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PROGNOSTIC VALUE OF CELLULAR CHANGES IN THE BLOOD TEST DURING COVID-19 INFECTION

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Changes in laboratory tests help in risk stratification and early adjustment of therapy in any pathology, COVID-19 infection is no exception. Therefore, work on the systematization of hematological changes in COVID-19 infection, which have clinical prognostic value, deserves attention. Established that important biomarkers of the severity of COVID-19 infection are lymphopenia, primarily due to CD8 T-lymphocytes, neutrophilia, thrombocytopenia, decreased monocyte count, leukocytosis or leukopenia, and an increase in eosinophils. The progression of inflammation with a high risk of death in COVID-19 infection is associated with the following changes in a blood test: an increased ratio of neutrophils/lymphocytes, neutrophils/platelets; decrease in the ratio of the number of lymphocytes/leukocytes, progression of lymphopenia, neutrophilia, decrease in eosinophils, progression of thrombocytopenia, anemia, increased distribution of erythrocytes by volume.

Key words: *COVID-19, blood tests, hematopoiesis, cellular changes, prognosis.*

Connection of the publication with planned research works.

The work is a fragment of the research work of the department «Clinical, functional and morphological changes in the cardiovascular system in patients with acute and chronic coronary heart disease, arterial hypertension and heart failure in combination with accompany pathology», state registration number 0120U102731.

Introduction.

Changes in laboratory tests help in risk stratification and early adjustment of therapy in any pathology, COVID-19 infection is no exception. There are numerous reports in the literature about changes in the blood test in this disease. Characteristic is their diversity and ambiguity. The latter depend on the pathogenesis prevailing in the patient from the different mechanisms of the cellular response in the development of infection. In particular: the direct effect of the virus on hematopoiesis, the immune response to the pathogen, the severity of destructive processes in tissues during the development of the inflammatory process. Therefore, work on the systematization of hematological changes in COVID-19 infection, which have clinical prognostic value, deserves attention. There are few publications on this problem [1], which requires further systematization of the database.

The aim of the study.

To review the database on changes in peripheral blood parameters and their prognostic value in COVID-19 infection.

Object and research methods.

We used English-language articles in PubMed databases over the past 10 years with keywords - peripheral blood, cellular composition, coronavirus infection, prognostic value.

Main part.

The database presents the most frequent reports of prognostic value in COVID-19 lymphopenia and neutrophilia. In the case of a severe course of the disease, lymphopenia is more pronounced, compared with a milder course [2-6].

The researchers analyzed subpopulations of lymphocytes. According to some authors, there was no significant difference in total T- and CD4 T-lymphocytes between groups of patients with severe and mild infection. However, in patients in the intensive care unit (ICU), the number of CD8 T cells (suppressor/cytotoxic)

was significantly reduced. There was a strong correlation between peak inflammation scores and a decrease in the percentage of CD8 T-lymphocytes. This effect was not observed with CD4 T lymphocytes. It was concluded that lymphopenia, mainly due to CD8 T-lymphocytes, together with overweight are predictors of poor prognosis in patients with COVID-19 [6]. In patients in the group of the dead, compared with those discharged from the hospital, a decrease in the number of total T-, CD4+, CD8+ T-lymphocytes, as well as NK cells was observed after 2 weeks during treatment [7].

Studies by Pozdnyakova and co-authors of blood test parameters in 90 patients with COVID-19 in the ICU revealed that all had pronounced numerical and morphological changes in leukocytes. Differences were observed between patients with mild and severe conditions. More severe disease was associated with significant lymphopenia and neutrophilia, with progression in critically ill patients [8].

Similar results have been obtained by other authors. Huang et al. [9] and Wang et al. [10] found an association between lymphopenia and the need for ICU treatment. Wu et al. found an association between lymphopenia and the development of ARDS in COVID-19 patients [11]. The Zhou F. et al. study, including 191 cases, showed that lymphopenia was more often observed in the deceased (76 %) compared with the survivors (26%) [12]. It persisted in non-survivors for up to 25 days after the onset of the disease. In survivors, the mean lymphocyte count increased from 1.08 x 10^9 /l to 1.43 x 10^9 /l. The authors conclude that COVID-19 lymphopenia is the most important biomarker of infection severity [13].

In severe patients with COVID-19, an increase in the number of neutrophils is also observed [14]. Fan B.E. et al. found that their lymphopenia and neutrophilia were associated with high LDH levels and advanced age [15].

