PROGNOSTIC VALUE OF THE SPECTRUM OF CYTOKINES AND THEIR CHANGES IN VIRAL INFECTION COVID-19COMPLICATED BY PNEUMONIA

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Abstract: The peculiarity of the immune status in viral infection is manifested in a long-term selective IgA deficiency, including in combination with a high level of IgE, a decrease in phagocytosis, and an increase in concentration. Viral infection is characterized by an increase in the level of B-lymphocytes and overproduction of IgA, IgG and IgE, as well as IL-4. Studies confirm the existence of a relationship between the concentrations of IFN-γ and IL-1ß, and this relationship is direct and decreases depending on the severity of the course of viral pneumonia, which indicates violations of immunoregulatory mechanisms.The level of cytokines - IL 1ß, TNF-α and IL-4 is sharply increased in patients with severe Covid-19 complicated by pneumonia. The results obtained indicate a violation of metabolic processes and pronounced immunological changes that contribute to the development of complications of this disease.The most common development was acute respiratory failure (ARF), disseminated intravascular coagulation syndrome (DIC), infectious toxic shock (ITS), pleurisy and abscess formation. In a number of patients, damage to the lung tissue and complications against this background developed rapidly, despite intensive therapy in the intensive care unit.

Key words: Viral infection, pneumonia, spectrum of cytokines, interleukins.

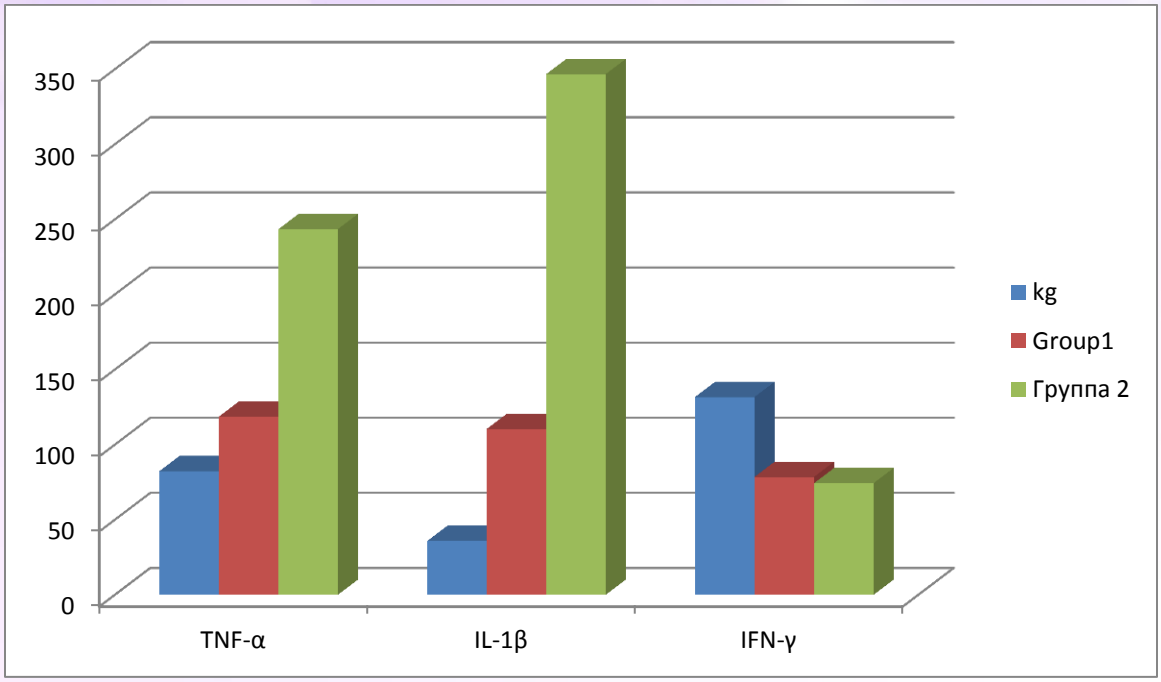
Relevance: The problem of combating coronavirus infections is currently the most urgent not only in medicine, but also in the whole of humanity [7,13]. The role of cytokines is of great importance for a more detailed understanding of the mechanisms of immunopathological changes in the body [3,9]. The study of the role of cytokines in COVID-19 is one of the fundamental points for understanding the pathogenesis of viral infections in general and, in particular, the nature of the pathogenicity of coronavirus [1,16]. For clinical practice, the study of the role of the cytokine status can hardly be overestimated, since it reflects an individual, primary response to a viral agent, makes it possible to assess the nature of the process and predict the outcome of the disease in many viral infections, including coronavirus, as well as to objectively assess the effectiveness of therapy [5 ,fourteen]. The high incidence of lung damage in COVID-19 is explained by the tropism of the virus to epithelial cells, including the endothelium, which determines the characteristic clinical picture of COVID-19 and pneumonia against this background [6,19]. Increased capillary permeability of the lungs, as well as excessive induction of cytokines, endothelial damage are the main mechanisms for the development of ARDS [2,11]. The data of various authors indicate that an important pathogenetic link in the unfavorable course and prognosis in pneumonia is the early hyperactivation of cytokine production (pro-inflammatory TNFα, and anti-inflammatory IL-10) against the background of depression of

