ACTIVATION OF IMMUNO-INFLAMMATORY RESPONSE IN PATIENTS WITH CORONAVIRUS DISEASE (literature review)

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ABSTRACT

The COVID-19 pandemic caused by the SARS-CoV-2 virus has become a global challenge. Community-acquired pneumonia associated with COVID-19 is still one of the most challenging medical problems. It is especially important to study the pathogenesis of Community-Acquired Pneumonia (CAP) and its relationship with various inflammatory processes that occur in the setting of coronavirus infection. The aim of this study was to analyze the pathogenesis of CAP that develops against the background of COVID-19, to study the mechanisms of immune response, inflammatory processes and their impact on the patient's body, and to identify possible approaches to the diagnosis and treatment of this disease. The following materials and research methods were used in the study: a review of scientific sources on the pathogenesis of CAP in COVID-19, the peculiarities of the immune response, cytokine storm and endothelial dysfunction in this pathology. The authors of the analyzed studies, in turn, used an analysis of inflammatory markers (C-reactive protein, D-dimer, cytokines). They report that patients with CAP developing against COVID-19 have activation of the neutrophil chain and a significant increase in the level of pro-inflammatory cytokines such as IL-6, IL-1β, TNF-α. These processes lead to the development of a severe inflammatory reaction in the lungs and diffuse alveolar damage, which in turn leads to the development of acute respiratory failure. It has been noted that excessive D-dimer release is a key indicator of the development of these complications. Prediction of severe forms of the disease based on the level of cytokines and other inflammatory markers can be an important tool for early detection of the risk of complications in patients. Thus, it was found that in order to improve the prognosis of patients, it is necessary to use methods of monitoring the level of inflammatory markers and individualise therapeutic strategies to correct immune system disorders.

Keywords: *community-acquired pneumonia, COVID-19, cytokine storm, D-dimer, immune response, thromboembolism.*

Introduction

The COVID-19 (COronaVIrus Disease 2019) pandemic has become a global challenge for healthcare systems and has led to an increase in the incidence of respiratory diseases. One of the most common and severe complications of COVID-19 is pneumonia, which can have a different course depending on the conditions of infection, physiological characteristics of the patient and the strain of the virus. Community-Acquired Pneumonia (CAP) associated with coronavirus infection is of particular interest because it occurs in patients outside of healthcare facilities and has different features compared to hospital-acquired pneumonia [1; 2].

Recent studies related to COVID-19 have focused on various aspects of respiratory complications, with pneumonia occupying a special place among them. Understanding the activation of the immuno-inflammatory response in patients with COVID-19-associated CAP may provide new information for predicting the severity of the disease and developing more effective treatment approaches [3–5].

The pandemic has drawn researchers' attention to the differences between hospital-acquired and CAP. CAP associated with coronavirus infection is distinguished by its specificity, as it occurs in patients who were not in medical facilities before

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the onset of symptoms. This requires special attention to diagnostic and prognostic markers, such as neurohumoral indicators, which can help identify the course of the disease in the early stages [6; 7].

Studies on CAP in the context of COVID-19 emphasize the importance of assessing the immune-inflammatory response, which may be one of the key factors in the development of complications. In particular, it is important to assess the level of endothelial function markers, such as endothelin-1, which may indicate the degree of damage to the vascular system during COVID-19. This is especially relevant for patients with CAP [8; 9].

However, despite a significant number of studies on COVID-19 and its impact on the body, the immune-inflammatory response in patients with CAP remains insufficiently studied. Most studies focus on hospital-acquired pneumonia or general changes associated with COVID-19, without taking into account the specifics of CAP. Therefore, the study of the immunoinflammatory response in patients with CAP associated with COVID-19 may provide new data on the diagnosis and treatment of this disease [10; 11].

Analysis of the immunoinflammatory response in patients with community-acquired pneumonia associated with COVID-19 will allow us to better understand the mechanisms behind severe pneumonia.

The **aim** of this systematic review is to analyze and summarize the available data on the immune-inflammatory response in patients with CAP associated with COVID-19 and to identify the main mechanisms that explain these changes.

Materials and Methods

To study the pathogenesis of CAP in patients infected with SARS-CoV-2, a systematic review of the literature was conducted, including sources published in leading scientific databases, including PubMed, Scopus, GoogleScholar and Web of Science, which provide access to peer-reviewed articles and other scientific publications. The following key terms were used to search for articles: "neurohormonal changes in COVID-19 pneumonia", "sympathetic nervous system and COVID-19", "inflammatory markers in pneumonia", "renin-angiotensin system in COVID-19", "neurohormonal imbalance and pneumonia", "COVID-19 and cytokine storm". Synonyms and alternative terms were also used to expand the search query, including "inflammatory response", "adrenal hormones", "stress hormones and pneumonia", "neurotransmitter changes in pneumonia".