An increase in the neutrophil-to-lymphocyte ratio (NLR) is considered as a clinical biomarker for the severity of inflammation in COVID-19. In addition, there are reports of increased neutrophil to CD4+ lymphocyte ratio (NCD4LR) and neutrophil to albumin ratio (NAR) [16]. An increase in NLR and NCD4LR values is associated with a longer time of negative conversion of the virus and its clearance, and a worsening of the immune response. Marwah et al. suggested that NLRs greater than 7.4 could be used by clinicians as indicators of infection severity and high risk of mortality in patients with COVID-19 [17].

There is a report that higher mortality is associated with higher NLR and lower absolute monocyte count. The value of the ratio of lymphocytes to monocytes (LMR) is also considered a clinical marker indicating the severity of the disease [14]. The latter is natural as a manifestation of depression of the macrophage link of nonspecific immunity.

There is a report on the relationship between the severity of the patient's condition and the risk of an unfavorable outcome with a decrease in the ratio of the number of lymphocytes/leukocytes [18]. These data are consistent with the results of a study based on 33 cases of other authors. In particular, the report indicates that in non-surviving patients with COVID-19, along with severe lymphopenia, neutrophilia, leukocytosis was observed, compared with survivors [10]. Also known to be unfavorable of leukocytosis on the course of infection with an increase in the absolute number of neutrophils [11].

Leukocytosis was detected in 11.4% of patients with severe disease, compared with 4.8% of patients with mild or moderate disease [19]. Studies based on 452 cases of COVID-19 confirm the presence of leukocytosis in severe cases, a decrease in the percentage of monocytes, eosinophils and basophils [20]. At the same time, other researchers point to a more pronounced leukopenia in the severe course of the disease, compared with the milder one (61.1% versus 28.1%) [21], which is close to the data of other authors [3].

Thus, the results of various researchers on the prognostic value of the number of leukocytes are ambiguous. However, they have in common the relationship between their increase or decrease in severe COVID-19.

There are a number of mixed reports in the literature about reactive changes in eosinophil counts in severe COVID-19 infection. In particular, a study of blood tests involving 138 patients showed that 60.7% of them had eosinophilia on the first day of hospitalization. The absolute number of circulating eosinophils positively correlated with the number of lymphocytes [22]. Fraisse M. et al. described prolonged late-onset eosinophilia presenting in the intensive care unit in one-third of critically ill COVID-19 patients [23].

In contrast to these results, Du Y. et al. report a decrease in the number of eosinophils during hospitalization in 81% of patients with a fatal outcome [24]. Sun DW et al. report a significant decrease in the number of eosinophils and basophils, along with lymphopenia and neutrophilia, in patients with severe infection compared with non-severe. These blood counts improved in the recovery phase but persisted or worsened in the acute phase of the disease [7].

Cavalcante-Silva LHA et al. also report as an independent risk factor for critically severe eosinopenia and lymphopenia at one month with worse outcome of COVID-19 therapy. In cases of successful treatment, eosinophil counts, which were low on admission, returned to normal before discharge [25].

The above results indicate that, along with lymphopenia and neutrophilia, the number of eosinophils is also associated with the severity of the disease. Both an increase and a decrease in the latter significantly correlate with progression in patients with COVID-19.

The role of platelet factors in the process of inflammation during infection with COVID-19 is known. Therefore, the reports of researchers concerning significant changes in the state of the platelet link of hematopoiesis deserve attention. Thrombocytopenia is largely associated with an increased risk of severe disease, need for ICU, and mortality. In the case of a severe course of the disease, thrombocytopenia is twice as pronounced as compared to a mild course [3, 21]. The number of platelets correlated with an increased risk of death [26].

At the same time, according to Qu R. et al. with a more severe course of the disease, peaks of an increase in the number of platelets were observed [27]. In patients with a fatal outcome, the median minimum hemoglobin level and platelet count were below normal (80×10^9/l) [26].

A study by a number of authors has shown that an increased ratio of neutrophils/lymphocytes and neutrophils/platelets may indicate myocardial damage and

increased mortality. When assessing the severity of COVID-19, the platelet/lymphocyte ratio (PLR) at the peak of thrombocytosis is predictive [27].

It is obvious to suggest reactive changes in the erythropoiesis system to the hypoxia factor in COVID-19 infection. There are mixed reports in the literature on the effect of erythropoiesis parameters on the course of the disease.

According to some authors, anemia in COVID-19 is not a serious problem, only 1.6% of patients needed blood transfusion. According to other researchers, anemia is an independent predictor of poor outcome in COVID-19, as it is in some other respiratory diseases. The mean hemoglobin level in severe cases was lower than in non-severe cases [28]. In patients with a fatal outcome, the median minimum hemoglobin level was below normal (105 g/l) [26].