markers of cell-mediated immune defense (IL-2, IFNγ) [10,12] ... Also, one of the promising areas of study of the systemic inflammatory response is the determination in the blood of soluble forms of adhesion molecules that characterize the processes of activation of endothelial cells and promote the interaction of leukocytes and endothelial cells [4,8]. However, the features of the cytokine profile and the level of intercellular adhesion molecules in pneumonia background of Covid-19.

In this regard, the aim of our study was to study the role of cytokines in the pathogenesis of coronavirus infection

Material and methods: The study is based on clinical and laboratory examination of 75 patients with coronavirus infection complicated by pneumonia, who were admitted to the infectious diseases hospital of the Samarkand region from July to September 2020. All examined patients were divided according to the severity of the course of the disease into 2 groups. Group 1 included 22 patients with severe disease, group 2 - 53 patients with moderate disease. In addition to general clinical, laboratory and instrumental research methods, all patients underwent MSCT research, which confirmed the presence of pneumonia, i.e. symptoms of frosted glass. At the same time, saturation in group 1 was on average 88 ± 1.4%. And in the second group 94 ± 1.8%. In addition, the percentage of lung damage in group 1 was on average 64.2 ± 2.8%, which corresponds to CT-III-stage, and in group 2, 38.8 ± 3.4% corresponds to CT-II-stage. As a control group, peripheral blood of 20 healthy individuals was examined. All immunopathological parameters of the blood of patients, including interferon α and γ: the level of antiviral (α-IFN) and proinflammatory (γ-IFN) interferons in the serum of peripheral blood were studied by the enzyme immunoassay using the "Vector-Best" test systems (Novosibirsk, Russia) To establish the role of the cytokine link in the pathogenesis of coronavirus infection, we determined the level of interferons IFN-α and IFN-γ, the level of IL-4 and the level of proinflammatory cytokines IL-1ß, IL-6. Our data demonstrate a significant dependence of the concentration of the level of proinflammatory cytokines in blood serum on forms of the disease. Particularly pronounced disorders were noted in patients with a severe form of CT-III-st disease, the lesion is mild. The detection of changes significantly differed from the values obtained in the group of patients with moderate severity of pneumonia. In the control group, immunopathological parameters remained normal.

Fig. one.



Our data demonstrate a significant dependence of the concentration of the level of proinflammatory cytokines in the blood serum on the severity of the course of coronavirus infection. Particularly pronounced disorders were noted in patients with a severe course of coronavirus infection. The revealed changes significantly differed from the values obtained in the group of patients with moderate severity. So, if in a severe course the level of serum TNF-α in the examined patients was significantly exceeded (243.5 ± 23.9 pg / ml compared with the data of the control group - 82.4 ± 7.0 pg / ml, P <0.001), then with an average severity of the course, only a moderate increase in this cytokine was noted (118.7 ± 9.3 pg / ml, compared with the control P <0.05). When analyzing the results of the study of the level of IL-1ß in the blood serum, it was revealed that in patients with severe course there is an almost tenfold increase in its level compared to the control - 346.7 ± 36.6 pg / ml, versus 35.8 ± 3.9 pg / ml (P <0.001). In patients with moderate severity, an increase in the level of IL-1ß was observed by more than 3 times compared with the control group of individuals - 110.4 ± 8.3 pg / ml (P <0.001). All this found its confirmation in the clinical picture of the course of the disease, indicators of blood oxygenation by MSCT studies, as well as other clinical laboratory and instrumental indicators. IFN-γ is known to be produced by activated Th1 cells and NK cells. In our studies, a lower level of IFN-γ was noted in comparison with the control group. Moreover, this decrease is observed: in severe form 74.3 ± 4.9 pg / ml (P <0.001), with an average severity of 78.5 ± 7.3 pg / ml (P <0.001). The level of IFN-γ, while in the control group of individuals was on average 131.7 ± 11.0 pg / ml When analyzing the level of a number of inflammatory cytokines in the blood serum of patients with coronavirus infection, compared with the control, we noted a significant significant increase in the level of TNF-α and IL-1ß in severe disease and a moderate increase in serum levels with moderate severity. The serum level of IFN-γ in coronavirus infection was significantly lower than

