UDC 616.24-008.4-07: 578

CYTOKINE STATUS IN DISEASES OF THE UPPER RESPIRATORY TRACT IN CORONAVIRUS DISEASE (COVID-19)

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✓ ***Resume***

The data of own examinations of 123 patients with laboratory and clinical and epidemiologically confirmed new coronavirus infection and inflammatory diseases of the upper respiratory tract are presented. The content of hemoglobin, the number of erythrocytes, the concentration of interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor alpha (TNF-α) and C-reactive protein (CRP) were studied. It was shown that in patients with novel coronavirus infection (COVID-19) and inflammatory diseases of the upper respiratory tract, the average values of the degree of saturation of hemoglobin with oxygen were 87.04%. Anemia was detected in 8.9% of examinations, an increase in CRP of more than 5 mg / l was noted in 81 (65.8%) patients. In 19 patients, in 24.3% of cases, the level of cytokines in the blood serum was assessed before the start of antibiotic therapy. At the same time, the content of IL-6 was increased in 17 (89.4%) patients. Demonstrated a positive correlation between the content of C-reactive protein and the level of TNF-α.

Key words: coronavirus; COVID-19; upper respiratory tract; cytokines; interleukin-10; interleukin-6; tumor necrosis factor-alpha; cytokine storm.

ЦИТОКИНОВЫЙ СТАТУС ПРИ ЗАБОЛЕВАНИЯХ ВЕРХНИХ ДЫХАТЕЛЬНЫХ ПУТЕЙ ПРИ КОРОНАВИРУСНОЙ БОЛЕЗНИ (COVID-19)

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✓ ***Резюме***

Представлены данные собственных обследований 123 пациентов с лабораторно и клинико-эпидемиологически подтвержденной новой коронавирусной инфекцией и воспалительных заболеваниях верхних дыхательных путей. Исследованы содержание гемоглобина, число эритроцитов, концентрация интерлейкина-6 (IL-6), интерлейкина-10 (IL-10), фактор некроза опухоли альфа (TNF-α) и С-реактивного белка (СРБ). Показано, что у пациентов с новой коронавирусной инфекцией (COVID-19) и воспалительных заболеваниях верхних дыхательных путей средние значения степени насыщения гемоглобина кислородом составили 87,04 %. Анемия выявлялась в 8,9 % обследований, повышение СРБ более 5 мг/л отмечалось у 81 (65,8 %) пациентов. У 19 пациентов в 24,3 % случаев оценка уровня цитокинов в сыворотке крови проводилась до начало антибактериальной терапии. При этом, содержание IL-6 было повышенным у 17 (89,4 %) пациентов. Продемонстрирована положительная корреляционная взаимосвязь между содержанием С-реактивного белка и уровнем TNF-α.

Ключевые слова: коронавирус; COVID-19; верхних дыхательных путей; цитокины; интерлейкин-10; интерлейкин-6; фактор некроза опухоли-альфа; цитокиновый шторм.

KORONAVIRUS KASALLIGIDA YUQORI NAFAS YO'LLARINING KASALLIKLARIDA SITOKIN HOLATI (COVID-19)

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Buxoro davlat tibbiyot instituti.

✓ ***Rezyme***

Laboratoriya va klinik-epidemiologik tasdiqlangan yangi koronavirus infektsiyasi va yuqori nafas yo'llarining yallig'lanish kasalliklari bilan kasallangan 123 bemorning o'z tekshiruvlari ma'lumotlari keltirilgan. Gemoglobin tarkibi, eritrotsitlar soni, interleykin-6 (IL-6), interleykin-10 (IL-10), o'sma nekroz omil alfa (TNF-a) va C-reaktiv oqsil (CRP) kontsentratsiyasi o'rganildi. Yangi koronavirus infektsiyasi (COVID-19) va yuqori nafas yo'llarining yallig'lanish kasalliklari bilan kasallangan bemorlarda gemoglobinning kislorod bilan to'yinganlik darajasi o'rtacha 87,04% ni tashkil etganligi ko'rsatildi. 8.9% tekshiruvlarda anemiya aniqlandi, 81 (65.8%) bemorda CRP ning 5 mg / l dan oshishi qayd etildi. 19 bemorda, 24,3% hollarda, qon zardobidagi sitokinlar darajasi antibiotik terapiyasi boshlanishidan oldin baholandi. Shu bilan birga, IL-6 ning tarkibi 17 (89,4%) bemorda ko'paytirildi. C-reaktiv oqsil miqdori va TNF-a darajasi o'rtasidagi ijobiy bog'liqlikni namoyish etdi.

