DOI: 10.20514/2226-6704-2023-13-5-335-343
УДК 616.98-036-07-08:578.834.11
EDN: ELNGUF

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# ИЗМЕНЕНИЕ ПОКАЗАТЕЛЕЙ СИСТЕМЫ КРОВИ ЧЕЛОВЕКА У БОЛЬНЫХ COVID-19

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# Changes in the Human Blood System in Patients with COVID-19

**Резюме**

Как известно, вирус SARS-CoV-2 влияет практически на все системы, органы и ткани человека, вызывая их поражение в большей или меньшей степени. Наблюдение за пациентами, перенесшими COVID-19, во всем мире указывает на значительные изменения, происходящие в системе кроветворения и морфологии клеток крови. Настоящий обзор посвящен анализу литературных данных о влиянии вируса SARS-CoV-2 на изменения показателей системы крови человека, что имеет важное значение в практической работе всех специалистов здравоохранения.

***Ключевые слова:*** *COVID-19, коронавирусная инфекция, анемия, тромбоцитопения, коагулопатия*

**Конфликт интересов**

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

**Источники финансирования**

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 19.04.2023 г.
Принята к публикации 10.08.2023 г.

**Для цитирования:** Сафуанова Г.Ш., Константинова А.С., Рябчикова Н.Р. и др. ИЗМЕНЕНИЕ ПОКАЗАТЕЛЕЙ СИСТЕМЫ КРОВИ ЧЕЛОВЕКА У БОЛЬНЫХ COVID-19. Архивъ внутренней медицины. 2023; 13(5): 335-343. DOI: 10.20514/2226-6704-2023-13-5-335-343. EDN: ELNGUF

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**Abstract**

As is known, the SARS-CoV-2 virus affects almost all human systems, organs and tissues, causing their damage to a greater or lesser extent. Follow-up of COVID-19 patients worldwide.indicates significant changes occurring in the hematopoiesis system and morphology of blood cells. This review is devoted to the analysis of literature data on the effect of the SARS-CoV-2 virus on changes in the indicators of the human blood system, which is important in the practical work of all healthcare professionals.

***Key words:*** *COVID-19, coronavirus infection, anemia, cytopenia, thrombocytopenia, coagulopathy*

**Conflict of interest**

The authors declare that this work, its subject, subject and content do not affect competing interests. Source of financing

**Sources of funding**

The authors claim that there is no funding for the study

Article received on 19.04.2023

Accepted for publication on 10.08.2023

**For citation:** Safuanova G.Sh., Konstantinova A.S., Ryabchikova N.R. et al. Changes in the Human Blood System in Patients with COVID-19. The Russian Archives of Internal Medicine. 2023; 13(5): 335-343. DOI: 10.20514/2226-6704-2023-13-5-335-343. EDN: ELNGUF

RT-DC – real-time deformability cytometry, PT – prothrombin time, APTT – activated partial thromboplastin time, WF – von Willebrand factor, CRP – C-reactive protein, IL-6 – interleukin6, ACE2 – angiotensin converting enzyme

In 2019, in Wuhan (China) the novel coronavirus infection broke out and spread globally as a pandemic. Currently, scientists all over the world continue to intensively study this disease in order to optimise preventive measures, since they realise its damaging effect over the body and organs, in attempt to develop new diagnostic and therapeutic methods. Most common conditions in the coronavirus infection patients were bilateral pneumonia (viral diffuse alveolar damage with microangiopathy); 3–4 % of patients had acute respiratory distress syndrome. Often patients had hypercoagulation syndrome with blood clots and thrombembolia, abnormal blood values, involvement of the central nervous system, myocardium, kidneys, liver, intestines, endocrine and immune systems, with possible sepsis and septic shock. In this review, we analysed literature sources on changes in blood values of patients who survived COVID-19. The discussed studies demonstrate that SARS-CoV-2 can be associated with significant changes in blood values as well as morphological changes in hematocytes, and it is essential for understanding of the problem, practical application and further studies.