in the control group and did not depend on its form. Of particular interest was the study of the IgE level in the blood and the IL-4 concentration in various biological fluids as markers of inflammatory activity in patients with coronavirus infection

Results of the study: The levels of IL-4 in the blood serum and smear, as well as the level of total IgE in the serum of all examined patients are presented in Table 1. As can be seen from the table, increased levels of total IgE are detected in the peripheral blood of patients. The highest level is observed in the group of patients with a severe form of the disease (362.0 ± 19.5 IU / l), which significantly exceeds the value of this indicator in patients with moderate severity (308.0 ± 13.5 IU / l) and indicators of the control group (103.0 ± 6.12 IU / l) (P <0.001). Thus, in severe cases, there is a higher IgE content in the blood serum compared to patients with moderate severity..

Indicators	Control group (n = 40)	Group 1 (n = 22)	2 group (n = 53)
IL-4 (smear), pg / ml	0	310,0±13,5***	76,0±3,6***^^^
IL-4 blood serum, pg / ml	2,850±0,19	12,0±0,38***	15,1±0,63***^^^
IgE in blood serum, IU / L	103,0±6,12	308,0±13,5***	362,0±19,5***^

Note: * - differences relative to the data of the control group are significant (* -P <0.05, ** - P <0.01, *** -P <0.001); ^ - differences between the data of groups 1 and 2 are significant (^ - P <0.05, ^^ - P <0.001).

When studying the level of IL-4 in the blood serum of patients, a similar pattern was revealed: the highest level of IL-4 is characteristic of patients with severe course (15.1 ± 0.63 pg / ml), which significantly (P <0.001) exceeds this value. indicator in patients with moderate severity (12.0 ± 0.38 pg / ml). As mentioned above, in patients with a severe course of the disease, the cytokine values were higher than in patients with a moderate form of the disease. This has been observed for all types of cytokines. The difference is that mild forms of the disease usually did not cause an increase in serum IL-1α and TNFα values. Based on the foregoing, we found it interesting to conduct a correlation study between the concentrations of these cytokines depending on the severity of the course of coronavirus pneumonia. Correlation analysis made it possible to establish the presence of a direct relationship between the serum levels of IFN-γ and IL-1ß. We found that the strength of this connection is inversely proportional to the course of the coronavirus infection. So, if in the control group the correlation coefficient was close to one (r = 0.95), then in groups 1 and 2, the values of the correlation coefficient were 0.59 and 0.37, respectively. Significant correlation coefficients between other pairs of indicators of cytokine content were not obtained in either group. The results of the study confirm the presence of a relationship between the concentrations of IFN-γ and IL-1ß, and this dependence is direct and decreases depending on the severity of the course of the disease, which indicates violations of the immunoregulatory mechanisms, and a reduced concentration of serum INF-γ indicates a violation of IL-1ß mediated by the production of IFN -γTh-1 cells.