Kalit so'zlar: koronavirus; COVID-19; yuqori nafas yo'llari; sitokinlar; interleykin-10; interleykin-6; o'sma nekrozi omil-alfa; sitokin bo'roni.

Relevance

At present, the attention of researchers and clinicians is focused on the treatment of complications associated with the novel coronavirus infection (COVID-19). L.Yu. Ilchenko et al. (2020) noted that coronaviruses are widespread in nature, approximately 12-25% of colds that do not cause serious harm to health are caused by coronaviruses [1]. The history of the study of human coronavirus dates back to the second half of the sixties of the twentieth century, when the phenomenon of respiratory failure was noted in a patient with an acute respiratory viral infection [2, 3]. According to the literature, a sample of B814 was isolated from the nose of volunteers for colds, which is described as a virus strain not associated with any other previously known human respiratory tract virus [4]. In 1968, the first communication by J.D. appeared in the journal 'Nature'. Almedia and co-authors, where the researchers called this virus a coronavirus - “more or less rounded in profile, with a characteristic stripe, resemble the solar corona characteristic of the mouse hepatitis virus” [2,3]. a significant contribution to the study of diseases caused by coronaviruses [2, 3].

In the publication of V.V. Nikiforov et al. (2020) noted that until 2002, coronaviruses were considered as agents causing mild diseases of the upper respiratory tract [5]. As studies show, at the end of 2002, a coronavirus (the causative agent of SARS) appeared, causing severe acute respiratory syndrome in humans [5]. It should be emphasized that since 2004, there have been no new cases of SARS caused by coronaviruses. In 2012, the first case of inflammatory respiratory disease caused by coronaviruses was recorded, which received the official name Middle East respiratory syndrome-related coroavirus (MERS-CoV) [6]. 2519 cases of coronavirus infection caused by the MERS-CoV virus, of which 866 were fatal [5]. Every year, the cases of Middle East respiratory syndrome caused by MERS-CoV continue to be recorded: from isolated cases to dozens. that person-to-person transmission of MERS-CoV occurs through close contact with an infected patient.

At the end of December 2019, an outbreak of SARS was described in China, which led to the development of a public health emergency around the world. The massive incidence of atypical (unknown) pneumonia in January 2020, observed in the city of Wuhan, was caused by a new type of coronavirus and subsequently led to a pandemic situation around the world. In the international community, since February 11, 2020, the new coronavirus is officially called SARS-CoV-2 (severe acute respiratory syndrome coronavirus) -infection, - COVID-19 ("SogonaVirus Disease -2019" - a disease caused by the new coronavirus-2019 Exactly one month later, the World Health Organization (WHO), in connection with the massive spread of COVID-19, announced the beginning of a pandemic worldwide. As of August 21, 2020, over 22.6 million cases were registered worldwide. diseases, more than 792 thousand people died and more than 14.5 million recovered. [7] Despite the measures taken to limit contacts between people, isolation of persons with suspected COVID-19, the number of cases does not decrease.

Etiology and pathogenesis of coronavirus disease-2019.

Coronavirus contains ribonucleic acid (RNA) and belongs to viruses of the genus Betacoronavirus of the Coronaviridae family.

V.T. Ivashkin et al (2020) noted that for the first time coronavirus RNA was isolated in feces in 2019 in the United States [8]. According to the International Committee on Virus Taxonomy, coronavirus belongs to the II pathogenicity group. The Coronaviridae

families include 43 RNA viruses, grouped into two subfamilies, that infect mammals, including humans, birds, and amphibians. It is worth noting here that there are currently seven known human coronaviruses. As noted, the name "coronavirus" is associated with the structure of the virus, the spines of which resemble the solar corona [2, 3].