## Anemia and COVID-19 (Hemoglobinopathies and Iron Dysmetabolism)

According to literature sources, scientists found out the ability of the SARS-CoV-2 virus to express ORF1ab, ORF10 and ORF3a proteins which initiate erythrocyte hemolysis and alveolar damage. Viral protein ORF8 and surface virus glycoprotein bind with porphyrin in Hb molecule, then other virus proteins (ORF1ab, ORF10 and ORF3a) push out iron ions from β1 heme in Hb chain, thus causing iron deficiency. A fee iron atom causes oxidative damage to organic molecules of cells, thus boosting inflammation in pulmonary parenchyma, damage and general hypoxia [1]. Eventually, these processes result in changes in pulmonary parenchyma seen on computer tomography (CT) scans as a ground-glass pattern.

It was demonstrated that SARS-CoV-2 can impair iron metabolism. The nature of this condition is that the structure of SARS-CoV-2 spike protein, which identifies host cell receptors and causes its penetration to cytoplasm, is similar to hepcidin [2]. Hepcidin is the main iron exchange regulator. It reacts with epithelial cell ferroportin and promotes iron penetration into a cell. Under normal conditions, hepcidin is regulated by the iron quantity in blood serum. At higher iron levels in the body, hepcidin destroys ferroportin and prevents excessive iron penetration into a cell and vice versa. Hepcidin-like impact of SARS-CoV-2 spike protein leads to pronounced impaired iron metabolism, higher ferritin and iron levels, its excessive accumulation in tissues and, eventually, cell destruction and death [3].

Thus, a combination of hemoglobinopathy and iron dysmetabolism can significantly affect the ability of erythrocytes to transport $O_2$ with hypoxia, initiating tissue modifications associated with hyperferritinaemia.

Hemolytic anemia in COVID-19 is also a result of oxidative damage from a free iron ion, which causes erythrocyte destruction. Figure 1 shows Hb being attacked by a non-structured viral protein described by Wenzhong L. et al (2020).

That is why, according to some authors, the most common erythroid abnormalities in COVID-19 were microcytosis (44 %), poikilocytosis (30 %) and reticulocytosis (6.3 %). Together with Jolly bodies, megaloblasts, normoblasts and sideroblasts, as well as reduced total erythrocyte count and Hb value, these changes represent hemolytic anemia and activation of bone marrow regeneration with incomplete erythropoiesis. This is also confirmed by an increase in the mean corpuscular volume in combination with reduced mean count and mean corpuscular hemoglobin concentration [4].

There are interesting information on increased risk of COVID-19 in subjects with blood type A as compared to blood groups without erythrocyte antigen. The lowest risk of the disease has been identified in subjects with blood type O(I). It is possible that SARS-CoV-2 interacts with erythrocytes in the presence of an additional CD147 receptor [5].

