МОРФОЛОГИЯ, ФИЗИОЛОГИЯ И ПАТОФИЗИОЛОГИЯ
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ASSESSMENT OF THE INFLAMMATORY RESPONSE IN CONVALESCENTS OF A NEW CORONAVIRUS INFECTION IN THE CATAMNESIS

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ABSTRACT

Background. *The pathogenetic mechanism of the development of a prolonged systemic inflammatory process in patients who have suffered a new coronavirus infection remains an urgent problem. One of the proposed mechanisms leading to hyperinflammation in COVID-19 is the involvement of the inflammasome of NOD-like receptor protein 3 (NLRP3), gasdermin D protein (GSDMD), which are effector molecules of pyroptosis, in triggering the continuous production of an increased number of inflammatory markers due to activation by the SARS-CoV-2 virus.*
The aim. *To evaluate the inflammatory response in convalescents of a new coronavirus infection in the catamnesis based on the dynamics of pyroptosis, interleukin response and indicators of the vascular link of hemostasis.*
Materials and methods. *The blood of 41 patients in the recovery period was examined; one month, three and six months after the infection. The cellular composition of peripheral blood, the level of ESR, CRP, ferritin, D-dimer were determined by classical methods; and the concentration of interleukins (IL) -1β, IL-6, IL-18, NLRP3 inflammasomes, and gasdermine D (GSDMD) was determined by ELISA methods.*
Results. *It was revealed that for all the parameters studied, there is a slow decrease in the level of values by six months. Despite the improvement in the morphological picture, altered cells are found in the peripheral blood after six months. The levels of GSDMD, platelets, IL-1β, D-dimer, ESR, IL-18, NLRP3 do not reach the values of the control group after six months, which indicates a stable hyperinflammatory response of the immune system.*
Conclusion. *Dysregulation of the NLRP3 inflammasome and gasdermine D can lead to an inadequate immune response of the body to infection, which contributes to the maintenance of the hyperinflammatory process and long-term recovery. Further study of triggers and inducers involved in the pathophysiological processes of inflammation triggered by COVID-19 will allow us to develop an approach to personalized treatment and rehabilitation of patients.*

Key words: *COVID-19, long-term effects, markers of inflammation, NLRP3, gasdermine D*

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ОЦЕНКА ВОСПАЛИТЕЛЬНОЙ РЕАКЦИИ У РЕКОНВАЛЕСЦЕНТОВ НОВОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИИ В КАТАМНЕЗЕ

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РЕЗЮМЕ

Обоснование. *Патогенетический механизм развития продолжительного системного воспалительного процесса у пациентов, перенёсших новую коронавирусную инфекцию, остаётся актуальной проблемой. Один из предполагаемых механизмов, приводящих к гипервоспалению при COVID-19, – это участие инфламмасомы NOD-подобного рецепторного белка 3 (NLRP3, NOD-like receptor protein 3), белка газдермина D (GSDMD, gasdermin D protein), являющихся эффекторными молекулами пироптоза, в запуске непрерывной продукции повышенного количества маркеров воспаления, обусловленном активацией вирусом SARS-CoV-2.*

Цель работы. *Установить особенности воспалительного ответа у пациентов после перенесённого COVID-19 в период от месяца до полугода.*

Материалы и методы. *Исследована кровь 41 пациента, находящегося в периоде выздоровления и через 1, 3 и 6 месяцев после перенесённой инфекции. Классическими методами определяли клеточный состав периферической крови, скорость оседания эритроцитов (СОЭ), уровни С-реактивного белка, ферритина, D-димера; иммуноферментным анализом – концентрацию интерлейкина (IL) 1β, IL-6, IL-18, инфламмасомы NLRP3, GSDMD.*

Результаты. *Выявлено, что по всем исследуемым параметрам происходит медленное снижение уровня значений к сроку 6 месяцев после перенесённой инфекции. Несмотря на улучшение морфологической картины, в периферической крови спустя 6 месяцев встречаются изменённые клетки. Уровни GSDMD, тромбоцитов, IL-1β, D-димера, СОЭ, IL-18, NLRP3 не приходят к значениям контрольной группы через полгода, что свидетельствует об устойчивом гипервоспалительном ответе иммунной системы.*