Virions are 80-220 nm in size, and the genome of the virus consists of more than 20 thousand nucleotides. It is well known that the virions of most viruses do not show any signs of biological activity until they come into contact with the host cell, after which they form a "virus-cell" complex capable of living and "producing" new virions. Coronaviruses have an RNA of about 26-30 thousand base pairs, i.e., coronaviruses have the largest non-segmented RNA among all known viruses and are the most complex in structure among known viruses. A series of review studies emphasized that coronavirus infects pneumocytes, cholangiocytes, cardiomyocytes and other cells expressing angiotensin converting enzyme 2 (ACE2 / angiotenzin converting enzyme 2, ACE2), which acts as a viral receptor [1, 5, 9- eleven]. It is also described that ACE2, which acts as a receptor for coronavirus, is expressed in intestinal epithelial cells, vascular endothelium and in the kidneys [8, 9], which explains the multiple organ dysfunction of the human body, the manifestation of which depends on the age, sex of the patient, geography, as well as from the comorbidity index.

M.L. Holshue et al (2020) reported on the detection of coronavirus RNA in a young patient on the 7th day of illness [12]. There is evidence that coronavirus RNA was detected on the mucous membrane of the esophagus, stomach, duodenum and rectum [13]. Often, gastroenterological manifestations of COVID-19 come to the fore [8]. Researchers W. Song et al (2020) described gastroenterological manifestations (diarrhea) of COVID-19 in the absence of other clinical symptoms [14]. As the authors note, the diagnosis of COVID-19 was established on the basis of X-ray studies of the chest organs (bilateral pneumonia), as well as the detection of coronavirus RNA [14]. There is evidence that no signs of coronavirus invasion into hepatocytes were found [15].

In the publication by E.A. Kogan et al (2020) described morphological and immunohistochemical confirmation of the development of lymphocytic viral myocardial damage in COVID-19. As the authors point out, the features of myocardial damage in COVID-19 are the presence of coronaritis and the possibility of a combination of myocarditis with lymphocytic endo- and pericarditis [16]. Recently, a clinical case of a 60-year-old patient was described in whom infection with a new coronavirus occurred in the immediate postoperative period after heart transplantation during therapy with methylprednisolone, tacrolimus, mycophenolate mofetil sulfamethoxazole / trimethoprim and amlodipine [17].

Numerous clinical and epidemiological studies have established that the respiratory tract is the initial “gateway to coronavirus infection,” and pneumonia is the leading clinical form of COVID-19 [1, 5, 8, 9, 18, 19]. With this, at present, the emphasis is on the clinical symptoms characteristic of lung lesions, which in most cases determine the prognosis of the disease.It would be appropriate to note the presence of pulmonary defense mechanisms in various infectious and non-infectious diseases [20, 21].

1.Mechanical barriers:

> nostril hairs filter particles larger than 10 microns;

> Mucociliary clearance and acute branching of the lower airways, which helps the mucous membrane to capture particles ranging in size from 5 to 10 microns.

2.Humoral immunity. Mucous immunoglobulins A (immunoglobulin A), alveolar immunoglobulins M (immunoglobulin M) and immunoglobulins G (immunoglobulin G) present in blood transudates.

3.Phagocytes:

> polymorphonuclear cells;

> alveolar cells;

> interstitial cells;

> intravascular macrophages;

> dendritic cells of the respiratory tract (involved in the activation and differentiation of CD8 + T cells);

> alveolar macrophages (provide the first level of protection associated with internalization and destruction of viral particles. Alveolar macrophages act as antigen-presenting and opsonin-producing cells).

4. Cellular immunity. A decrease in the number of CD4 + T cells, CD8 + T cells in COVID-19 indicates a severe course of the pathological process.