Research was focused on pathophysiological changes in the respiratory and cardiovascular systems. Levels of inflammatory markers, such as D-dimer, C-Reactive Protein (CRP) and cytokines, as well as the mechanisms of thromboembolic complications and pathological changes in lung tissue were studied.

Results

The immunoinflammatory response is a multilevel and complex biological process that integrates the mechanisms of innate and adaptive immunity to maintain the body's homeostasis in response to exogenous and endogenous threats. When these mechanisms are disrupted, various pathological conditions and diseases occur [11; 12].

This process is initiated by the recognition of Pathogen-Associated Molecular Patterns (PAMPs) or endogenous damage-associated signaling molecules (Damage-Associated Molecular Patterns, DAMPs). By means of specialized Pattern Recognition Receptors (PRRs), including Toll-Like Receptors (TLRs), NOD-Like Receptors (NLRs) and RIG-I-Like Receptors (RLRs). The activation of these receptors initiates signaling cascades, in particular NF-κB- and MAPK-dependent pathways, leading to transcriptional regulation of proinflammatory mediators such as TNF-α, IL-1β, IL-6, and other effector molecules of the inflammatory response [13–15].

Acute inflammation is accompanied by complex changes in the microcirculatory system, including increased vascular permeability, endothelial activation and expression of adhesive molecules, which in turn promotes leukocyte migration to the site of injury. The main effector cells of the acute inflammatory response are neutrophils, monocytes and macrophages, which phagocytose pathogens and secrete cytokines and chemokines (in particular IL-8, MCP-1) that regulate chemotaxis and activation of immune cells. Dendritic cells process and present antigens on Major Histocompatibility Complex (MHC) molecules, which is a very important component for the activation of adaptive immunity [16–18].

T-cell activation is mediated by signals from antigen-presenting cells (APCs) and the cytokine microenvironment. Th1 and Th17 cells contribute to a prolonged pro-inflammatory response through the production of IFN-γ, IL-17 and GM-CSF, which stimulate the activity of macrophages and granulocytes. CD8+ T cells exert a cytotoxic effect on infected or altered cells, thereby inducing apoptosis through the perforin-granzyme mechanism or the Fas/FasL-mediated pathway. B lym-

phocytes, under the influence of Th2 cell cytokines (IL-4, IL-5, IL-13), synthesize antibodies involved in the neutralization of pathogens, opsonization and activation of complement [19; 20].

Inflammatory mediators, which include the following substances: proinflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines (CXCL8, CCL2) and lipid derivatives (prostaglandins, leukotrienes), play a key role in modulating the immune response. Prostanoids, synthesized from arachidonic acid under the influence of CycloOXygenases (COX-1, COX-2), regulate vascular changes, pain and fever, while leukotrienes are involved in stimulating leukocyte adhesion and migrations [21; 22].

Inflammation resolution involves the activation of mechanisms that limit the intensity and duration of the immune response, preventing the development of chronic inflammation and pathological tissue destruction. Anti-inflammatory cytokines such as IL-10 and TGF-β promote apoptosis of proinflammatory effector cells, macrophage polarization into the M2 phenotype and restoration of tissue architecture. The dysfunction of resolution mechanisms leads to chronic inflammation, which is associated with pathologies such as rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, and neurodegenerative processes [23; 24].

In addition, the pathological immunoinflammatory response can mediate the mechanisms of neoplastic cell transformation, promoting the development of tumors by chronic stimulation of proliferative signaling pathways, inhibition of apoptosis and creation of an immunosuppressive microenvironment. For example, chronic inflammation caused by persistent viral infections or autoimmune disorders is an important factor in carcinogenesis, in particular in cases of hepatocellular carcinoma, colorectal cancer, and gastrointestinal tumors [25; 26].

Thus, the immunoinflammatory response is a fundamental component of the body's defense mechanisms, but its dysregulation can be a trigger for a wide range of pathological conditions. A deep understanding of the mechanisms of inflammation regulation is essential for the development of innovative therapeutic strategies aimed at modulating immune responses in inflammatory, autoimmune and oncological diseases. In the future, the study of immune-inflammatory mechanisms may contribute to the development of new biological therapies, including cytokine receptor inhibitors, specific antagonists of inflammatory mediators, and cellular immunotherapeutic approaches that can selectively regulate pathologically activated immune mechanisms [27; 28].

CAP associated with COVID-19 coronavirus infection is a serious pathological condition accompanied by profound immunoinflammatory disorders. SARS-CoV-2 causes a significant activation of innate and acquired immunity, which leads to an uncontrolled inflammatory process, an imbalance between proinflammatory and anti-inflammatory mechanisms, and secondary immunosuppression. These mechanisms result in complications such as Acute Respiratory Distress Syndrome (ARDS), thromboembolic events, and secondary bacterial infections [29; 30].