Заключение. *Нарушения регуляции инфламмасомы NLRP3 и GSDMD могут приводить к неадекватному иммунному ответу организма на инфекцию, что способствует поддержанию гипервоспалительного процесса и длительному выздоровлению. Дальнейшее изучение триггеров и индукторов, участвующих в патофизиологических процессах воспаления, запускаемых COVID-19, позволит разработать подход к персонифицированному лечению и реабилитации пациентов.*

Ключевые слова: *COVID-19, отдалённые последствия, маркеры воспаления, NLRP3, газдермин D*

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INTRODUCTION

The XXI century pandemic caused by SARS-CoV-2 has brought severe consequences for humanity, posing numerous questions to the medical community and is still considered an unresolved global health problem [1–4]. Currently, there is a significant decline in the disease, but the long-term effects of the infection remain a global issue [5, 6]. After recovering from COVID-19, patients are diagnosed with cardiovascular disorders, respiratory failure, and metabolic disorders [7, 8]. These problems have manifested even in patients who had a mild case of the coronavirus. Numerous studies confirm immune system dysfunction even long after recovery [9, 10].

The pathophysiological mechanism of inflammation that persists after recovery cannot be considered separately from the pathogenesis of the novel coronavirus infection. It is associated with a peculiar virus-induced dysregulation of innate and acquired immunity and damage to the vascular endothelium, leading to a hyperinflammatory response. An essential link in the immunopathogenesis of COVID-19 is pyroptosis, caused by stimulation of the inflammasome response, which contributes to excessive release of inflammatory mediators and further activation of innate immune cells [11]. Moreover, immune cells undergoing pyroptosis and secreting proinflammatory interleukins (IL) -1ß, IL-18, and IL-6 can exacerbate lymphocyte dysfunction, contributing to the dysregulation of adaptive immunity [12, 13]. Thus, it can be assumed that the ongoing clinical manifestations after recovery may be associated with the persistence of the proinflammatory profile caused by COVID-19 [14].

The NOD-like receptor protein 3 (NLRP3) inflammasome is a protein complex that regulates innate immune responses by activating caspase-1 with further cleavage of gasdermin D with an N-terminal fragment that triggers the production of inflammatory cytokines IL-1ß and IL-18 [15–18]. Numerous studies have demonstrated the importance of the NLRP3 inflammasome in the development of inflammation-related diseases [19–23]. However, at the moment, there are practically no studies devoted to considering the inflammasome-mediated mechanisms of COVID-19 in the long term. The study of markers of inflammation, the inflammasome (NLRP3), and gasdermin D (GSDMD) will allow us to observe the involvement of the body's immune response in the decreed periods of the body's recovery after infection.

The aim of the work was to evaluate the inflammatory response in convalescents of a new coronavirus infection in the catamnesis based on the dynamics of pyroptosis, interleukin response and indicators of the vascular link of hemostasis.

MATERIALS AND METHODS

On the basis of the City Allergo-Respiratory Center of the Vladivostok Polyclinic No. 3, the Far Eastern Federal University Medical Complex, patients were recruited in 2021. The study included 56 people (age 38 ± 5 years). The inclusion criterion for patients was a previous novel coronavirus infection confirmed by a PCR test. Exclusion criteria were the presence of chronic diseases in the acute stage, obesity, diabetes mellitus, oncological diseases, bad habits, and the presence of an acute inflammatory process of a non-infectious nature in patients. The main group (41 people, average age – 42 ± 5 years) included individuals who tested positive for SARS-CoV-2 by PCR, and the disease was mild. The contingent was represented by 12 males (30 %) and 29 females (70 %). One person (2.4 %) had chronic pyelonephritis in remission, two (4.8 %) had chronic pharyngitis, and one (2.4 %) had chronic cystitis. The control group consisted of employees of the medical center who underwent weekly PCR and ELISA examinations for admission to work. The control group consisted of 15 people (average age – 41 ± 5 years) who did not have COVID-19 (confirmed by PCR test, IgG ELISA). The control group included 4 males (26 %) and 11 females (74 %). Chronic diseases in remission: one person (6.6 %) with chronic pharyngitis.