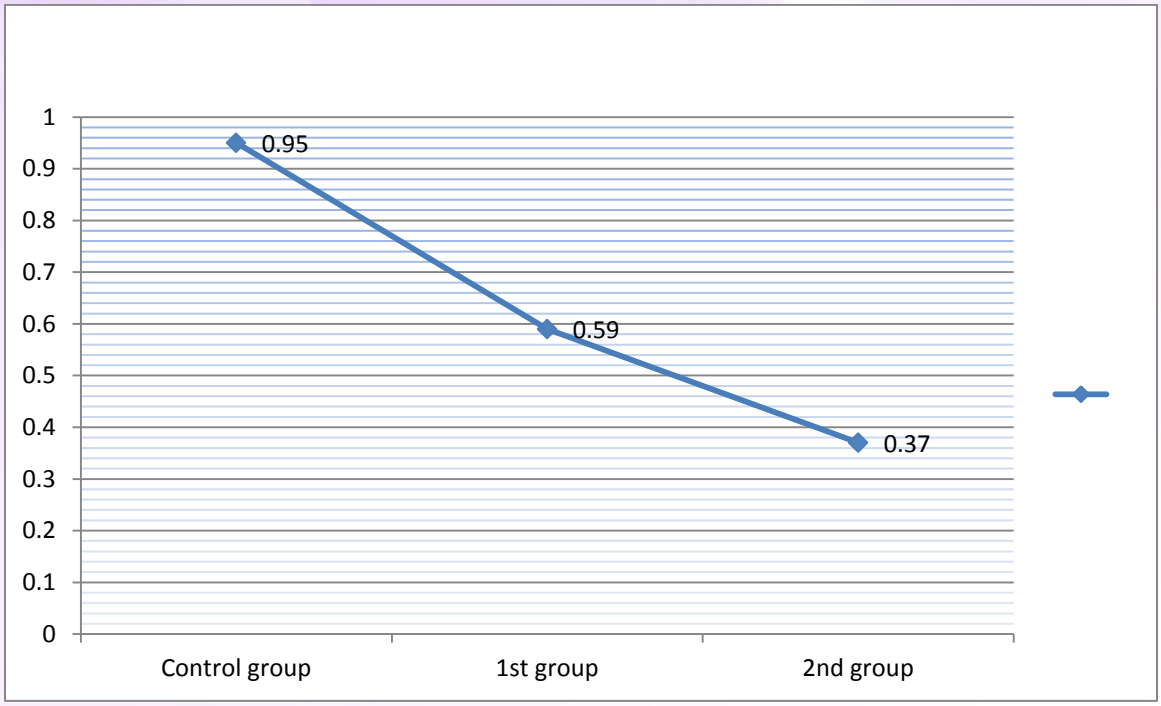


Fig. 2. Values of the correlation coefficient (r) between the serum levels of IFN-γ and IL-1β in different forms of coronavirus infection.

At the same time, it is possible that the activation of the macrophage link of immunity, which occurs with COVID-19, may increase the production of substances by macrophages that inhibit the synthesis of IFN-γ. Thus, we have found that in most patients with coronavirus infection complicated by pneumonia, a reduced content of T cells is observed. A low content of CD3 + cells indicates a reduction in the reserves of the pool of circulating T-lymphocytes and, therefore, a possible risk of their failure if an intense immune response is required. A decrease in the content of functionally active T cells naturally affects the content of specialized phenotypes that perform helper and suppressor functions. There is no doubt that a decrease or increase in their number can have a negative impact and, in all likelihood, is one of the pathogenetic factors of the inflammatory process. As you know, NK cells play an important role in anti-infectious protection, and their changes in one direction or the other, apparently, are explained by several reasons: partial immunodeficiency, insufficient production of non-toxic antibodies that block the activity of immunocompetent cells. As can be seen from the results, the study reveals a relationship between the concentrations of IFN-γ and IL-1β, and this relationship is direct and decreases depending on the severity of the course of coronavirus pneumonia.

Conclusions: Our results show a significant dependence of the concentration of the level of proinflammatory cytokines in the blood serum on the form of coronavirus infection.
The results of the study confirm the existence of a relationship between the concentrations of IFN-γ and IL-1β, and this relationship is direct and decreases depending on the severity of the course of coronavirus pneumonia, which indicates violations of the immunoregulatory mechanisms.

Thus, our results indicate a violation of metabolic processes and pronounced immunological changes, which contribute to the development of complications of this disease.