In COVID-19, the activation of the neutrophil chain is one of the key aspects of CAP pathogenesis. Neutrophils, which are effector cells of the early immune response, play a critical role in the body's response to pathogens. They are the first cells to migrate to the site of infection and provide the primary line of defense by phagocytozing viral particles and neutralizing pathogens through various mechanisms. However, in COVID-19, excessive activation of neutrophils can lead to increased inflammation and the development of serious complications, including severe pneumonia, which is accompanied by the development of ARDS [31; 32].

The initial stage of neutrophil activation is contact with viral particles that enter the body. Once the SARS-CoV-2 virus enters the epithelial cells of the respiratory tract, it initiates their interaction with Toll-like receptors (TLRs), which trigger a cascade of signals that lead to the activation of pro-inflammatory molecules. This, in turn, promotes the release of chemokines, in particular interleukin-8 (IL-8), which play a crucial role in the chemotaxis of neutrophils, facilitating their mobilization to the site of infection. The production of cytokines and chemokines increases vascular permeability, which allows neutrophils to migrate to the site of infection, where they perform their primary function of phagocytosis and neutralization of pathogenic agents. However, in COVID-19, there is an excessive release of these molecules, which is accompanied not only by local inflammation but also by systemic effects, including activation of thrombosis and endothelial dysfunction [33; 34].

Excessive activation of neutrophils can cause serious pathological consequences. They activate mechanisms that promote the production of Reactive Oxygen Species (ROS), serine proteases and

various pro-inflammatory molecules, such as tumour necrosis factor alpha (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6), which in turn intensifies the inflammatory process and tissue damage. These reactions result in tissue damage, particularly in the lungs, where interstitial edema, fibrosis, and decreased gas exchange develop. One of the most destructive processes is the formation of neutrophil extracellular traps (NETs), which are a network of DNA that appears during neutrophil activation. These traps are capable of trapping viral particles, but also increase inflammation and tissue homeostasis, contributing to the development of chronic inflammation in the lungs [35; 36].

At the same time, other immune cells, in particular T-lymphocytes, dysfunction occurs, leading to an imbalance in the immune response. Excessively activated neutrophils can not only neutralize pathogens but also damage healthy tissues, which is the main cause of prolonged inflammation in the airways and the development of pulmonary fibrosis. Chronic infectious burden and inflammation can lead to prolonged changes in lung tissue, impairing the functionality of the respiratory system and significantly increasing the risk of developing secondary bacterial infections, which often complicate the course of COVID-19 [37; 38].

Another key pathogenetic mechanism is the "cytokine storm", which significantly affects the severity of CAP caused by SARS-CoV-2. This phenomenon, which involves uncontrolled and excessive release of proinflammatory cytokines, is one of the main factors that determine the progression of the disease and complications associated with COVID-19 pneumonia. Cytokines, which normally control the immune response and contribute to the effective fight against viral infections, cause tissue and organ destruction in COVID-19, which worsens the clinical condition of patients [39; 40].

The activation of the "cytokine storm" in COVID-19-induced CAP begins with the penetration of viral particles into the body, where they interact with Toll receptors, which initiates a cascade of immune responses. As a result, macrophages and dendritic cells are activated, which are the main participants in anti-viral immunity, leading to the release of significant amounts of pro-inflammatory cytokines, among which IL-6, TNF-α, IL-1β, and interferons play a special role. Under normal conditions, these molecules contribute to the effective destruction of viral particles, but in the context of COVID-19, their excessive release is out of control, leading to inflammatory lung damage and the development of pneumonia [41; 42].

The excessive release of cytokines, in particular IL-6, contributes to the development of interstitial inflammation in the lungs, which is the main feature of COVID-19-induced CAP. Cytokines activate fibroblasts and other cells, which causes lung swelling and fibrosis, disrupting their ability to exchange gas normally. In addition, the activation of pro-inflammatory molecules increases vascular permeability, which leads to interstitial edema, reduces the efficiency of blood oxygenation and creates conditions for the development of ARDS, which is a serious complication that can threaten the lives of patients [43; 44].

In addition, as a result of immune system hyperactivation, patients with CAP caused by COVID-19 have activation of the hemostatic system. Cytokines, in particular IL-6 and TNF-α, can initiate thrombosis, which leads to increased levels of D-dimers and the development of thromboembolic complications such as venous thromboembolism, deep vein and pulmonary thrombosis [45; 46].

An important factor that determines the severity and progression of the disease is the imbalance in the immune response in community-acquired pneumonia caused by COVID-19. The SARS-CoV-2 virus, when it enters the body, initiates a complex immune response, including the activation of innate and adaptive immunity. However, it should be noted that in the context of COVID-19, there is a significant imbalance between different parts of the immune system, which in turn leads to an excessive inflammatory response, disruption of normal tissue function and the development of serious complications [47, 48].