The examination was performed at different time periods: 0 – early (after recovery and confirmation of negative status for SARS-CoV-2), then after 1 month, 3 months, and 6 months. At the first visit, participants filled in a questionnaire, where they gave details of the timing of infection, the conditions under which treatment was received (inpatient or outpatient), a description of their condition (complaints), prescribed medications, allergic reactions, obesity, and diabetes mellitus. Informed consent was obtained from all participants in accordance with the requirements of the Declaration of Helsinki (2013) under a protocol approved by the Biomedical Ethics Committee of the Far Eastern Federal University. Throughout the study period, testing for IgM to SARS-CoV-2 was performed using an enzyme-linked immunosorbent assay with reagent kits (Vector-Best, Russia) using a BEPP 2000 analyzer (Siemens, Germany). Sera that did not contain IgM to SARS-CoV-2 were used in the work.

Biochemical, hematological, and coagulation tests were performed directly on the day of biomaterial collection. For enzyme-linked immunosorbent assays, the selected blood serum was stored at a temperature of minus 80 °C for no more than 3 months. Samples with hemolysis and high lipid content were excluded. The content of hematological parameters of peripheral blood was determined using a Nihon Kohden MEK 6010 analyzer (Japan). The content of ferritin and C-reactive protein (CRP) was determined using Rendox FN3452 and CP 7950 test systems on a Sapfir 500 biochemical analyzer (Japan). Morphological changes in blood cells were determined by microscopic method using Axioscope 5 with magnification ×10; 100. The content of IL-1B, -6, and -18 in peripheral blood serum was determined by ELISA (Vector-Best, Russia). The content of NLRP3 (inflammasome) cytosolic polyprotein complexes was determined using a reagent kit Human NACHT, LRR and PYD Domains-Containing Protein 3 (NLRP3/C1 or f7/CIAS1/NALP3/PYPAF1) (Biomatik ELISA Kit, Israel). And gasdermin D protein (GSDMD) was determined using Human GSDMR Simple Step ELISA Kit (Abcam, UK) by ELISA on a BEP 2000 analyzer (Siemens, Germany).

Ethical review

The clinical study was approved by the Ethics Committee (Protocol No. 15/2021 dated December 27, 2021).

Statistical analysis

Statistical processing was performed using the Statistica 10.0 program (StatSoft, currently maintained by TIBCO Software Inc., USA). Data were presented as median and quartiles. The statistical significance of differences between groups was assessed using the Kruskal – Wallis test. The critical level of significance (p) when testing statistical hypotheses was taken at $p < 0.05$.

RESULTS

In patients who had undergone coronavirus infection in the early period after recovery and confirmation of negative status for SARS-CoV-2, elevated values of a number of indicators were revealed compared to the control group. The level of D-dimer increased by 376 % ($p < 0.001$), CRP – by 292 % ($p < 0.001$), NLRP3 – by 86 % ($p < 0.001$), ESR – by 50 % ($p = 0.022$), and leukocytes – by 39 % ($p = 0.034$). The cytokine status was also characterized by increased levels of indicators: IL-1ß increased by 220 % ($p < 0.001$), IL-18 – by 90 % ($p < 0.001$), and IL-6 by 58 % ($p = 0.004$). This picture may indicate the activation of the inflammasome by the remnants of the virus's vital activity products and the fading inflammatory process in the early stages of recovery.

Changes in the morphology of lymphocytes and monocytes were noted. Lymphocytes with broad cytoplasm containing granules were detected; the nucleus of monocytes acquired irregular shapes, and the cytoplasm contained a large number of vacuoles. Such a morphological picture of immunocompetent cells is characteristic of their active production of cytokines and the absorption of microorganisms by phagocytes, as well as the remnants of the cell mass resulting from pyroptosis (Fig. 1).

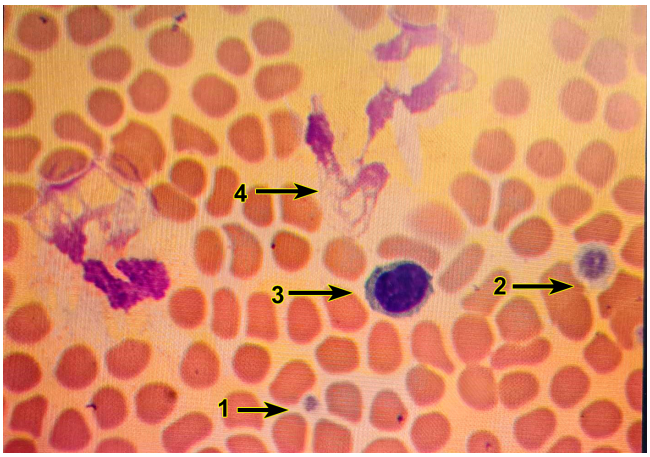

FIG. 1.