Literature

1. Jasur A. Rizaev, Ezozbek A. Rizaev, N.N. Akhmadaliev. October-December 2020, Indian Journal of Forensic Medicine & Toxicology, Current View of the Problem: A New Approach to Covid-19 Treatment. Vol. 14, No. 4.RR 7341-7347.
2. Dadazhanov U.D, Mamatkulova F.Kh., Rozibaeva O.N. Issue 03, 2020, Europen JOURNAL OF Molecular Clinical Medicinc. Features Of Thrombophilia In Covid-19 ISSN-2515-8260 vol 07, 5119-5205
3. Ibatova Sh. M. Mamatkulova F. Kh. Ruzikulov N.Y. (2020). International Journal of Current Research and Review. The Clinical Picture of Acute Obstructive Bronchitis in Children and the Rationale for Immunomodulatory Therapy - P.152-155 ..
4. Muhammadieva L.A., Shavazi N.M., Rustamova G.R. (2020). Journal of Advanced Research in Dynamical and Control systems. Diagnosis and Treatment of Developmental Defects of the Bronchopulmonary System in Children. P. 157-161.
5. Khaydarova S., Shavazi N.M. 2020. Journal of Advanced Research in Dynamical and Control systems. Diagnostic aspects of formation of a protracted course of community-acquired pneumonia in children. R 147-156.
6. Muhamadieva L.A. Shavazi N.M. Rustamova G.R. 2020. Journal of Adv Research in dynamical and control systems. Diagnosis and Treatment of Developmental Defects of the Bronchopulmonary System in Children. Pg 157-161Vol 12, # 5.
7. Bobomuratov Turdikul Akramovich. SharipovaOliyaAskarovna. Mamatkulova Dilrabo Hamidovna. Bakhronov Sherzod Samiyevich. Research 12.01.2020. International Journal of Pharmaceutical. "Features of sexual development, state of the pituary gonad system and measures of secondary prevention in sick children with chronic bronchitis" p. 377-381.
8. Yarmukhamedova, Saodat Khabibovna, and Makhsuda Salohiddinovna Bekmuradova. "Features of diastolic dysfunction of the right ventricle in patients with arterial hypertension and heart failure." National Association of Scientists 1 (2016): 18-18.
9. Turdumatov, J., Mardieva, G. (2020). European Journal of Molecular and Clinical Medicine7 (2). Clinical and x-ray peculiarities of the course of chronic obstructive pulmonary disease in combination with diabetes mellitus. 3009-3028
10. Kholzhigitova M.B. 2020. Journal of critical reviews issn- 2394-5125 "The state of changes in the immune system in patients with chronic obstructive bronchitis and the effect of immunotherapy on the dynamics. vol 7, Issue 14, pp. 3277-3279.
11. Aralov N. R., Mahmatmuradova N, Ibadova O, Safarova M. 2020. Journal of critical reviews ISSN-2394-5125 "Causes and differential diagnostic criteria for non-specific interstitial pneumonia" Vol 7, Issue 09, pp. 2484-2488.
12. Ibatova Sh. M.F. Kh. Mamatkulova. N. B. Abdukadirova. Yu. A. Rakhmonov. M. M. Kodirova. 2020. International Journal of Current Research and Review. Risk Factors for Development of Broncho-Ostructive Syndrome in Children. Vol 12. Issue 23 December – P. 3-6.
13. Arinenko R.Yu., Anikin V.B., Golovkin V.I. -2007. TerraMedica. -№4 The system of interferons: the first line of defense of the body. from. 11-14.

14. Bekmuradova, Makhsuda Salhiddinovna, Khudoyor Khudoyberdievich Gafforov, and Suvon Totliboevich Yarmatov. "The value of brain natriuretic peptide determination in the diagnosis of chronic heart failure." Achievements in science and education 4 (58) (2020).
15. M. E. Kohl S. Higl -1997. Pediatr. Scott Level inteleukin-12 production, but diminished interferon-gamma production, by cord blood mononuclear cell. Res.–V. 4194 –Pt. 1 - P. 547-553.
16. O. P. Zinkevich, V. M. Bondarenko. - 1999. ZhMikrobiolImmunobiolThe characteristics of the humoral antibacterial immunity of patients with respiratory organ diseases / / VluDelian et al. - Vol. 2. –P. 65-68.
17. Gelfand B.R., Kassil V.L. 2007 .. Acute respiratory distress syndrome. - M .: Litter, - 232s
18. Gusev E.Yu., Yurchenko L.N., Chereshnev V.A., Zotova N.V. - 2008. Methodology for studying systemic inflammation // Cytokines and inflammation. - No. 1. - S. 15-23.
19. Ketlinsky S.A., Simbirtsev A.S. 2008. Cytokines. - SPB: Folio, - 552s.
20. Markelova E.V., Kostyushko A.V., Krasnikov V.E. - 2008. Pacific Medical Journal. - Number 3. Pathogenetic role of disorders in the cytokine system in infectious and inflammatory. - S. 24-29.
21. Bermejo-Martin J.F. - 2009. et al. Th l and Th 17 hypercytocinemia as early host response signature in severe pandemic influenza // Crit. Care. - Vol. 13. - P. R201-R201.
22. To K.K. - 2010. Clip. Infect. Dis. et al. Dealayed clearance of viral load and marked cytokine activation in severe cases of pandemic H1N1 2009 influenza virus influenza. - Vol. 50. - P. 850-859.