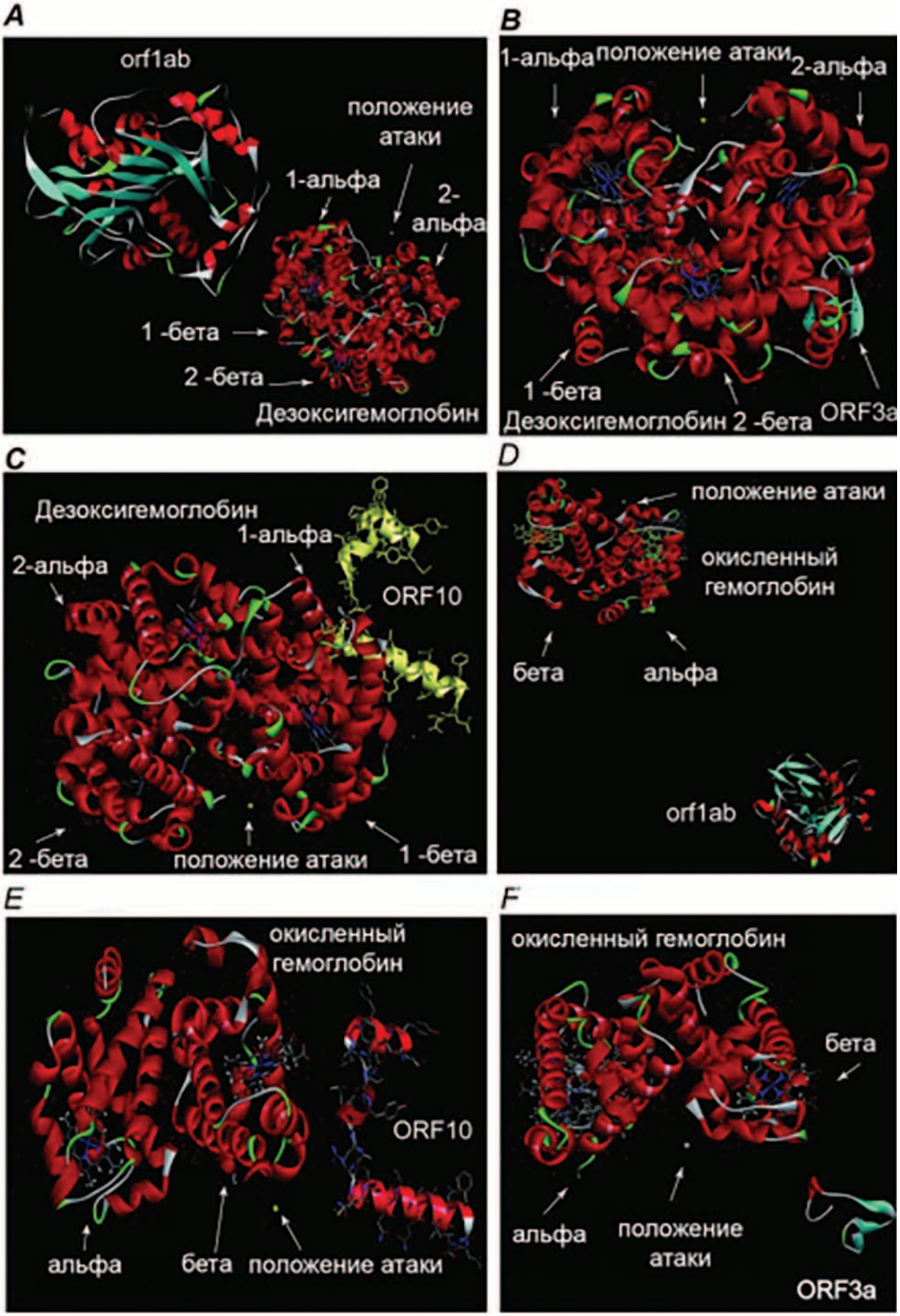


***Figure 1.*** *Viral nonstructural protein attacks hemoglobin*

**Note:** A — orf1ab attacks deoxyhemoglobin, B — ORF3a attacks deoxyhemoglobin, C — ORF10 attacks deoxyhemoglobin, D — orf1ab attacks oxidized hemoglobin, E — ORF10 attacks oxidized hemoglobin, F — ORF3a attacks oxidized hemoglobin

## White Cell Count and COVID-19

According to some authors, during the incubation period and at an early stage of the disease, when non-specific symptoms appear, white blood cell and lymphocyte count is normal or is slightly lower than the normal value. Very often, the advanced disease is associated with lymphopenia and neutrophilia. The total WBC count can be normal, higher or lower than the normal value, since this is a non-specific parameter. However, more severe COVID-19 or death cases are associated with leukocytosis and low lymphocyte count. Surviving patients have the lowest lymphocyte count approximately on day 7 after onset of symptoms of viral pneumonia, later patients recover in full. Impaired granulocytic myelopoiesis is manifested through absolute or relative neutrocytosis in combination with band cell count up to 20 % and myeloid-like leukemoid response when myelocytes and metamyelocytes appear in blood in 11 % of cases. These changes evidence a systemic inflammatory reaction and correlate with a high level of pro-inflammatory cytokines, which stimulate granulocytic myelopoiesis. Researchers point out that very often leukocytosis is a result of an increased neutrophil count with a slightly higher absolute monocytosis and normal basophil and neutrophil count. Lymphocite count was lower than normal in a majority of patients; mean lymphopenia (both absolute and relative) was moderate, but evidenced adaptive immunity suppression in COVID-19 [4, 6].