*Morphological picture in patients who have undergone a new coronavirus infection; the arrows in the photo show a large platelet (**1**, **2**); broad-plasma granular lymphocyte (**3**), granulocyte residues (**4**); magnification ×1000*

Giant platelets (less mature forms) are often (10–15 cells per 100 leukocytes) found in a stained hematological preparation. Macroplatelets can appear in the peripheral blood as a result of secondary thrombocythemia [8], as a consequence of an infectious disease and the inflammatory process.

The revealed disorders characterize the continuing high intensity of the inflammatory process and indicate the risk of complications during this period.

One month after recovery, a significant decrease in the content of D-dimer (by 31.4 %; $p = 0.004$) in blood plasma in patients who had a coronavirus infection was revealed compared to the previous period, which may be associated with anticoagulant therapy, as well as indicate a decrease in the formation of fibrin clots and their lysis. A decrease in NLRP3 by 56 % ($p = 0.006$), monocytes by 29 % ($p = 0.021$), and, to a lesser extent, leukocytes by 16 % ($p = 0.034$) may indicate a decrease in the activation of the immune system by the SARS-CoV-2 virus. A decrease in platelet levels (by 21 %; $p = 0.019$) during the first month is a positive prognostic sign. However, upon microscopy of a stained peripheral blood preparation, 2–4 % (per 100 leukocytes) of giant platelets are found. The morphological picture in this period continues to maintain similar tendencies with the initial time point, 5–10 % of granular broad-plasma lymphocytes, 3–5 % of destroyed granulocytes.

One month after recovery, patients who had suffered a new coronavirus infection showed a decrease in peripheral blood ESR by 25 % ($p = 0.027$) was revealed, however, a decrease in CRP level by 84 % ($p = 0.003$) is more informative than ESR, since it is a more specific indicator of inflammation, and its production starts earlier and decreases faster. With adequate therapy, the CRP level falls approximately on the 6–10th day, while the ESR falls after 2 weeks or later. Cytokines one month after recovery tend to decrease in peripheral blood: IL-6 – by 55 % ($p = 0.002$), IL-1 – by 40 % ($p = 0.004$), which shows a decrease in inflammation. A slower decrease in IL-18 is observed compared to other studied cytokines – by 16 % ($p = 0.005$). The morphological changes in lymphocytes and platelets observed in the current period most likely indicate this process. Quantitative changes in the studied parameters one month after recovery from the novel coronavirus infection are presented in Figure 2.

The picture of a decrease in markers of inflammation in peripheral blood one month after the period of convalescence indicates a decrease in the inflammatory process, the beginning of the body's recovery after infection. In patients who had a new coronavirus infection, there was a decrease in blood serum by the third month a further decrease, compared to the previous period, by the third month of the NLRP3 level (by 20 %; $p = 0.006$), is also an important indicator characterizing the tendency to decrease the activation of inflammasomes. There is also a decrease in the number of leukocytes by 9.3 % ($p = 0.03$), which indicates a positive dynamic of a decrease in the inflammatory response. The continued decrease in the number of platelets by 29 % ($p = 0.033$) and D-dimer by 43 % ($p = 0.024$) confirms the improvement in thrombodynamics and the reduction of inflammation in the vascular bed.

