MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SUMY STATE UNIVERSITY
ACADEMIC AND RESEARCH MEDICAL INSTITUTE

Eastern Ukrainian Medical Journal

116, Kharkivska st., Sumy 40007, Ukraine eumj.med.sumdu.edu.ua
e-mail: eumj@med.sumdu.edu.ua ISSN: 2663-5909 (print)/2664-4231 (online)

How to cite / Як цитувати статтю: Name. Changes in indicators of endogenous intoxication, nonspecific reactivity, and inflammation caused by SARS-COV-2. *East Ukr Med J*. 2024;12(2):422-430

DOI: https://doi.org/10.21272/eumj.2024;12(2):422-430

ABSTRACT

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CHANGES IN INDICATORS OF ENDOGENOUS INTOXICATION, NONSPECIFIC REACTIVITY, AND INFLAMMATION CAUSED BY SARS-COV-2

Introduction: Despite the fact that the entire scientific world is concerned about COVID-19, about 65 million people are living with Long COVID, suffering from general weakness, fatigue, cognitive dysfunction, and shortness of breath. This problem is global for humanity because of the decrease in the ability to work and mental activity of the population, which leads to economic losses. The problem remains open and requires further research.

Materials and Methods: a total of 108 patients were examined and divided into three groups: group A – 31 patients with confirmed COVID-19, group B – 35 patients with Long COVID, and group C – 42 practically healthy individuals. Hematologic and nonspecific immunologic changes were studied. Statistical data processing was performed using STATA software by StataCorp (Texas, USA) with the calculation of parametric and non-parametric criteria.

Results: middle-aged women predominated in the study groups. Among the hematologic parameters, an increase in leukocytes, erythrocytes, and ESR was observed in the COVID-19 group. Patients in group A had 2.5 times more rods of neutrophils than in group B and 2.3 times more than in group C. In patients with COVID-19, integrative indicators of endogenous intoxication exceeded the corresponding data compared to the Long COVID group ($p<0.05$). In patients with Long COVID, there was a tendency ($p=0.055 – 0.588$) to increased integrative indicators of endogenous intoxication (the intoxication index was 2.6 times higher ($p<0.05$)) compared to the group of practically healthy individuals. The indices of nonspecific reactivity in group A (resistance coefficient, lymphocyte index, eosinophil to lymphocyte ratio index, allergy index) and B (resistance coefficient, lymphocyte index) were lower than in group C ($p<0.05$). In patients with COVID-19, indices of inflammation activity (total inflammation index, Krebs index, leukocyte/

ESR ratio index) were higher than in the group of practically healthy individuals (p<0.05).

Conclusions: patients with COVID-19 are characterized by a leftward shift of the leukocyte formula, increased integrative indicators of endogenous intoxication, a pronounced inflammatory process, and activation of tissue breakdown. For people with Long COVID, there is a slight increase in integrative indicators of endogenous intoxication, with a low degree of inflammation and increased nonspecific reactivity compared to the COVID-19 group.

Key words: COVID-19, Long COVID, intoxication, inflammation, immunology, hematological changes, health.

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РЕЗЮМЕ

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ЗМІНИ ПОКАЗНИКІВ ЕНДОГЕННОЇ ІНТОКСИКАЦІЇ, НЕСПЕЦИФІЧНОЇ РЕАКТИВНОІСТІ ТА ЗАПАЛЕННЯ СПРИЧИНЕНИХ SARS-COV-2

Актуальність: незважаючи на те, що весь науковий світ стурбований проблемою COVID-19, із Long COVID живе близько 65 млн людей, яких турбують загальна слабкість, втома, когнітивні дисфункції, задишка. Дана проблема є глобальною для людства через зниження працездатності, розумової активності населення, що призводить до економічних втрат. Проблема залишається відкритою та потребує подальших досліджень.

Матеріали та методи: всього було обстежено 108 осіб та поділено на три групи: група А – 31 пацієнт із підтвердженим COVID-19, група В – 35 осіб із з Long COVID та група С – 42 практично здорові особи. Досліджувалися гематологічні та неспецифічні імунологічні зміни. Статистична обробка даних проводилася за допомогою програмного забезпечення STATA компанії StataCorp (Texas, USA) із розрахунком параметричних та непараметричних критеріїв.