## Thrombocytopenia and Functional Activity of Platelets in COVID-19

Thrombocytopenia in COVID-19 patients was observed in 5–42 % (depending on disease severity); usually, thrombocytopenia was mild, platelet count was 100–150×$10^9$/L [7-10]. Moderate thrombocytopenia 50–100×$10^9$/L was diagnosed in 58–95 % of severe COVID-19 cases [8, 11, 12]. In patients with severe disease, reduction in platelet count was just 23–31×$10^9$/L more than in patients with mild disease [13, 14]. Satisfactory platelet count in patients with severe disease and systemic coagulation activation can be a result of the marked compensatory response of platelet production by bone marrow. Severe thrombocytopenia in COVID-19 patients is rare, usually in case of immune thrombocytopenic purpura [15].

Thrombocytopenia in COVID-19 can be associated with various causes [16]. Hypoproliferative thrombocytopenia is observed in late viral infections; fast thrombocytopenia progression in response to viral infections is usually mediated by increased platelet destruction. Platelets can be activated by viral antigen-antibody complex or in systemic inflammatory response. Activated platelets are more easily removed from blood flow by the reticulo-endothelial system, and their levels fall [17]. Viruses can also interact with megakaryocytes and inhibit platelet synthesis in bone marrow [18]. Table 1 presents possible mechanisms of COVID-19-associated thrombocytopenia.

Thrombocytopenia can be associated with increased platelet consumption due to endothelial damage and formation of platelet aggregates in lungs; also, it can result from bone marrow suppression and immune reactions [19]. It is assumed that platelets are consumed for pulmonary blood clots in order to prevent virus spread with blood [12].

COVID-19 patients with thrombocytopenia have higher mean platelet volume vs. COVID-19 patients with preserved platelet count [1]. In addition to congenital platelet disorders, increased mean platelet volume is typical of increased number of new circulating platelets and is a compensatory reaction of the body to thrombocytopenia [20]. An optimal range of mean platelet volume (MPV) in healthy adults with a normal platelet count is 9.0–12.4 μL [21]. The size of platelets demonstrates direct correlation with a number of surface receptors and ATP content in platelets. The number of ribosomes is higher in large platelets, showing a higher potential for protein synthesis. Larger platelets have higher haemostatic potential; they bind more fibrinogen and have a higher aggregation ability after thrombin stimulation than small platelets [22].

***Table 1.*** *Presumptive mechanisms of COVID-19-related thrombocytopenia*

| Causes of thrombocytopenia | Mechanisms of thrombocytopenia |
|---|---|
| Platelet activation and subsequent utilization by the reticular-endothelial system | – Activation due to increased thrombin production and consumption coagulopathy<br>– Direct activation during the interaction of the virus and platelets<br>– Associated with the formation of platelet and leukocyte aggregates<br>– FcR-mediated interaction of platelets with immune complexes |
| Platelet consumption due to increased endothelial damage | – In the endothelium of the pulmonary vessels<br>– Suppression of bone marrow/megakaryocytes |
| Sequestration in the spleen and liver | – Due to an inflammatory reaction<br>– Destruction due to the direct action of the virus<br>– Due to a decrease in the level of thrombopoietin<br>– Formation of platelet autoantibodies with subsequent destruction of platelets |
| Formation of platelet autoantibodies with subsequent destruction of platelets | |

A majority of authors are of the opinion that COVID-19 patients often present with an increase in production of large immature platelets, since megakaryocytes respond to increased platelet consumption and boost their production. Of note, COVID-19 is associated with an increase in the amount of immature platelets, even where the platelet count is normal. Since immature platelets are known to be more functional, it can be another mechanism of more intense blood clotting in COVID-19 [19, 21, 22]. Recently, some information appeared on finding expression of ACE2 molecules by platelets and direct stimulating effect of SARS-CoV-2 spike protein on platelets. Development of recombinant human ACE2 protein, which is an anti-spike monoclonal antibody, revealed its ability to inhibit platelet activation by this protein [23, 24]. Also, it was found out that platelets and monocytes demonstrated enhanced interaction and that patients with severe COVID-19 had associated expression of tissue factor by monocytes.