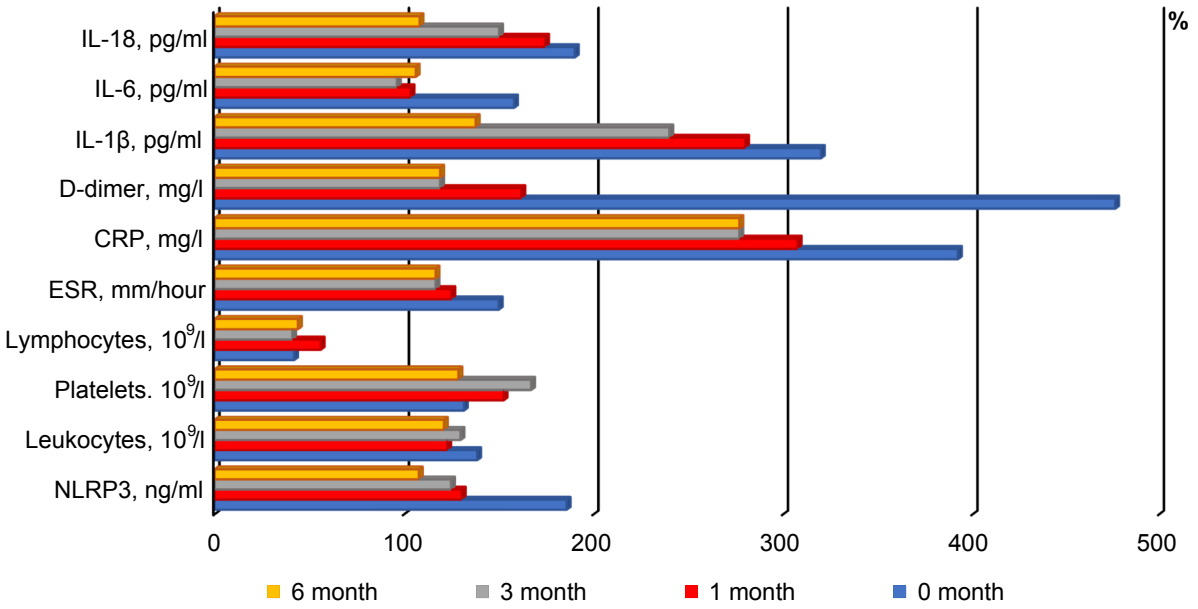

FIG. 2.

Dynamics of peripheral blood parameters after 1, 3 and 6 months; the indicators are presented as a percentage relative to the control group, the parameters of which are taken as 100 %

Other markers of inflammation, such as CRP and ESR, decreased by 31 % ($p = 0.029$) and 25 % ($p = 0.025$), respectively, indicating a decrease in the acuteness of the inflammatory process. This fact is also evidenced by the level of cytokines, which decreased by 7 % ($p = 0.041$) for IL-18, by 40 % ($p = 0.032$) for IL-1ß, and by 24 % ($p = 0.036$) for IL-6, demonstrating a positive trend in the reduction of inflammatory response activity. The dynamics of inflammation markers in this period are shown in Figure 2.

The morphological picture in this recovery period has changed in a positive direction, with granular broad-plasma lymphocytes being less common at 3–6 % per 100 leukocytes, and giant platelets are practically not encountered at 1–3 % per 100. In the third month, there is a continued decrease in inflammatory markers in peripheral blood, with the exception of platelets, which indicates a slower recovery of disorders in the platelet hemostasis link. High hemostasis parameters draw close attention during this period and deserve monitoring and assessment of the risk of thrombosis and disorders of vascular microcirculation in patients.

In patients who had a new coronavirus infection by the sixth month of the recovery period, compared with the previous period, NLRP3 decreased in serum by 17 % ($p = 0.021$), which indicates a decrease in the activation of inflammasomes by pathogens. A 38 % decrease in platelet count ($p = 0.024$) and an 18 % decrease in leukocytes ($p = 0.037$) indicate a reduction in inflammation. At the same time, D-dimer remains at the same level, not reaching the values of the control group, and ESR is at the upper limit of normal. In patients who had a new coronavirus infection, a decrease in the number of cytokines in serum by six months: IL-18 – by 42 % ($p = 0.018$), IL-6 – by 18 % ($p = 0.035$), and IL-1ß – by 17 % ($p = 0.032$) indicates a significant improvement in the recovery process and a subsiding of the inflammation syndrome. The dynamics of indicators are presented in Figure 2.

Despite a significant decrease in inflammation parameters in the first six months from the convalescence period, not all studied inflammation markers reach the level of the control group values, which may indicate an ongoing sluggish inflammation process. One of the significant indicators in the study is gasdermin D. Its dynamics at the decreed periods are presented in Figure 3. After recovery, the level of gasdermin D is high – 752 % ($p < 0.001$) compared to the control group, then there is a decrease in GSDMD one month from the convalescence period by 37 % ($p = 0.004$), three months – by 22 % ($p = 0.011$), six months – by 15 % ($p = 0.026$). The analysis suggests that gasdermin D, along with other markers of inflammation, tended to decrease after 6 months, but at a significantly slower rate.