Active replication of coronavirus significantly reduces the protective functions of goblet cells

(mucus formation), which also contributes to the penetration of the virus into the human body [1]. Human infection with coronavirus occurs in the last days of the incubation period and maximum in the first three days from the onset of the disease [1]. In the publication by E.L. Nasonova (2020) showed that the replication of coronavirus has a cytopathic effect on target cells, causing the pro-inflammatory form of programmed cell death - pyroptosis [9]. At the same time, by activating immune cells, the coronavirus expresses proteins that suppress the synthesis of type I interferon, which leads to a weakening of the antiviral immune response [9]. Recall that coronavirus primarily infects type II pneumocytes. Expression of ACE2 protects the lungs from damage, but it decreases due to its binding to the ligamentous protein of the coronavirus, which increases the risk of infection [1].

It is interesting to note that increased expression of ACE2 does not exclude the possibility of increased binding to the coronavirus protein [1, 5, 9]. It should be emphasized that up to three coronaviruses can attach to one ACE2 target. The latter, infecting the endothelium of blood vessels, interacts with ACE2 located there and leads to the development of endothelial dysfunction, hyperpermeability, impaired microcirculation, the development of vascular thrombophilia and thrombosis [1, 5, 9]. It was found that in patients with COVID-19, during morphological examination in the lungs, massive infiltration of lymphocytes with a "pro-inflammatory" phenotype (CCR4 + CCR6 + Th 17 + CD4 T cells), neutrophils and macrophages, diffuse damage to alveoli with the formation of hyaline membranes, capillary microthrombi, microinfarctions and hemorrhages [22-24] Violation of alveolar ventilation and a decrease in pulmonary blood flow lead to further progression of impaired ventilation-perfusion relationship with COVID-19.

As noted, the rapid replication of the virus promotes an increase in the viral load, followed by an increase in its cytopathic action, which leads to a rapid progression of the immune-inflammatory process [9]. Many researchers have confirmed that with COVID-19, a pronounced increase in the concentration of cytokia signals the severity and critical form of this pathology [1, 5, 9]. Determination of risk groups, the spectrum of the studied cytokines and other inflammatory markers of COVID-19 finds a different solution in countries with different healthcare systems.

Based on this, the purpose of this work was to study the concentration of cytokines in patients with COVID-19.

Material and methods

Our research was carried out at the clinical departments of the BukhMI named after Abu Ali ibn Sina from 06/18/2020 to 08/18/2020. It would be appropriate to emphasize that at these departments, as well as in the pulmonology department of the Bukhara multidisciplinary medical center, for several years, the cytokine mechanisms of the progression of renal, cardiovascular and pulmonary diseases have been studied. -leaving [25, 26].

The current study included 123 patients aged 16 to 80 years. The average age was 46.6 ± 14.4 years, the number of men and women was 75 (61%) and 48 (39%), respectively. In all cases, clinical and epidemiological, radiological data and the results of computed tomography of the lungs, as well as the level of antibody titers to coronaviruses, were taken into account. The indicators of saturation of hemoglobin (Hb) of blood with oxygen in the microvasculature were measured by an integral method - pulse oximetry. We also studied the content of Hb, the number of erythrocytes

and blood C-reactive protein (CRP) levels. In 78 patients (in 63.4% of cases), the cytokine status was investigated: interleukin (IL) -6, IL-10 and tumor necrosis factor-alpha (TNF-α). In 59 (75.6%) patients, the level of cytokines was assessed during the completion of antibiotic therapy. The reference values of the concentration of the studied cytokines were as follows: IL-6 - up to 10 pg / ml, IL-10 - up to 31 pg / ml, TNF-α - up to 6 pg / ml.

Statistical analysis of the obtained data was carried out using the software package "Statistica 10.0". All quantitative variables are presented as mean (M) ± standard deviation (80), median and quartiles [Me (Q25; Q75)] Correlation analysis was carried out according to Spearman's criterion, and the criterion $p < 0.05$ was taken as the critical level of reliability.

Result and discussion

The number of patients with damage to only the upper respiratory tract and pneumonia complicated by acute respiratory distress syndrome, sepsis, septic shock or multiple organ failure was 9 and 5.6%, respectively (Figure 1). The proportion of patients with pneumonia without respiratory failure was 61.8%, and pneumonia with the development of respiratory failure, the appearance of

infiltrates in the lungs in the form of "ground glass" occupied more than half of the lungs within 24-48 hours - 23.6% (see figure 1).