In addition to an increased number of immature platelets, COVID-19 patients can have an increased level of circulating activated platelets and a higher level of P-selectin observed on their surface membranes, in comparison to healthy subjects. Young platelets have a higher level of activation in response to antagonists (based on assessment of P-selectin, a platelet protein, which promotes WBC adhesion to vascular endothelium in inflammation, and low-concentration (2.5 μm) thrombin receptor activating peptide (TRAP)), therefore, they enter into platelet aggregation reaction more easily. Young and older platelets of healthy subjects have a low P-selectin level [21, 25].

## Blood-clotting Disorder in COVID-19

SARS-CoV-2 virus itself in unable to cause blood-clotting disorder. More likely, blood-clotting disorder is a result of a marked inflammatory reaction in COVID-19 and endothelial damage [26]. In patients with pneumonia and COVID-19, blood-clotting disorders are usually associated with a higher level of fibrinogen and D-dimer, very often with mild thrombocytopenia [11, 26]. Increased D-dimer levels are associated with higher mortality rates. Also, patients can present with abnormally short prothrombin time (PT) and activated partial thromboplastin time (APTT) [27]. Shorter APTT values are often associated with a higher factor VIII (FVIII) level [28], which is an acute phase protein, in response to a systemic inflammation. Patients with more severe damages can have a condition which is similar to DIC syndrome, with a relatively insignificant increase in PT and APTT, whereas fibrinogen can remain normal or can increase [26].

Unlike classic DIC syndrome caused by bacterial sepsis or a trauma, in COVID-19, an increase in PT and/or APTT is minimal [29], thrombocytopenia is moderate (platelet count is $100–150\times10^9$/L), hypofibrinogenemia and lab results confirming hyperfibrinolysis are rare [30].

There are three stages of COVID-19-associated blood-clotting disorder:

Stage 1 is characterised by a higher D-dimer level

Stage 2 is characterised by a higher D-dimer level together with moderately longer prothrombin time and APTT, as well as mild thrombocytopenia

Stage 3 is manifested by typical signs of DIC syndrome [31].

COVID-19 pneumonia is associated with endothelial cell destruction, tissue factor expression and activation of a blood-clotting cascade. Direct endothelial damage by the virus and endothelial activation by cytokines released during COVID-19 infection are possible blood-clotting mechanisms [32]. Activated and damaged endothelial cells release Weibel-Palade bodies containing von Willebrand factor with extremely high molecular weight (WF factor). Extremely large vWF molecules can bind platelets and result in microthrombosis. It was found out that WF factor contributes to the development of thrombocytopenia in viral infections. COVID-19 patients have significantly higher WF factor levels, with the mean value being 455–529 % [16, 28]. Increased values and functions of vWF, as well as increased blood-clotting ability of FVIII in COVID-19 patients is probably a result of a combined effect of release of a large amount of Weibel-Palade bodies from endothelial cells and acute phase reaction which boosts FVIII levels [32, 33]. Activity of protease, which cleaves von Willebrand factor in COVID-19 patients, is reduced and is mild or moderate [34-36]. Intravenous adenovirus injection (like in gene therapy studies) is associated with platelet activation and acute thrombocytopenia. However, such thrombocytopenia is not observed in mice who do not have WF factor and who have adenovirus injection [33].

It is known that some COVID-19 patients had a lower antitrombin level, whereas protein C level was normal in all examined patients. Antitrombin is known to be consumed during clotting, and described mild antitrombin deficiency correlated with it. Absence of significant protein C deficiency is unusual for standard DIC syndrome, and this is an additional evidence that COVID-19-associated blood-clotting disorder can differ from DIC syndrome [36].