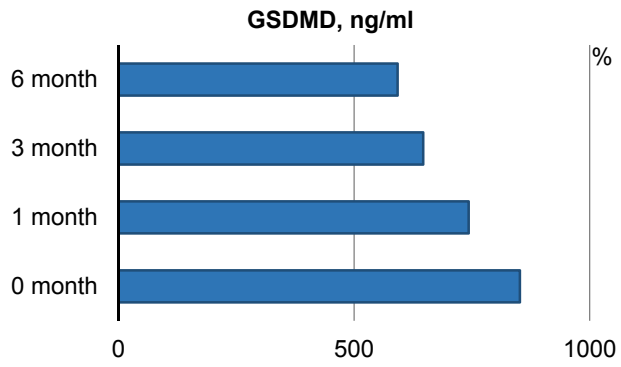

FIG. 3.

Dynamics of gasdermin D in the decreed terms; the indicators are presented as a percentage relative to the control group, the parameters of which are taken as 100 %

As the study showed, indicators such as gasdermin D, IL-1ß, D-dimer, ESR, platelets, and NLRP3 did not reach the level of the control group's values, which characterizes the ongoing process of the body's recovery after infection six months later. The morphological picture in this period has changed in a positive direction, with granular broad-plasma lymphocytes being less common at 1–2 % per 100 leukocytes, and giant platelets are practically not encountered at 0–1 % per 100. Despite the improvement in the morphological picture, the altered cells found in peripheral blood six months after recovery indicate a sluggish inflammation process.

DISCUSSION

According to official statistics, more than 18 million cases of COVID-19 infection have been detected in Russia since the beginning of the pandemic. The consequences of this disease among the population are still making themselves felt. This is due to the fact that COVID-19, unlike "classical" acute respiratory viral infections, is characterized by peculiarities of the course and complications that can affect almost all organs and systems of the human body [23].

Examination of patients at different decreed periods allows us to identify the main markers of inflammation studied in clinical medical practice, determine their significance, and develop tactics for treatment and rehabilitation. In our study, it was found that, mainly for all the studied analytes, there is a slow decrease in the level of parameters by six months, which gives us an idea of the dynamics of the body's recovery. However, not all parameters reached the values of the control group. This poses a certain threat to health and requires adequate therapeutic correction and dynamic control.

The NLRP3 inflammasome is involved in the formation of pathological processes based on an inflammatory reaction. The mechanism of NLRP3 inflammasome activation is closely related to the GSDMD protein. Recent studies have shown that signaling pathways associated with NLRP3 activation affect the production of a large number of cytokines, which further forms hyperinflammation and leads to an imbalance of innate and acquired immunity.

GSDMD is an important mediator of the body's defense against microbial infection and danger signals. The pore-forming activity of the N-terminal cleavage product causes cell swelling and lysis, causing cell pyroptosis. As a result of cell death, the reproduction of intracellular pathogens is prevented, but at the same time, the cytoplasmic contents – the inflammatory interleukin-1, are released into the extracellular space to attract and activate immune cells to the site of infection. The proposed pathophysiological mechanism is schematically presented in Figure 4.

IL-18, synthesized by monocytes and macrophages, can significantly increase the production of IFN-γ and increase the activity of NK lymphocytes. COVID-19 in the acute period is characterized by an increase in the above markers, which is reflected in a number of publications [15, 17]. Our study demonstrated a slow, uneven attenuation of this process for almost 6 months after the disease, but the pyroptotic process, as the data analysis shows, continues to remain at a fairly high level.

Leukocytes play a significant role in the "utilization" of the virus and the products of its vital activity, and actively respond to inflammasome signals, which cannot but affect their morphofunctional picture detected by microscopy of peripheral blood smears, as shown in the photo. Morphofunctional disorders are observed for a long time, up to six months after recovery from the novel coronavirus infection, which suggests a long-term multiorgan inflammatory process mediated by an imbalance in the immune system response.