Результати: у досліджуваних групах переважали жінки середнього віку. Серед гематологічних показників спостерігалося підвищення лейкоцитів, еритроцитів, ШОЕ у групі з COVID-19. У хворих групи А паличкоядерних нейтрофілів було у 2,5 рази більше ніж у В та у 2,3 рази ніж у С. У пацієнтів з COVID-19 інтегративні показники ендогенної інтоксикації перевищували відповідні дані порівняно з групою Long COVID (p <0,05). В осіб з Long COVID спостерігалася тенденція (p=0,055 – 0,588) до підвищення інтегративних показників ендогенної інтоксикації (показник інтоксикації був вищим у 2,6 рази (p <0,05)) порівняно з групою практично здорових осіб. Індекси неспецифічної реактивності у групі А (коефіцієнт резистентності, лімфоцитарний індекс, індекс співвідношення еозинофілів в лімфоцитів, індекс алергізації) та В (коефіцієнт резистентності, лімфоцитарний індекс) були нижчими ніж у групі С (p <0,05). У хворих на COVID-19 індекси активності запалення (сумарний індекс запалення, індекс Кребса, індекс співвідношення лейкоцитів і ШОЕ) були вищими ніж у групі практично здорових осіб (p <0,05).

Висновки: для пацієнтів з COVID-19 характерно зміщення лейкоцитарної формули вліво, підвищення інтегративних показників

ендогенної інтоксикації, виражений запальний процес, активація тканинного розпаду. Для осіб з Long COVID - незначне підвищення інтегративних показників ендогенної інтоксикації, з низьким ступенем запалення та підвищенням неспецифічної реактивності порівняно з групою COVID-19.

Ключові слова: COVID-19, Long COVID, інтоксикація, запалення, імунологія, гематологічні зміни, здоров'я.

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INTRODUCTION / ВСТУП

The coronavirus infection (COVID-19) has become a major challenge for society. According to the latest data from the Ministry of Health of Ukraine, there are 5,557,995 infected people, of whom 112,418 have died. The causative agent of this infection is SARS-CoV-2, which can lead to both acute (COVID-19) and chronic consequences (Long COVID) [1, 2].

Worldwide, about 65 million people suffer from Long COVID (10 – 20 % of people with COVID-19), living with a debilitating post-infectious multisystemic condition, with symptoms of cognitive dysfunction and general fatigue [3].

Severe COVID-19 induces excessive inflammation caused by the innate immune system, involving monocytes and macrophages. Monocytes produce a significant amount of inflammatory cytokines during SARS-CoV-2 infection. Studies have shown an increased number of classical monocytes expressing inflammatory genes in the blood and lungs of patients with COVID-19. Activation of monocyte macrophages contributes to the cytokine storm. Many patients experience post-acute sequelae of the infection (PASC) or Long COVID after initial recovery. Symptoms of Long COVID include persistent fatigue, shortness of breath, and more, lasting up to 12 weeks. Elevated levels of inflammatory biomarkers indicate persistent inflammation in various organs. This may be related to the concept of "learned immunity," when immune cells show an increased response after interacting with SARS-CoV-2 [4–6].

Long COVID can be caused by tissue damage caused by virus-specific pathophysiological changes or secondary to a pathological long-term inflammatory response due to viral persistence, immune dysregulation, and autoimmune reactions. Some risk factors, such as gender, age, more than five early symptoms, and specific biomarkers, have been identified as likely predictors of Long COVID [7, 8].

Other parameters of severity in SARS-CoV-2 infection included: increased levels of proinflammatory cytokines such as IL-6, high levels of ferritin, increased D-dimers, increased CRP (C-reactive protein), and decreased lymphocyte counts [9-11].

Given the ambiguous data obtained by scientists, the problem remains open and requires further research.

Aim: to determine the dependence of changes in hematological parameters and indices of nonspecific reactivity, inflammation, and endogenous intoxication on the period of illness in patients with COVID-19.