One of the aspects that exacerbates the imbalance of the immune response in COVID-19 is the disruption of the interaction between the immune system and the vascular endothelium. The SARS-CoV-2 virus interacts with Angiotensin-Converting Enzyme 2 (ACE2), which is expressed not only in lung epithelial cells but also in vascular endothelial cells. This leads to impaired endothelial function, activation of inflammatory processes, and increased vascular permeability, which contributes to the development of edema, thrombosis, and tissue damage [49; 50].

Hypoxia and inflammation are two interrelated processes that are important in the development of CAP caused by COVID-19. In this case, there is

not only a disruption of the normal functioning of the respiratory system due to the inflammatory process, but also the development of severe hypoxia, which occurs as a result of lung damage and impaired gas exchange [51; 52].

Hypoxia in COVID-19 is a consequence of progressive inflammation, which is accompanied by a violation of the alveolar capillary barrier and fibrin deposition in the interalveolar space. All of this, in turn, impairs the normal process of blood oxygenation, leading to a decrease in the level of oxygen in the tissues and the development of hypoxia. Under conditions of hypoxia, a number of adaptive mechanisms are activated, including increased lung ventilation, activation of the sympathetic nervous system, and changes in cell metabolism to provide the necessary oxygen level for vital organs [53; 54].

The inflammatory process is an integral part of the body's response to infection, which in the case of COVID-19 is amplified many times over due to viral invasion of vascular endothelial cells and alveolar epithelial cells. This inflammatory process is accompanied by the release of proinflammatory cytokines, including interleukins (IL-6, IL-1β), tumour necrosis factors (TNF-α) and chemokines that stimulate the recruitment and activation of neutrophils and macrophages. Such a "cytokine storm" contributes to the development of relative hypoxia, which increases inflammation and reduces the body's ability to fight infection [55; 56].

Hypoxia is an important component for further exacerbating inflammation, as it activates adaptive mechanisms, such as activation of hypoxia-inducible factor 1 alpha (HIF-1α), which triggers the transcription of genes that help the body survive in low oxygen conditions. However, it should be noted that in the case of severe COVID-19, these mechanisms can cause excessive inflammation, which leads to an uncontrolled body response and damage to lung tissue. All of the above increases the risk of developing pulmonary fibrosis, which is a common cause of prolonged hypoxia in patients after COVID-19 [57; 58].

Discussion

Our literature review indicates the importance of understanding the mechanisms of the immune-inflammatory response in COVID-19 to optimize therapeutic approaches and predict the course of the disease. A detailed study of the literature revealed that the activation of the neutrophil chain in COVID-19 is an important factor determining the course of pneumonia and the development of serious complications such as ARDS, thromboembolism, and chronic pulmonary inflammation. Understanding the mechanisms of neutrophil activation is important for the development of therapeutic strategies that can reduce the inflammatory response and prevent tissue damage [59; 60].

The "cytokine storm" in COVID-19-induced CAP also causes significant changes in the cardiovascular system. The development of myocardial dysfunction, arrhythmias, and cardiac performance disorders is observed as a result of the inflammatory process, including the activation of inflammatory molecules and reactive oxygen species. Such changes in the circulatory system significantly worsen the prognosis for patients and contribute to the development of multiple organ failure [61; 62].

The main goal of treatment of CAP caused by COVID-19 is to control the "cytokine storm". Treatment includes the use of anti-cytokine therapy (e.g., tocilizumab) and corticosteroids, such as dexamethasone. A balanced approach to the correction of the immune response is critical, as excessive suppression of the immune system can lead to an increased risk of infectious complications [63; 64].

The negative consequences of an imbalance in the immune response include not only overactivation of the innate immune system, but also underactivation of adaptive immunity. Disruption of the interaction between innate and adaptive immunity cells, in particular T-lymphocytes, which are responsible for the effective fight against viral infections, is observed in patients with severe COVID-19. A decrease in the function of T lymphocytes, especially T helper cells, which contribute to the activation of B lymphocytes and the production of antibodies, can lead to an ineffective immune response and a weakening of the body's ability to fight the virus [65; 66]. Inflammation that develops and is maintained in hypoxia may be one of the key factors in the development of respiratory failure in patients with COVID-19, especially in patients with severe CAP. Hypoxia and inflammation are not only the result of viral damage, but also the main factors that determine the severity and prognosis in patients with COVID-19. This process is also closely related to hypercoagulability. High levels of D-dimers and activated coagulation contribute to the formation of microthrombi in the lungs and other organs, which worsens the clinical picture and increases the risk of serious complications. Timely detection of hypoxia and inflammation can help to correct treatment, which includes the use of antiviral, anti-inflammatory

and anticoagulant drugs. The administration of these drugs will improve the outcomes of patients with severe CAP caused by COVID-19 [67; 68].