Foy BH et al found that in patients with COVID-19, an increased RBC distribution by volume (RDW > 14.5%) during hospitalization increases the risk of mortality. They were 6 times more likely to die within 48 hours than those with normal RDW. An increase in RDW > 0.5% increases mortality from 6% to 24% [29]. Other researchers also point to RDW as a marker of complications in COVID-19 [28].

There is a report about the main reasons for the decrease in hemoglobin during this viral infection: SARS-CoV-2 damages the membranes of erythrocytes due to the presence of angiotensin and proteins that interact with the angiotensin-converting enzyme (ACE2) of the virus on the surface of erythrocytes; direct damage by the heme virus; dysregulation of iron metabolism; blood loss; autoimmune hemolytic anemia during a cytokine storm [30].

Conclusions.

1. Important biomarkers of the severity of COVID-19 infection are lymphopenia, primarily due to CD8 T-lymphocytes, neutrophilia, thrombocytopenia, decreased monocyte count, leukocytosis or leukopenia, and an increase in eosinophils.

2. The progression of inflammation with a high risk of death in COVID-19 infection is associated with the following changes in a blood test: an increased ratio of neutrophils/lymphocytes, neutrophils/platelets; decrease in the ratio of the number of lymphocytes/leukocytes, progression of lymphopenia, neutrophilia, decrease in eosinophils, progression of thrombocytopenia, anemia, increased distribution of erythrocytes by volume.

Prospects for further research.

An analysis of literature data on changes in the blood in patients with COVID-19 and their significance for short-term and long-term prognosis, which are under study and have prospects for application in this infection, will be our further research.

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ПРОГНОСТИЧНЕ ЗНАЧЕННЯ КЛІТИННИХ ЗМІН В АНАЛІЗІ КРОВІ ПРИ ІНФЕКЦІЇ COVID-19

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Резюме. Метою роботи був огляд літератури за останні 10 років, що містить дані про зміни показників периферичної крові та їх прогностичне значення при інфекції COVID-19. Охарактеризовано різноманітність і неоднозначність змін клітинн ого складу гемограми. Останнє залежить від переважаючого патогенезу розвитку інфекції у хворого, пов'язаного з реактивністю кровотворення, імунної системи. Зокрема, безпосередній вплив вірусу на кровотворення, імунну відповідь на збудника, вираженість деструктивних процесів у тканинах при розвитку запального процесу.

Найбільш характерними змінами в аналізі периферичної крові при COVID-19 є лімфопенія та нейтрофільоз, які мають прогностичне значення. Існує стійкий кореляційний зв'язок між максимальними значеннями показників запалення та зниженням процентного вмісту Т-лімфоцитів CD8. У пацієнтів з несприятливим результатом лікування протягом до трьох тижнів спостерігається зниження кількості загальних Т-, CD4+, CD8+ Т-лімфоцитів, а також NK-клітин.

Біомаркерами тяжкості інфекції COVID-19 є лімфопенія, збільшення співвідношення нейтрофілів до лімфоцитів, збільшення співвідношення лімфоцитів до моноцитів і зниження співвідношення кількості лімфоцитів/лейкоцитів. Дані літератури щодо прогностичного значення кількості лейкоцитів неоднозначні. Однак зв'язок між збільшенням або зниженням важкої форми COVID-19 є загальним.

Спостерігається зниження кількості еозинофілів і базофілів разом із лімфопенією та нейтрофільозом у пацієнтів із поганим результатом.

При тяжкому перебігу захворювання тромбоцитопенія вдвічі більша, ніж при більш легкому перебігу. Кількість тромбоцитів корелює з підвищеним ризиком смерті.

Дослідження, проведене декількома авторами, показало, що співвідношення нейтрофілів/лімфоцитів і нейтрофілів/тромбоцитів може вказувати на пошкодження міокарда та підвищену смертність. При оцінці тяжкості COVID-19 прогностичне значення має співвідношення тромбоцити/лімфоцити (PLR) на піку тромбоцитозу.

Пацієнти, які померли від COVID-19, мали медіану мінімального рівня гемоглобіну нижче норми. Підвищений розподіл еритроцитів за об'ємом (RDW > 14,5%) під час госпіталізації підвищує ризик смертності.

Ключові слова: COVID-19, дослідження крові, гемопоез, клітинні зміни, прогноз.