Materials and methods. A total of 108 people were examined. Recruitment to the study was conducted randomly among patients treated at the Krasovitsky Medical Clinical Center for Infectious Diseases and Dermatology. The main inclusion criterion was a positive PCR result for SARS-CoV-2 or a rapid test for COVID-19. The comparison group consisted of individuals who underwent a routine medical examination at the University Clinic of Sumy State University and had no confirmatory data on the presence or history of COVID-19. This study was conducted in accordance with the Declaration of Helsinki. Before participating in this study, each participant gave written informed consent for inclusion.

The exclusion criteria for participation in the study were: age under 18 and over 60, treatment in the intensive care unit, diabetes mellitus, hepatitis, obesity above grade 2 inclusive, autoimmune diseases known to the patient at the time of the study (thyroid disease, rheumatoid arthritis, glomerulonephritis, rheumatic heart disease, psoriasis, etc.)

The subjects were divided into three groups: group A - patients with confirmed COVID-19 at the time of the study; group B - patients with Long COVID, group C consisted of practically healthy individuals (comparison group).

All subjects underwent a general blood test using CobasMicros and Elite 3 analyzers, and general integrative indicators were calculated: integral severity index (ISI), entropy of leukocyte formula (Elph); intoxication indices: leukocyte intoxication index

(LII), aggression index (Iaggr), hematological index of intoxication (HII), leukocyte shift index (LSI), intoxication index (II), neutrophil reactive response (NRR); indices of nonspecific reactivity: resistance coefficient (RC), immunoreactivity index (IRI), neutrophil-monocyte ratio index (NMRI), lymphocyte-monocyte ratio index (LMRI), lymphocyte index (Ilimph), eosinophil-lymphocyte ratio index (ELRI), allergy index (AI), nuclear index (NI) and inflammatory activity indices: total inflammation index (TII), Krebs index (KI), lymphocyte-granulocyte index (LGI), index of leukocytes and ESR ratio (IL ESR) [1-3].

Input data were collected, corrected, and systematized using Microsoft Office Excel 2016 spreadsheets. Statistical data processing was carried out using the licensed STATA software by StataCorp (Texas, USA).

During the statistical processing of the data, the Pearson's test was used to compare qualitative indicators. Compliance with the normal distribution was checked using the Kolmogorov-Smirnov and Shapiro-Wilk criteria. The Mann-Whitney U-test was used as a non-parametric analysis method, Student's t-test for values that corresponded to the normal distribution, respectively. The criteria were recognized as significantly significant at $p < 0.05$. The median (Me), 25th and 75th quartiles were used to describe quantitative indicators.

Results. In the study groups, there were 1.3 times more women than men (56 % and 44 %, respectively). The distribution in the groups by gender is as follows: group A – 55 % of men and 45 % of women; B – 41 % and 59 %, respectively; C – 40 % and 60 %, respectively. There was no significant difference between the groups by gender ($p>0.05$).

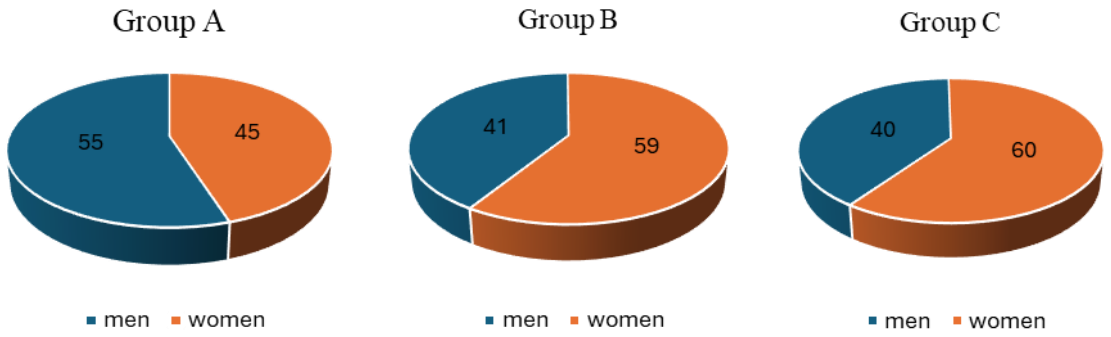

Figure 1. Distribution in groups by gender (%)

The average age of patients was 41.44 (32.25 - 50.00) years. The age composition of the patients in the groups did not differ: in group A the average age was 43.42 (34.00 - 52.00), in group B - 43.20 (34.00 - 53.00), in group C - 38.52 (32.00 - 45.00) ($p>0.05$).