Thus, understanding the processes of activation of the immune-inflammatory response that occur in CAP in the context of SARS-CoV-2 infection can significantly improve approaches to treatment and prevention. Another important aspect is the modulation of the "cytokine storm", in particular the inhibition of IL-6. Drugs such as tocilizumab have proven effective in patients with high levels of this cytokine, which helps reduce the severity of the disease and improve prognosis. Special attention should be paid to studies that examine patterns of activation of the immune-inflammatory response in CAP against the background of COVID-19. The study of these mechanisms may open up new therapeutic opportunities to correct pathological changes in patients with COVID-19, in particular those with comorbidities that increase the risk of complications.

Conclusions

1. High levels of immune and inflammatory markers serve as an indicator of disease severity. In patients with CAP associated with COVID-19, elevated levels of key inflammatory markers were found.

2. Changes in immuno-inflammatory markers are significant indicators of disease severity and can be used for early diagnosis and monitoring of complications.

3. The need for a comprehensive approach to treatment. The results of many studies emphasize the need for a comprehensive approach to the treatment of patients with COVID-19, including not only antibiotic therapy and respiratory support, but also the correction of immune and inflammatory disorders.

Prospects for further research

Further research is needed to better understand the mechanisms of CAP in association with COVID-19, as well as to improve prognosis and treatment methods. In particular, it is important to study molecular markers associated with endothelial dysfunction and evaluate the effectiveness of new therapeutic approaches to correct neurohumoral disorders in these patients. Increased attention to monitoring immune and inflammatory markers and correcting neurohumoral disorders is an important step to improve the outcomes of patients with CAP associated with COVID-19.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Data Transparency

The data can be requested from the authors.

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References

1. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109:102433. DOI: 10.1016/j.jaut.2020.102433. PMID: 32113704.

2. Pokhrel S, Chhetri R. A literature review on impact of COVID-19 pandemic on teaching and learning. Higher education for the future. 2021;8(1):133-41. DOI: 10.1177/2347631120983481.

3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. New England Journal of Medicine. 2020;382(8):727-33. DOI: 10.1056/NEJMoa2001017. PMID: 31978945.

4. Heinrich F, Mertz KD, Glatzel M, Beer M, Krasemann S. Using autopsies to dissect COVID-19 pathogenesis. Nature Microbiology. 2023;8(11):1986-94. DOI: 10.1038/s41564-023-01488-7. PMID: 37798476.

5. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine. 2020;382(18):1708-20. DOI: 10.1056/NEJMoa2002032. PMID: 32109013.

6. Nowak B, Szymanski P, Pankowski I, Szarowska A, Zycinska K, Rogowski W, et al. Clinical characteristics and short-term outcomes of patients with coronavirus disease 2019: a retrospective single-center experience of a designated hospital in Poland. Pol Arch Intern Med. 2020;130(5):407-11. DOI: 10.20452/pamw.15361.

7. Dziublyk YA. Community-acquired pneumonia and COVID-19: discussion issues. Ukrainian Pulmonology Journal. 2020;4:12-4. DOI: 10.31215/2306-4927-2020-110-4-12-14. [In Ukrainian].

8. Avgaitis SS, Sid EV. Activation of the immune-inflammatory response among patients with community-acquired pneumonia associated with coronavirus infection. Actual Problems of the Modern Medicine: Bulletin of Ukrainian Medical Stomatological Academy. 2024;1:4-9. DOI: 10.31718/2077–1096.24.1.4. [In Ukrainian].

9. Benvenuto D, Giovanetti M, Ciccozzi A, Spoto S, Angeletti S, Ciccozzi M. The 2019-new coronavirus epidemic: evidence for virus evolution. J Med Virol. 2020;92(4):455-59. DOI: 10.1002/jmv.25688. PMID: 31994738.

10. Chen G, Wu DI, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. The Journal of clinical investigation. 2020;130(5):2620-9. DOI: 10.1172/JCI137244. PMID: 32217835.

11. Melnyk VP, Panasiuk OV, Sadomova-Andrianova OV, Antoniuk IV, Sliusarchuk IO, Solonynka HY. Pneumonia caused by SARS-CoV-2: diagnosis and treatment in outpatient settings. Zaporozhye Medical Journal. 2021;23(3):395-401. DOI: 10.14739/2310-1210.2021.3.224926. [In Ukrainian].

12. Fushtey IM, Mochonyi VA, Sid EV, Efimenko NF. The state of the SIRS and endothelial function in hypertensive patients, stage II in the process of ischemic heart disease developing. Zaporozhye Medical Journal. 2015;17(4):40-3. DOI: 10.14739/2310-1210.2015.4.50308. [In Ukrainian].

13. Rai V, Mathews G, Agrawal DK. Translational and clinical significance of DAMPs, PAMPs, and PRRs in trauma-induced inflammation. Archives of Clinical and Biomedical Research. 2022;6(5):673-85. DOI: 10.26502/acbr.50170279. PMID: 36147548.