As shown in Table 1, the average values of the degree of peripheral blood saturation corresponded to respiratory failure, which required low-flow oxygen therapy. According to the WHO criteria, laboratory signs of anemia were observed in 11 (8.9%) examined persons.

It is important to note that in 19 patients (24.3% of cases), the level of cytokines in the blood serum was assessed before the start of antibiotic therapy. At the same time, the content of IL-6 was increased in 17 (89.4%) patients. As for the level of IL-10, its content in the blood serum did not exceed the reference values. The proportion of persons with an increased TNF-α content in the blood serum was small.

The median and interquartile values of the studied cytokines and blood CRP are shown in Figures 2-5. The median pro-inflammatory cytokines (IL-6 and TNF-α) in blood serum were 2.3900 pg / ml and 1.3185 pg / ml, respectively. Noteworthy is the fact that the maximum level of IL-6 reached 264.0500 pg / ml.

As can be seen, the maximum content of TNF-α was 6.5090 pg / ml, while the maximum level of the anti-inflammatory cytokine IL-10 reached 16.8220 pg / ml with a reference value of 31 pg / ml. The median of this cytokine was 3.7500 pg / ml.

When considering the indicators of acute phase blood protein, the median and quarterly indicators of CRP were 4.3500 (1.1850-25.8000) mg / l.

An increase in CRP of more than 5 mg / l was detected in 81 (65.8%) patients. It must be said that the maximum CRP level in the patients examined by us, increasing many times over, reached 239.9000 mg / l. This fact served as the basis for the correlation analysis of pro- and anti-inflammatory cytokines. As shown in Table 2, a statistically significant positive relationship was found between the content of CRP and TNF-α ($r = 0.3214$; $p = 0.031$).

Meanwhile, no reliable correlation relationship between the CRP level and the content of interleukins in blood serum was obtained (see Table 2).

Discussion. Back in 2013 M.V. Shipilov published an article in the journal “Healing Business” entitled “Molecular mechanisms of a cytokine storm in acute infectious diseases.” [27] It notes that cytokines are low molecular weight proteins that are produced mainly by effector blood cells and are universal. regulators that control the most important processes of cellular homeostasis [27]. Currently, more than 100 cytokines are known. EV 'Gyulandina and DA Piskov report that “cytokine storm” is a form of systemic inflammatory body reactions, characterized by excessive synthesis of cytokines in the inflammation focus through a positive feedback mechanism (28).