Among the hematological parameters, a significant difference in the number of white blood cells (WBC) was found: the lowest was in group C (5.91 (4.95 - 6.75)), the highest - in A (6.71 (5.04 - 8.13)) ($p<0.05$). The number of red blood cells (RBC) was 1.1 times higher in group A (4.53 (4.13 - 4.96)) than in the comparison group (4.04 (3.84 - 4.23)) ($p<0.05$).

The number of rods of neutrophils in group A (7.23 (3.00 - 10.00)) was 2.5 times higher than in groups B (2.86 (1.00 - 4.00)) and 2.3 times higher than in group C (3.14 (2.00 - 4.00)) ($p<0.05$). Segmented neutrophils in group B were 1.1 times lower than in group A and 1.1 times higher than in group C ($p<0.05$). The number of lymphocytes and monocytes was the lowest in group A, 1.2 and 1.7 times lower than in groups B and 1.2 and 1.5 times lower than in group C ($p<0.05$) (Table 1).

The erythrocyte sedimentation rate (ESR) was the highest in patients with COVID-19 (14.29 (5.00 - 24.00)), which is 1.6 times higher than in patients with Long COVID (8.97 (5.00 - 11.00)) and 3.4 times higher than in the group of practically healthy individuals (3.23 (2.00 - 5.00)) ($p<0.05$) (Table 1).

Indicators of hemoglobin, platelets, and eosinophils in the blood did not differ between the study groups ($p>0.05$).

ISI had the highest values in patients with COVID-19, it was 6.5 % lower in patients with Long COVID and 10.3 % lower in healthy people ($p<0.05$) (Table 2). The Elph index was highest in group A (14.28 (9.12 - 19.32)), which was 2.2 times higher than in group B and 1.4 times higher than in group C (Table 2).

Table 1 – Changes in hematologic parameters in patients with COVID-19 and Long COVID

Indicator	Group, Me (Q25–Q75)			p
	A (n-31)	B (n-35)	C (n-42)	
WBC (1×10^9 /l)	6,71 (5,04–8,13)	6,23 (5,30–7,10)	5,91 (4,95–6,75)	p1=0,003*; p2=0,002*; p3=0,887
RBC (1×10^{12}/l)	4,53 (4,13–4,96)	4,65 (4,39–4,84)	4,04 (3,84–4,23)	p1=0,109; p2=0,001*; p3=0,185
Hemoglobin (g/l)	136,84 (131,00–144,00)	132,40 (127,00–140,00)	126,02 (117,75–136,00)	p1=0,863; p2=0,267; p3=0,358
Platelets (1×10^9/l)	214,84 (168,00–267,00)	256,69 (217,00–294,00)	238,40 (204,00–275,00)	p1=0,872; p2=0,095; p3=0,262
Neutrophils with a rod-shaped nucleus (%)	7,23 (3,00–10,00)	2,86 (1,00–4,00)	3,14 (2,00–4,00)	p1=0,000*; p2=0,000*; p3=0,549
Segmented neutrophils (%)	60,45 (50,00–67,00)	57,23 (53,00–60,00)	53,83 (49,75–59,25)	p1=0,001*; p2=0,065; p3=0,029*
Eosinophils (%)	1,50 (1,00–2,00)	1,83 (1,00–2,00)	2,33 (1,00–4,00)	p1=0,116; p2=0,052; p3=0,232
Lymphocytes (%)	26,65 (19,00–36,00)	31,26 (28,00–34,00)	33,00 (28,75–37,00)	p1=0,000*; p2=0,001*; p3=0,083
Monocytes (%)	5,00 (3,00–6,00)	8,57 (5,00–8,00)	7,57 (5,00–10,00)	p1=0,002*; p2=0,000*; p3=0,152
ESR (secs)	14,29 (5,00–24,00)	8,97 (5,00–11,00)	4,17 (2,00–5,00	p1=0,033*; p2=0,000*; p3=0,000*