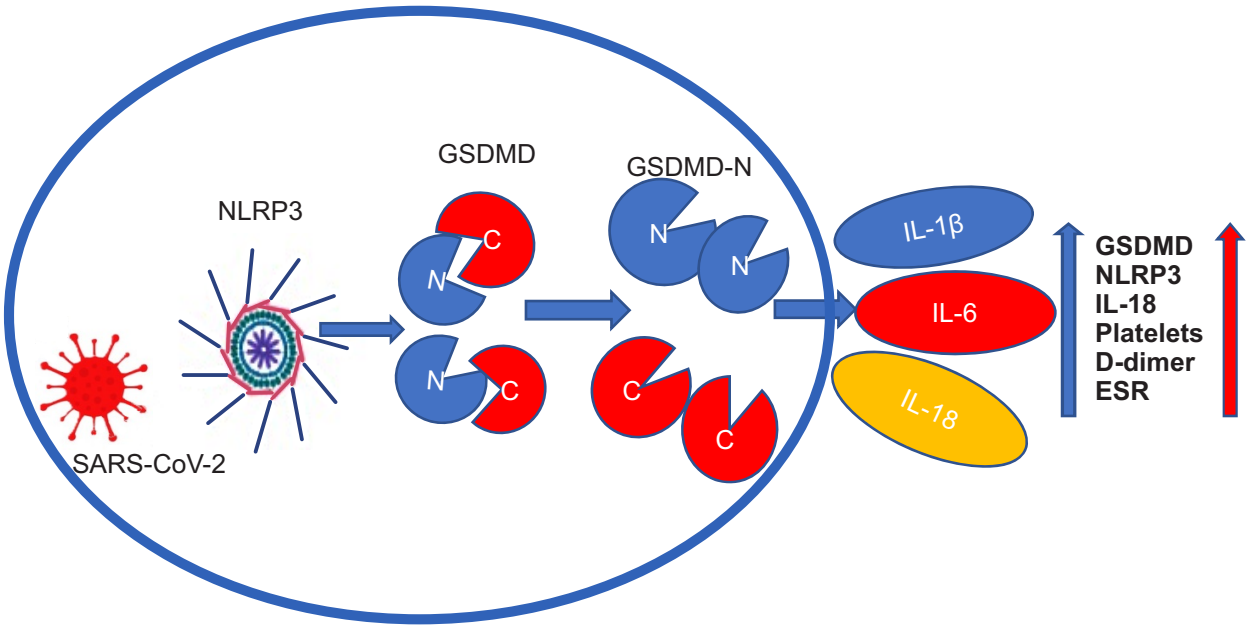

FIG. 4.
Diagram of the pathogenetic mechanism of cytokine formation affecting the content of inflammatory markers

A meta-analysis of 11 large clinical trials was published in a scientific article in March 2023. Four hundred fifty thousand patients out of 5 million participants had cardiovascular complications. The incidence of cardiovascular complications is 2.3 times higher in individuals with long-term COVID-19 compared with those in the control group [24]. Numerous scientific studies demonstrate to us that inflammasomes and pyroptosis contribute to the progression of inflammatory diseases, metabolic disorders, including those associated with damage to the vascular link of the hemostasis. The mechanisms of these associations require further clarification.

Thus, despite a gradual decrease in inflammatory markers, the value of a number of studied parameters, such as GSDMD, platelets, IL-1ß, D-dimer, ESR, IL-18, and NLRP3, does not reach the level of the control group by the sixth month, which indicates a stable hyperinflammatory response of the immune system, requiring further study of triggers and inducers involved in the pathophysiological processes of inflammation triggered by this infection. Monitoring these indicators makes it possible to assess the immune system's response at different periods of recovery after a novel coronavirus infection and to carry out prognostic and preventive measures in terms of improving the algorithm for the management of convalescents of a new coronavirus infection, prevention of post-COVID syndrome and complications from the cardiovascular system.

The limitation of the study is the relatively small sample size. A positive point is a comprehensive assessment of the inflammatory process with the involvement of highly specific markers of the inflammasome-mediated inflammation process.

CONCLUSION

The study shows the dynamics of the inflammatory process, accompanied by morphological and coagulation disorders, and highlights the significant role of the inflammasome-mediated component in the formation of a long-term immune response in patients who have undergone a novel coronavirus infection. Activation of NLRP3 by the SARS-CoV-2 virus, the critical role of GSDMD in pore formation during pyroptosis, and the secretion of large amounts of cytokines as a consequence of the above processes open up new opportunities for the future development of drugs aimed at blocking GSDMD and the NLRP3-mediated immune response, preventing the consequences of the novel coronavirus infection.

Conflict of interest

The authors declare that the presented article, its topic, subject, and content do not affect competing interests.

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