерійної інфекції або ендогенної інтоксикації, що підтверджується зниженням показників активності запалення (ІЛГ, ІЛШОЕ, ЗІ). Зниження індексів неспецифічної реактивності (Ілімф, ІА) підтверджували активацію клітинної ланки імунітету, враховуючи зниження кількості лімфоцитів відносно гранулоцитів. Зміни інтегративних показників не залежали від яскравості симптомів Long-COVID. У період від 12 місяців після перенесеної коронавірусної хвороби можливий розвиток автоімунних процесів, оскільки спостерігалась тенденція до зниження індексів ендогенної інтоксикації (ІЗЛК, ІСНЛ) одночасно з підвищенням індексів активності запалення (ІЛГ, ІЛШОЕ, ЗІ) та індексів неспецифічної реактивності (КР, Ілімф, ІА).*

Ключові слова: *Long-COVID; COVID-19; інтегративні показники; ендогенна інтоксикація; міцне здоров'я; запалення.*

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