Notes: * - significant difference by Student/Mann-Whitney test ($p<0.05$); p1 (group A/group B), p2 (group A/group C), p3 (group B/group C)

In patients with COVID-19, indicators of endogenous intoxication (LII, Iaggr, HII, LSI, II, NRR) exceeded the corresponding values by 3.8, 3.5, 4.5, 1.5, 8.2, 2.5 times compared with the group of patients with Long COVID ($p<0.05$). In patients with Long COVID, there was a tendency to increase endogenous intoxication indicators (LII, Iaggr, HII, LSI, NRR) compared with the group of practically healthy people ($p=0.588$, $p=0.208$, $p=0.175$, $p=0.055$, $p=0.337$), except for II, which was 2.6 times higher ($p<0.05$).

The indices of nonspecific reactivity RC and Ilimph in group B were lower than in group C (1.1 times each) ($p<0.05$), among the indices of IRI ($p=0.539$), LMRI ($p=0.425$), ELRI ($p=0.336$), AI ($p=0.125$), and NI ($p=0.349$) there was a tendency to decrease. In group A, a decrease in nonspecific reactivity was evidenced by RC and Ilimph (1.2 times lower than in group B each), ELRI (3 times lower than in group B and 3.5 times lower than in group C), AI (1.5 times lower than in group B and 1.8 times lower than in group C) ($p<0.05$). The indices of NMRI and NI were higher in group A compared to group B (2.1 and 2.6 times) and C (2.2 times each) ($p<0.05$). The indices of the IRI ($p=0.210$) and the LMRI ($p=0.141$) tended to decrease in group A compared with group B.

In patients with COVID-19, the indices of inflammatory activity (TII, KI, IL ESR) were higher than in the group of practically healthy individuals: TII - by 1.4 times, KI - by 1.8 times, IL ESR - by 2.6 times ($p<0.05$).

In patients with Long COVID - TII (1.3-fold) and KI (1.6-fold) were lower than in patients with COVID-19 ($p<0.05$), and there was a tendency ($p=0.411$) to decrease IL ESR. Compared to a group of healthy people, IL ESR was 2 times higher ($p<0.05$), TII and KI tended to increase ($p=0.122$, $p=0.088$). The LGI did not correspond to the general trend and amounted to 5.12 (4.24 - 5.59), which is 1.2 times higher than in group A and 1.1 times lower than in group C.

Table 2 – Integrative indices of endogenous intoxication, nonspecific reactivity and inflammatory activity in patients with COVID-19 and Long COVID