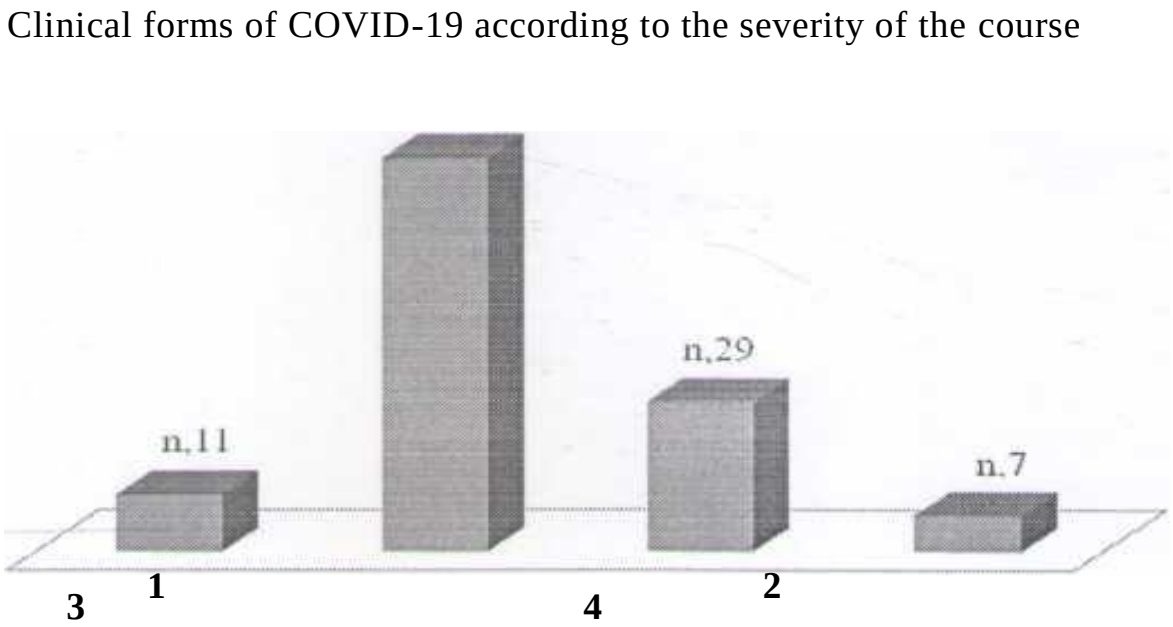

Figure 1 - Characteristics of study participants with COVID-19

Note: 1-light; 2-moderate; 3-heavy; 4-very heavy; n-number of participants

Table 1 - Indicators of oxygen saturation and red blood

Indicator	Indicator value, M ± 80
Degree of saturation of Hb with oxygen,%	87,04 ±5,17
Hb, g / l	139,8 ± 17,1
Erythrocytes, 1012 / l	4.82 ± 0,55

Note. Hb – hemoglobin

In the medical lexicon, the term “cytokine storm” was first used by J.L. Ferrara et al. (29). In infectious pathologies, including in patients with COVID-19, activation of the population of T-lymphacytes or lysis of immune cells increases the production of TNF-α. This leads to the activation of alveolar macrophages, dendritic, immune and endothelial cells, followed by the production of cytokines (1,5,9). It is important to emphasize that alveolar macrophages and endothelial cells of the pulmonary circulation produce a large amount of IL-6, which is activated by a positive feedback mechanism.

Table 2 - Correlation analysis between CRP and cytokines in patients with COVID-19

Indicators	CRP, mg / l	
	K = P =	P=
1b-6, pg / ml	0,1632	0,284
1b-! 0, pg / ml	0,2433	0,107
Tyr-a, pg / ml	0,3214	0.031

Note. CRP - C-reactive protein; IL - interleukin; TNF, tumor necrosis factor-alpha; R - correlation; P - reliability

T-lymphocytes and other immune cells, leading to the development of a “cytokine storm” [28]. Considering the problem of "cytokine storm", it should be noted that this phenomenon is more often observed in older people suffering from chronic diseases. Many researchers are inclined to believe that, as diagnostic criteria for a "cytokine storm", first of all, attention should be paid to an increase in IL-6, IL-10 and ferritin [1, 5, 8, 9].

Researchers from the First Moscow State Medical University named after I.M. Sechenov, headed by P.V. Glybochko emphasize [30] that cytokine release syndrome should be thought of with a rapid deterioration of lung function in combination with an increasing content of CRP and ferritin, cytopenia (thrombocytopenia and lymphopenia), coagulopathy (low platelet count and decreased fibrinogen levels, as well as increased content of D-dimer), signs of liver damage (increased activity of lactate dehydrogenase and aminotransferases) [30]. It is obvious that the development of a "cytokine storm" in patients with COVID-19 indicates the addition of complications, or a protracted nature of the course of the infectious and inflammatory process. Determination of the leading cytokines will allow a targeted effect on the pathogenesis of the “cytokine storm” and prevent the development of a reaction cascade in the early stages of the development of systemic inflammation in COVID-19.

In our study, the content of IL-6 was increased only in 17 (89.4%) patients out of 19 (100%). It should be emphasized here that in these patients the cytokine indices were studied prior to the initiation of antibiotic therapy. In addition, in our work, persons with a very severe / critical form of COVID-19 were few (see Figure 1). The accumulated results of clinical studies indicate the important role of IL-

6 in the immunopathogenesis of COVID-19, as well as an increase in the content of this cytokine in the blood serum of patients, primarily in severe disease [21-26]. From a clinical point of view, it is important to note that according to computed tomography data, with COVID-19, an increased content of IL-6 in the blood serum indicates a large volume of lung damage (> 50%), a pronounced decrease in the number of CD4 + and CD8 + cells [27], and also speaks of a significant association with the need for mechanical ventilation [14-16], the risk of thromboembolic complications and increased mortality [22, 23].