14. Haftcheshmeh SM, Abedi M, Mashayekhi K, Mousavi MJ, Navashenaq JG, Mohammadi A, et al. Berberine as a natural modulator of inflammatory signaling pathways in the immune system: Focus on NF-κB, JAK/STAT, and MAPK signaling pathways. Phytotherapy Research. 2022;36(3):1216-30. DOI: 10.1002/ptr.7407. PMID: 35142403.

15. Lu Q, Zhu Z, Tan C, Zhou H, Hu Y, Shen G, et al. Changes of serum IL-10, IL-1β, IL-6, MCP-1, TNF-α, IP-10 and IL-4 in COVID-19 patients. International journal of clinical practice. 2021;75(9):e14462. DOI: 10.1111/ijcp.14462. PMID: 34107113.

16. Astuti I, Ysrafil. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020;14(4):407-12. DOI: 10.1016/j.dsx.2020.04.020. PMID: 32335367.

17. Carlberg C, Velleuer E, Molnar F. Molecular medicine: How science works. Cham, Switzerland: Springer Nature; 2023. DOI: 10.1007/978-3-031-27133-5.

18. Klomp M, Ghosh S, Mohammed S, Nadeem Khan M. From virus to inflammation, how influenza promotes lung damage. J Leukoc Biol. 2021;110(1):115-22. DOI: 10.1002/JLB.4RU0820-232R. PMID: 32895987.

19. Sompayrac LM. How the immune system works. 6th ed. Hoboken, NJ, USA: John Wiley & Sons; 2022. 176 p.

20. Rich R, Fleisher T, Shearer W, Schroeder H, Frew A, Weyand C. In: Clinical immunology: principles and practice. 5th ed. Amsterdam: Elsevier; 2019. 1504 p.

21. Pius-Sadowska E, Niedzwiedz A, Kulig P, Baumert B, Sobus A, Roginska D, et al. CXCL8, CCL2, and CMV seropositivity as new prognostic factors for a severe COVID-19 course. International Journal of Molecular Sciences. 2022;23(19):11338. DOI: 10.3390/ijms231911338.

22. Hsu RJ, Yu WC, Peng GR, Ye CH, Hu S, Chong PCT, et al. The role of cytokines and chemokines in severe acute respiratory syndrome coronavirus 2 infections. Frontiers in Immunology. 2022;13:832394. DOI: 10.3389/fimmu.2022.832394. PMID: 36232655.

23. Hasanvand A. COVID-19 and the role of cytokines in this disease. Inflammopharmacology. 2022;30(3):789-98. DOI: 10.1007/s10787-022-00992-2. PMID: 35505267.

24. Harne R, Williams B, Abdelaal HF, Baldwin SL, Coler RN. SARS-CoV-2 infection and immune responses. AIMS Microbiology. 2023;9(2):245-76. DOI: 10.3934/microbiol.2023015. PMID: 37091818.

25. Candido J, Hagemann T. Cancer-related inflammation. Journal of clinical immunology. 2013;33:79-84. DOI: 10.1007/s10875-012-9847-0. PMID: 23225204.

26. Liu Y, Tian S, Ning B, Huang T, Li Y, Wei Y. Stress and cancer: The mechanisms of immune dysregulation and management. Frontiers in immunology. 2022;13:1032294. DOI: 10.3389/fimmu.2022.1032294. PMID: 36275706.

27. Koyama S, Nishikawa H. Mechanisms of regulatory T cell infiltration in tumors: implications for innovative immune precision therapies. Journal for Immunotherapy of Cancer. 2021;9(7):e002591. DOI: 10.1136/jitc-2021-002591. PMID: 34330764.

28. Medzhitov R. The spectrum of inflammatory responses. Science. 2021;374(6571):1070-5. DOI: 10.1126/science.abi5200. PMID: 34822279.

29. Avgaitis SS, Sid EV. The role of coronavirus infection in lung injury, which contributes to the occurrence of complicated course of community-acquired pneumonia. Reports of Vinnytsia National Medical University. 2024;28(3):545-9. DOI: 10.31393/reports-vnmedical-2024-28(3)-28. [In Ukrainian].

30. Konopkina LI, Rybalka KV. Community-Acquired Pneumonia Associated with COVID-19: Diagnostic Significance of Imaging Methods (CT, LUS) and Comparative Characteristics of CT- and LUS-Patterns. Tuberculosis, Lung Diseases, HIV Infection (Ukraine). 2023;4:39-48. DOI: 10.30978/TB-2023-4-39. [In Ukrainian].

31. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62. DOI: 10.1016/S0140-6736(20)30566-3. PMID: 32171076.

32. Wang X, Tang G, Liu Y, Zhang L, Chen B, Han Y, et al. The role of IL-6 in coronavirus, especially in COVID-19. Frontiers in Pharmacology. 2022;13:1033674. DOI: 10.3389/fphar.2022.1033674. PMID: 36506506.