Indicator	Group, Me (Q25–Q75)			p
	A (n-31)	B (n-35)	C (n-42)	
General integrative indicators				
ISI	15,29 (14,33–16,41)	14,29 (13,75–14,55)	13,70 (13,46–13,80)	p1=0,000*; p2=0,000*; p3=0,000*
Elph	14,28 (9,12–19,32)	6,50 (3,35–9,23)	10,37 (5,63–14,24)	p1=0,000*; p2=0,014*; p3=0,002*
Індекси ендогенної інтоксикації				
LII	2,45 (1,23–3,75)	0,64 (0,48–0,74)	0,60 (0,35–0,80)	p1=0,000*; p2=0,000*; p3=0,588
Iaggr	3,24 (1,67–5,50)	0,92 (0,71–1,09)	0,87 (0,52–1,11)	p1=0,000*; p2=0,000*; p3=0,208
HII	3,08 (1,11–4,90)	0,67 (0,48–0,84)	0,57 (0,32–0,74)	p1=0,000*; p2=0,000*; p3=0,175
LSI	2,57 (1,50–3,35)	1,67 (1,44–1,94)	1,53 (1,17–1,80)	p1=0,012*; p2=0,000*; p3=0,055
II	3,04 (0,35–4,55)	0,37 (0,19–0,44)	0,14 (0,58–0,21)	p1=0,000*; p2=0,000*; p3=0,000*
NRR	20,31 (5,11–31,46)	7,98 (3,54–11,20)	6,51 (3,21–9,73)	p1=0,002*; p2=0,000*; p3=0,337
Indices of nonspecific reactivity				
RC	0,48 (0,28–0,67)	0,56 (0,47–0,63)	0,64 (0,48–0,74)	p1=0,000*; p2=0,135; p3=0,017*
IRI	7,80 (3,33–9,00)	5,42 (4,25–6,20)	5,47 (3,64–6,16)	p1=0,210; p2=0,133; p3=0,539
NMRI	20,33 (8,83–25,67)	9,81 (7,25–12,40)	9,06 (5,50–11,70)	p1=0,001*; p2=0,000*; p3=0,031*
LMRI	7,65 (3,33–9,00)	5,12 (4,00–5,83)	5,16 (3,29–5,66)	p1=0,141; p2=0,071; p3=0,425
Ilimph	0,43 (0,25–0,60)	0,53 (0,44–0,59)	0,60 (0,46–0,72)	p1=0,001*; p2=0,174; p3=0,027*
ELRI	0,02 (0,00–0,03)	0,06 (0,04–0,07)	0,07 (0,03–0,10)	p1=0,000*; p2=0,000*; p3=0,336
AI	0,60 (0,36–0,75)	0,90 (0,78–1,00)	1,05 (0,83–1,31)	p1=0,000*; p2=0,000*; p3=0,125
NI	0,13 (0,05–0,18)	0,05 (0,02–0,07)	0,06 (0,04–0,08)	p1=0,000*; p2=0,000*; p3=0,349
Indices of inflammatory activity				
TII	9,02 (7,08–10,29)	6,87 (6,26–7,45)	6,63 (6,12–7,04)	p1=0,000*; p2=0,000*; p3=0,122
KI	3,25 (1,68–4,00)	1,99 (1,70–2,29)	1,83 (1,40–2,17)	p1=0,017*; p2=0,001*; p3=0,088
LGI	4,22 (2,50–5,81)	5,12 (4,24–5,59)	5,75 (4,45–6,88)	p1=0,000*; p2=0,101; p3=0,039*
IL ESR	3,64 (1,44–5,25)	2,78 (1,45–3,41)	1,42 (0,74–1,55)	p1=0,411; p2=0,000*; p3=0,000*

Notes: * - significant difference by Student/Mann-Whitney test ($p<0.05$); p1 (group A/group B), p2 (group A/group C), p3 (group B/group C)

Discussion. The analysis of scientific studies revealed the dependence of the occurrence of long-term complications and the development of the clinical picture of concomitant pathology in patients with COVID-19 on the severity of the immune response and the degree of endogenous intoxication [12].

Literature data are ambiguous regarding the gender distribution of patients with COVID-19 and Long COVID, which corresponds to the results of our study [13, 14].

A slight increase in WBC in patients with COVID-19, combined with an increased number of RBC, indicates an inflammatory reaction and blood clotting, which is consistent with the clinical picture of the disease. An increase in the number of neutrophils, both rods and segmented neutrophils, and a decrease in lymphocytes and monocytes confirms the data from previous studies on frequent bacterial complications (but not identified at the time of enrollment) that join in the form of infection mixtures. Elevated ESR confirms the data on the involvement of acute-phase proteins in inflammation (C-reactive protein, protein, alpha-1 haptoglobin, ceruloplasmin, fibrinogen, immunoglobulins, antitrypsin, etc.), which in turn increase the degree of RBC cell aggregation. Other links in the pathogenesis of ESR elevation may include a change in the acid-base state of the plasma to an alkaline state, the degree of blood viscosity, plasma ionic charge, lipids, the presence of anti-erythrocyte antibodies, and anemia. The platelet count, which did not change in the study groups, was maintained in COVID-19 due to a relative increase, as was hemoglobin (blood clotting) [15, 16].

The ISI, together with the Elph score, reflect the severity of the disease and correlate with the clinical picture. Abnormal humoral and cellular immune responses, markers of systemic inflammation, such as interleukin-6 and autoantibodies directed at cell receptors, may be involved in the systemic consequences of Long COVID and determine the severity of the course.