In the above study, it was shown that an increase in IL-6 content occurs more often in severe COVID-19 [9]. As noted earlier, an increase in the level of IL-10 in the blood serum is also characteristic of the “cytokine storm” [28,29]. However, among the examined individuals, we did not observe pathological changes in IL-10. Perhaps this is due to blood sampling after antibiotic therapy, a small sample size, and the small number of patients with severe forms of COVID-19. Outside of the inflammatory reaction and the immune response, cytokines in the blood are contained in extremely small amounts [20]. Enhanced synthesis of cytokines begins in response to the penetration of microorganisms into the body or tissue damage [21]. In addition to IL-6, in patients with COVID-19, an increase in the content of CRP is recorded as a “surrogate biomarker” reflecting the hyperproduction of proinflammatory cytokines [9].

Analyzing changes in cytokines in persons with COVID-19, we revealed a correlation between CRP and TNF-α (see table 2). Extremely high levels of CRP indicate the presence of a bacterial infection (100 mg / l and higher), and further dynamics of the content of this indicator makes it possible to judge the effectiveness of therapy. Our study showed that the maximum CRP level in the examined patients was 239.9000 mg / L.

T.Yu. Salina and T.N. Morozov reported that TNF-α is a polypeptide mediator and cytokine of the immune response, which plays an important role in the pathogenesis of inflammation and maintenance of homeostasis [42]. It was found that TNF-α takes an active part in the development of the immune response as a cofactor of growth cytokines, causing the proliferation and cooperation of T- and B-lymphocytes, activating macrophages. TNF-α induces the release of IL-1, has a regulatory effect on the activity of fibroblasts, and enhances the migration of immunocompetent cells to the inflammation focus [43]. Under natural conditions, TNF-α is produced by polymorphonuclear leukocytes, mast cells and basophils, fibroblasts, vascular endothelial cells and is the most important pleiotropic cytokine that regulates the functioning and maintenance of the immune system [24].

However, the mechanisms of development of COVID-19 with the participation of TNF-α are very diverse and require further study. The foregoing suggests that the content of TNF-α may reflect the activity of the immunological process in COVID-19, and its excessive production in combination with an increase in the level of CRP negatively affects the overall prognosis. Currently, the problem of COVID-19 is being actively and comprehensively studied, and the results of clinical and epidemiological, socio-economic research show the need for a multidisciplinary approach, taking into account the climatic, geographical and ethnic characteristics of the region.Limitations of the study. The study is limited to the simultaneous determination of the content of cytokines in the blood serum when it is impossible to take into account all factors affecting the severity and outcome of COVID-19, the absence of PCR analysis data for a new coronavirus infection.

In fairness, it should be noted that in real clinical practice, patients during a pandemic independently take various drugs (anti-inflammatory, antibacterial and others) in the hope of recovery. However, taking these drugs not only changes the clinical picture of the disease, but also affects the final results of a biochemical blood test. This fact was also not excluded in our study.

Conclusion. Thus, our study shows that patients with COVID-19 have an increase in the level of interleukin-6 and CRP in the blood serum. The content of TNF-α is closely correlated with the level of CRP. In this connection, in patients with COVID-19, it is necessary to monitor the content of TNF-α and CRP as predictors of the adverse consequences of the new coronavirus infection. Despite the knowledge gained in the field of studying the functions of cytokines in COVID-19, intensive interdisciplinary studies of this disease in the human body are highly relevant. Through the efforts of researchers and scientists, important directions for future fundamental research in COVID-19 have been identified, which include a deeper understanding of the molecular mechanisms of cytokine-induced signaling pathways in the cell.

Conclusion

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Entered 09.02.2021