PROGNOSTIC VALUE OF CELLULAR CHANGES IN THE BLOOD TEST DURING COVID-19 INFECTION

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Abstract. The aim of the work was to review the literature over the past 10 years containing data on changes in peripheral blood parameters and their prognostic value in COVID-19 infection. The diversity and ambiguity of changes in the cellular composition of the hemogram is charactered. The last depends on the pathogenesis prevailing in the development of the patient's infection, associated with the reactivity of hematopoiesis, the immune system. Particularly, the direct effect of the virus on hematopoiesis, the immune response to the pathogen, the severity of destructive processes in tissues during the development of the inflammatory process.

The most charactered changes in the analysis of peripheral blood in COVID-19 are lymphopenia and neutrophilia, which have prognostic value. There is a stable correlation between the maximum values of inflammation indicators and a decrease in the percentage of CD8 T-lymphocytes. Patients with an unfavorable outcome during treatment for up to three weeks have a decrease in the number of total T-, CD4+, CD8+ T-lymphocytes, as well as NK cells.

Biomarkers for the severity of COVID-19 infection include lymphopenia, an increase in the ratio of neutrophils to lymphocytes, an increase in the ratio of lymphocytes to monocytes, and a decrease in the ratio of the number of lymphocytes / leukocytes. The literature data on the prognostic value of the number of leukocytes are ambiguous. However, the association between increase or decrease in severe COVID-19 is in common.

There is a decrease in the number of eosinophils and basophils, along with lymphopenia and neutrophilia for patients who have an poor outcome.

In case of a severe course of the disease, thrombocytopenia is twice as pronounced as in a milder course. Platelets count correlated with an increased risk of death.

A study by several authors has shown that ratio of neutrophil/lymphocyte and neutrophil/platelet ratios may indicate myocardial injury and increased mortality. While assessing the severity of COVID-19, the platelet/lymphocyte ratio (PLR) at the peak of thrombocytosis has a predictive value.

That patients who have died from COVID-19 had the median of the minimum level of hemoglobin below normal. An increased RBC distribution by volume (RDW > 14.5%) during hospitalization increases the risk of mortality.

Key words: COVID-19, blood tests, hematopoiesis, cellular changes, prognosis.

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THE ROLE OF THE GLYMPHATIC SYSTEM IN MAINTAINING CEREBRAL HOMEOSTASIS IN NORMAL AND NEUROPATHOLOGICAL CONDITIONS

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This review presents an analysis and synthesis of the world literature, forming an up-to-date vision of the functional system of utilisation of end metabolites from the central nervous system, discussing impaired brain clearance in some neurodegenerative nosologies, as well as in strokes and traumatic brain injury. The central nervous system, lacking a classically conventional lymphatic system, requires alternative systems to clear the brain of potentially toxic cellular metabolic products. Over the past decade, world scientific sources have highlighted a new system of views, or the concept of the so-called glymphatic system, which makes it possible to drain the brain from extracellular harmful substances dissolved in the interstitium. Water channels such as aquaporin-4 (AQP4) are an important system component associated with neuropathologies such as Alzheimer's. The clearance of amyloid β (Aβ) and tau (tau) proteins associated with Alzheimer's disease, for example, is reduced due to the impaired function of the glymphatic system in the absence of AQP. The detected changes in AQP4 expression associated with certain pathologies make it possible to predict that this water channel could be a potentially interesting pharmacological target. Recent studies in this context have also shown that biomarkers of traumatic brain injury are eliminated from the brain through the glymphatic system. The degree of suppression of glymphatic function under these conditions may affect the likely prognosis after traumatic brain injury. The obtained results predict the clinical value of pharmacological manipulations of the glymphatic system after acute traumatic brain injury. It has also been shown that with ageing, the processes of glymphatic drainage in the CNS decrease, which can contribute to the accumulation of misfolded and hyperphosphorylated proteins and thus make the brain susceptible to the development of neurodegenerative pathology. According to the experimental evidence presented in modern scientific sources, the concept of "acute or chronic glymphatic insufficiency" should be distinguished, and the issue of finding criteria for their correct assessment should be updated. It is known that the number of vasteosomes or starchy bodies can be considered a marker of chronic glymphatic insufficiency. According to the researchers, this knowledge will facilitate the study of glymphatic insufficiency and allow us to understand which moderating variables will critically impact the functioning or failure of this system. Moreover, the fact that they are markers of chronic glymphatic insufficiency gives them promising clinical significance.

Key words: *glymphatic system, neurodegenerative diseases, aquaporins 4 (AQP-4).*