A pronounced inflammatory process, activation of tissue breakdown, and systemic immune response are less pronounced in Long COVID compared to COVID-19, due to a decrease in the number of cytokines such as IL-6 and IL-1β, which play a key role in the inflammatory process, with potential consequences for tissue repair and exacerbation of autoimmune diseases.

The II was more sensitive than the LII because of the use of ESR in its calculation, which made it possible to confirm a significant difference in all groups. Further clinical studies are needed to directly evaluate inflammatory mediators and epigenetic changes in hematopoietic progenitor cells and monocytes in patients who have recovered from COVID-19.

On the contrary, indices of nonspecific reactivity tend to decrease in Long COVID compared to COVID-19 and the comparison group, which is associated with the body's sensitization to persistent infection and probably a reduced number of T_{RM} cells, which under normal conditions provide protection against infection localized in tissues, primarily due to the limitation of their migration capabilities. However, RC had the opposite trend, due to the predominance of neutrophils over leukocytes [17-19].

CONCLUSIONS / ВИСНОВКИ

1. Women aged 42 (32-50) years are more likely to get COVID-19 and Long COVID.
2. COVID-19 is characterized by a leftward shift in the leukocyte count, a tendency to bacterial complications, and the involvement of the granulocyte sprout in the process. Increased rates of endogenous intoxication indicate a severe inflammatory process and activation of tissue breakdown.
3. Patients with Long COVID are characterized by a slight increase in endogenous intoxication, with a low degree of inflammation compared to the group of practically healthy individuals, an increase in nonspecific reactivity compared to the COVID-19 group, which is associated with the circulation of immune complexes.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

FUNDING / ДЖЕРЕЛА ФІНАНСУВАННЯ

The work was carried out within the framework of: National Research Institute of the Department of Infectious Diseases and Epidemiology of Sumy State University (SSU) "Clinical-epidemiological features of the course of viral, bacterial and parasitic infections depending on immunological, genetic and metabolic factors, optimization of diagnostic and therapeutic measures" (number of state registration 0121U11571) (implementation period: 2022–2027).