33. Mudatsir M, Fajar JK, Wulandari L, Soegiarto G, Ilmawan M, Purnamasari Y, et al. Predictors of COVID-19 severity: a systematic review and meta-analysis. F1000Research. 2021;9:1107. DOI: 10.12688/f1000research.26186.2. PMID: 33163160.

34. Kaiser R, Leunig A, Pekayvaz K, Popp O, Joppich M, Polewka V, et al. Self-sustaining IL-8 loops drive a prothrombotic neutrophil phenotype in severe COVID-19. JCI insight. 2021;6(18):e150862. DOI: 10.1172/jci.insight.150862. PMID: 34403366.

35. Huang J, Li J, Zou Z, Kandathil A, Liu J, Qiu S, et al. Clinical Characteristics of 3 Patients Infected withCOVID-19: Age, Interleukin 6 (IL-6), Lymphopenia, and Variations in Chest Computed Tomography (CT). The American Journal of Case Reports. 2020;21:e924905-1. DOI: 10.12659/AJCR.924905. PMID: 33052896.

36. Lytvyn KY, Bilokon OO. Factors associated with variability in IL-6 levels in patients with COVID-19. Infectious diseases. 2023;2(112):9-14. DOI: 10.11603/1681-2727.2023.2.14097.

37. Velavan TP, Meyer CG. Mild versus severe COVID-19: Laboratory markers. International Journal of Infectious Diseases. 2020;95:304-7. DOI: 10.1016/j.ijid.2020.04.061. PMID: 32344011.

38. Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodriguez L. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. Cytokine & growth factor reviews. 2020;54:62-75. DOI: 10.1016/j.cytogfr.2020.06.001. PMID: 32513566.

39. Zhang L, Xu D, Zhang T, Hou W, Yixi L. Correlation between interleukin-6, interleukin-8, and modified early warning score of patients with acute ischemic stroke and their condition and prognosis. Annals of Palliative Medicine. 2021;10(1):148-55. DOI: 10.21037/apm-20-2200. PMID: 33440979.

40. Zanza C, Romenskaya T, Manetti AC, Franceschi F, La Russa R, Bertozzi G, et al. Cytokine storm in COVID-19: immunopathogenesis and therapy. Medicina. 2022;58(2):144. DOI: 10.3390/medicina58020144. PMID: 35208467.

41. Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: the current evidence and treatment strategies. Frontiers in Immunology. 2020;11:1708. DOI: 10.3389/fimmu.2020.01708. PMID: 32754163.

42. Soy M, Keser G, Atagündüz MP. Pathogenesis and treatment of cytokine storm in COVID-19. Turkish Journal of Biology. 2021;45(7):372-89. DOI: 10.3906/biy-2105-37. PMID: 34803441.

43. Potere N, Batticciotto A, Vecchie A, Porreca E, Cappelli A, Abbate A, et al. The role of IL-6 and IL-6 blockade in COVID-19. Expert Review of Clinical Immunology. 2021;17(6):601-18. DOI: 10.1080/1744666X.2021.1919086.

44. Zhou YZ, Teng XB, Han MF, Shi JF, Li CX, Zhang XH, et al. The value of PCT, IL-6, and CRP in the early diagnosis and evaluation of COVID-19. Eur Rev Med Pharmacol Sci. 2021;25(2):1097-100. DOI: 10.26355/EURREV_202101_24680. PMID: 33577066.

45. Duz ME, Balcı A, Menekse E. D-dimer levels and COVID-19 severity: Systematic Review and Meta-Analysis. 2020;68(4):353-60. DOI: 10.5578/tt.70351. PMID: 33448732.

46. Si D, Du B, Yang B, Jin L, Ni L, Zhang Q, et al. IL-6 and D-Dimer at Admission Predicts Cardiac Injury and Early Mortality during SARS-CoV-2. Infection. medRxiv. 2021;2021-03. DOI: 10.1101/2021.03.22.21254077.

47. Lowery SA, Sariol A, Perlman S. Innate immune and inflammatory responses to SARS-CoV-2: Implications for COVID-19. Cell Host & Microbe. 2021;29(7):1052-62. DOI: 10.1016/j.chom.2021.05.004. PMID: 34022154.

48. Boechat JL, Chora I, Morais A, Delgado L. The immune response to SARS-CoV-2 and COVID-19 immunopathology-current perspectives. Pulmonology. 2021;27(5):423-37. DOI: 10.1016/j.pulmoe.2021.03.008. PMID: 33867315.

49. Bourgonje AR, Abdulle AE, Timens W, Hillebrands JL, Navis GJ, Gordijn SJ, et al. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). The Journal of pathology. 2020;251(3):228-48. DOI: 10.1002/path.5471. PMID: 32418199.

50. Li Y, Zhou W, Yang L, You R. Physiological and pathological regulation of ACE2, the SARS-CoV-2 receptor. Pharmacological research. 2020;157:104833. DOI: 10.1016/j.phrs.2020.104833. PMID: 32302706.

51. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host & Microbe. 2020;27(6):992-1000. DOI: 10.1016/j.chom.2020.04.009. PMID: 32320677.

52. Crayne CB, Albeituni S, Nichols KE, Cron RQ. The immunology of macrophage activation syndrome. Frontiers in immunology. 2019;10:119. DOI: 10.3389/fimmu.2019.00119. PMID: 30774631.

53. Rahman A, Tabassum T, Araf Y, Al Nahid A, Ullah MA, Hosen MJ. Silent hypoxia in COVID-19: pathomechanism and possible management strategy. Molecular biology reports. 2021;48(4):3863-9. DOI: 10.1007/s11033-021-06358-1. PMID: 33891272.

54. Kashani KB. Hypoxia in COVID-19: sign of severity or cause for poor outcomes. Mayo Clinic Proceedings. 2020;95(6):1094-6. DOI: 10.1016/j.mayocp.2020.04.021. PMID: 32498766.

55. Frisoni P, Neri M, D'Errico S, Alfieri L, Bonuccelli D, Cingolani M, et al. Cytokine storm and histopathological findings in 60 cases of COVID-19-related death: from viral load research to immunohistochemical quantification of major players IL-1β, IL-6, IL-15 and TNF-α. Forensic Science, Medicine and Pathology. 2022;18(1):4-19. DOI: 10.1007/s12024-021-00414-9. PMID: 34463916.

56. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. Journal of medical virology. 2021;93(1):250-6. DOI: 10.1002/jmv.26232. PMID: 32592501.

57. Serebrovska ZO, Chong EY, Serebrovska TV, Tumanovska LV, Xi L. Hypoxia, HIF-1α, and COVID-19: from pathogenic factors to potential therapeutic targets. Acta Pharmacologica Sinica. 2020;41(12):1539-46. DOI: 10.1038/s41401-020-00554-8. PMID: 33110240.

58. Jahani M, Dokaneheifard S, Mansouri K. Hypoxia: A key feature of COVID-19 launching activation of HIF-1 and cytokine storm. Journal of inflammation. 2020;17:1-10. DOI: 10.1186/s12950-020-00263-3. PMID: 33139969.

59. Veronese N, Demurtas J, Yang L, Tonelli R, Barbagallo M, Lopalco P, et al. Use of corticosteroids in coronavirus disease 2019 pneumonia: a systematic review of the literature. Frontiers in medicine. 2020;7:170. DOI: 10.3389/fmed.2020.00170. PMID: 32391369.

60. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet respiratory medicine. 2020;8(4):420-2. DOI: 10.1016/S2213-2600(20)30076-X. PMID: 32085846.

61. Zanza C, Romenskaya T, Manetti AC, Franceschi F, La Russa R, Bertozzi G, et al. Cytokine storm in COVID-19: immunopathogenesis and therapy. Medicina. 2022;58(2):144. DOI: 10.3390/medicina58020144. PMID: 35208467.

62. Kim JS, Lee JY, Yang JW, Lee KH, Effenberger M, Szpirt W, et al. Immunopathogenesis and treatment of cytokine storm in COVID-19. Theranostics. 2021;11(1):316-29. DOI: 10.7150/thno.49713. PMID: 35208467.

63. Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: the current evidence and treatment strategies. Frontiers in Immunology. 2020;11:1708. DOI: 10.3389/fimmu.2020.01708. PMID: 32754163.

64. Saha A, Sharma AR, Bhattacharya M, Sharma G, Lee SS, Chakraborty C. Tocilizumab: a therapeutic option for the treatment of cytokine storm syndrome in COVID-19. Archives of Medical Research. 2020;51(6): 595-7. DOI: 10.1016/j.arcmed.2020.05.009. PMID: 32482373.

65. Fenoglio D, Dentone C, Parodi A, Di Biagio A, Bozzano F, Vena A, et al. Characterization of T lymphocytes in severe COVID-19 patients. Journal of Medical Virology. 2021;93(9):5608-13. DOI: 10.1002/jmv.27037. PMID: 33913544.

66. Kwiecien I, Rutkowska E, Klos K, Wiesik-Szewczyk E., Jahnz-Rozyk K, Rzepecki P, Chcialowski A. Maturation of T and B Lymphocytes in the Assessment of the Immune Status in COVID-19 Patients. Cells. 2020;9(12):2615. DOI: 10.3390/cells9122615.

67. Konopkina LI, Shchudro OO. Cardiovascular system status in patients with dyspnea after COVID-19-associated pneumonia. Ukrainian Pulmonology Journal. 2022;31(4):14-21. DOI: 10.31215/2306-4927-2023-31-4-14-21. [In Ukrainian].

68. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. Expert Review of Hematology. 2020;13(11):1265-75. DOI: 10.1080/17474086.2020.1831383. PMID: 33291439.

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