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

REFERENCES/СПИСОК ЛІТЕРАТУРИ

1. Tsetr hromadskoho zdorovia MOZ Ukrainy. *Koronavirus v Ukraini* [Public Health Center, Ministry of Health]. Retrieved from: https://index.minfin.com.ua/ua/reference/coronavirus/ukraine/
2. Saienko O, Chemych M, Svitailo V. Long-COVID, neurological and cardiovascular disorders. *Journal of Education, Health and Sport*. 2023;13(3):381-393. eISSN 2391-8306. http://dx.doi.org/10.12775/JEHS.2023.13.03.048
3. The Lancet. Long COVID: 3 years in. *Lancet*. 2023;401(10379):795. https://doi.org/10.1016/S0140-6736(23)00493-2. PMID: 36906338; PMCID: PMC9998094.
4. Svitailo VS, Chemych MD, Saienko OS. [LONG-COVID and associated cardiovascular and nervous system disorders]. *Infectious diseases*. 2023;14(4):49–54. https://doi.org/10.11603/1681-2727.2022.4.13701.
5. Laaribya S, Alaoui A, Azmi R. Contribution to the identification of medicinal plants used against COVID-19 in North-West Morocco. *Regul. Mech. Biosyst*. 2022;13(4):339-45. https://doi.org/10.15421/022244
6. Cervia-Hasler C, Brüningk SC, Hoch T, et al. Persistent complement dysregulation with signs of thromboinflammation in active Long Covid. *Science*. 2024;383(6680):eadg7942. https://doi.org/10.1126/science.adg7942.
7. Astin R, Banerjee A, Baker MR, Dani M, Ford E, Hull JH, Lim PB, McNarry M, Morten K, O'Sullivan O, Pretorius E, Raman B, Soteropoulos DS, Taquet M, Hall CN. Long COVID: mechanisms, risk factors and recovery. *Exp Physiol*. 2023;108(1):12-27. https://doi.org/10.1113/EP090802. Epub 2022 Nov 22. PMID: 36412084; PMCID: PMC10103775.
8. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. 2023;21(3):133-146. https://doi.org/10.1038/s41579-022-00846-2. Epub 2023 Jan 13. Erratum in: Nat Rev Microbiol. 2023 Jun;21(6):408. PMID: 36639608; PMCID: PMC9839201.
9. Low RN, Low RJ, Akrami A. A review of cytokine-based pathophysiology of Long COVID symptoms. *Front Med (Lausanne)*. 2023;10:10:1011936. https://doi.org/10.3389/fmed.2023.1011936. PMID: 37064029; PMCID: PMC10103649.
10. Abdel Moneim A, Radwan MA, Yousef AI. COVID-19 and cardiovascular disease: manifestations, pathophysiology, vaccination, and long-term implication. *Curr Med Res Opin*. 2022;38(7):1071-1079. https://doi.org/10.1080/03007995.2022.2078081. Epub 2022 Jun 3. PMID: 35575011.
11. Yin JX, Agbana YL, Sun ZS, Fei SW, Zhao HQ, Zhou XN, Chen JH, Kassegne K. Increased interleukin-6 is associated with long COVID-19: a systematic review and meta-analysis. *Infect Dis Poverty*. 2023;12(1):43. https://doi.org/10.1186/s40249-023-01086-z. PMID: 37095536; PMCID: PMC10123579.
12. Pryshliak OY, Marynchak OV, Kondryn OY, Hryzhak IH, Henyk NI, Makarchuk OM, Golovchak IS, Boichuk OP, Protsyk AL, Prokofiev MV. Clinical and laboratory characteristics of COVID-19 in pregnant women. *J Med Life*. 2023;16(5):766-772. https://doi.org/10.25122/jml-2023-0044. PMID: 37520486; PMCID: PMC10375343.
13. Podavalenko, A., Malysh, N., Zadorozhna, V., Chemych, M., Birukova, S., Chorna, I. The current epidemic situation of infections with airborne transmission of viral etiology in Ukraine. *Bangladesh Journal of Medical Science*. 2022;21(3):610–619. https://doi.org/10.3329/bjms.v21i3.59575
14. Mykola D. Chemych, Dmytro S. Sosnovenko, Zoryana V. Kobliuk, & Nataliia V. Skrypka. The impact of the pandemic caused by covid-19 on the epidemiological state of HIV infection in Ukraine. *Eastern Ukrainian Medical Journal*. 2022;10(2):173-181. https://doi.org/10.21272/eumj.2022;10(2):173-181
15. Altmann DM, Whettlock EM, Liu S, Arachchillage DJ, Boyton RJ. The immunology of long COVID. *Nat Rev Immunol*. 2023;23(10):618-634. https://doi.org/10.1038/s41577-023-00904-7. Epub 2023 Jul 11. Erratum in: Nat Rev Immunol. 2023 Sep 18; PMID: 37433988.
16. Li Y, Hook JS, Ding Q, Xiao X, Chung SS, Mettlen M, Xu L, Moreland JG, Agathocleous M. Neutrophil metabolomics in severe COVID-19 reveal GAPDH as a suppressor of neutrophil extracellular trap formation. *Nat Commun*. 2023;14(1):2610. https://doi.org/10.1038/s41467-023-37567-w. PMID: 37147288; PMCID: PMC10162006.
17. Chemych MD, Lishnevska AG. The role of galectin-9 in patients with chronic viral hepatitis C and its connection with the type of therapy, the degree of fibrosis, clinical, laboratory, autoimmune and integrative indicators. *Wiad Lek.* 2021;74(5):1180-1188. PMID: 34090287.
18. Lishnevska, A. H., Chemych, M. D. Changes in clinical, biochemical, immunological and integrative parameters in patients with chronic hepatitis C virus infection according to the virus genotype and the grade of activity. *Zaporozhye Medical Journal.* 2020;22(4):485-494. https://doi.org/10.14739/2310-1210.2020.4.208363.

19. Lishnevska A, Chemych M, Chemych O, Chernetsky I. Immunoreactivity and intoxication syndrome in patients with chronic viral hepatitis C. *Bangladesh Journal of Medical Science*. 2023;22(3):508–514. https://doi.org/10.3329/bjms.v22i3.65314

Received 09.05.2024
Accepted 29.05.2024

Одержано 09.05.2024
Затверджено до друку 29.05.2024

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