## Morphological Changes in Blood Cells in COVID-19

It was found out that COVID-19 changes morphological properties of blood cells. They were identified using the method of real-time deformability cytometry (RT-DC), which allows conducting an express cell analysis based on images with the rate of up to 1000 cells/s [37]. COVID-19-associated changes in the morphology of RBC, lymphocytes, monocytes and neutrophils of peripheral blood were studied. The following COVID-19-associated changes were identified: significant reduction in lymphocyte hardness, increased monocyte size, smaller and less deformed RBCs and large, deformed, activated neutrophils. During a repeated analysis, a part of examined subjects did not have their

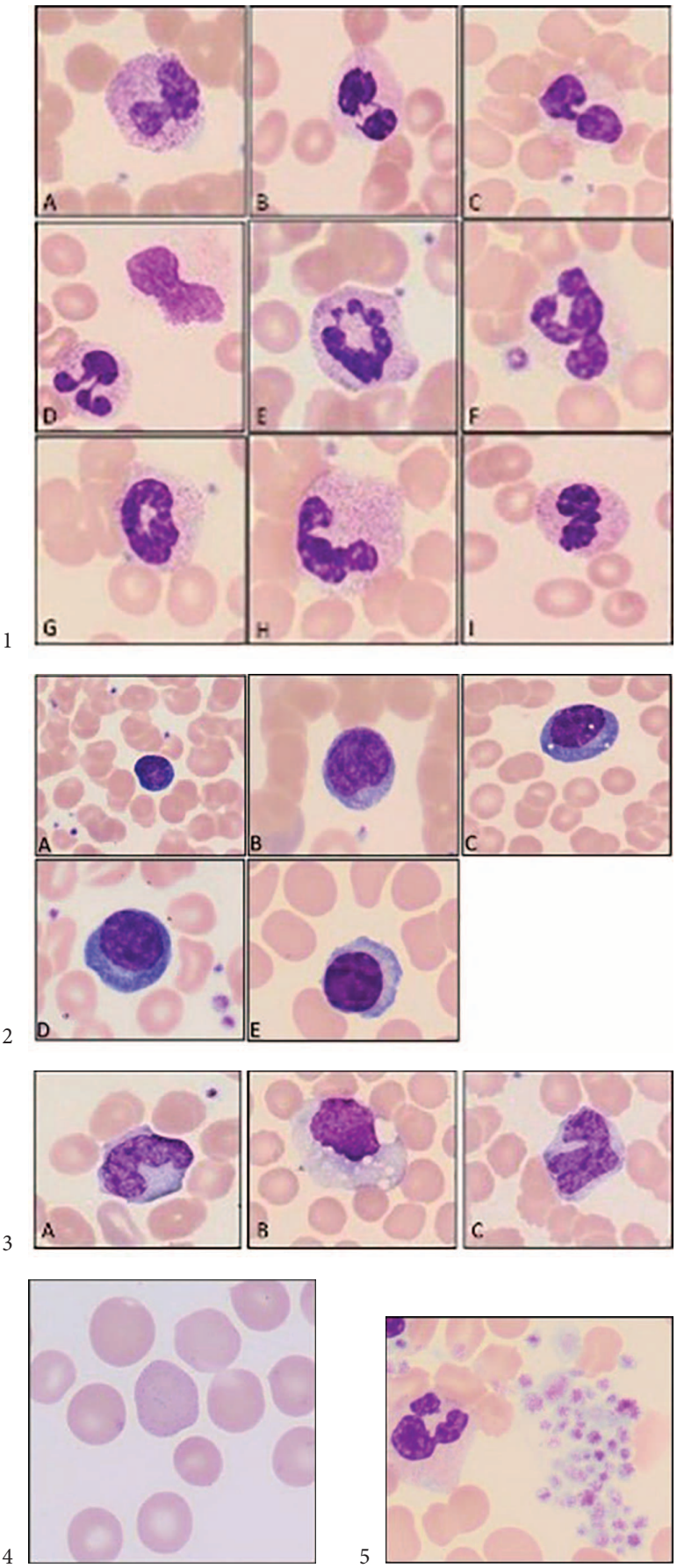


***Figure 1.*** *Morphological changes in blood cells (Romanowsky-Giemse staining, magnification × 1000 oil immersion)*

**Note:** 1. Neutrophilosis with left shift, neutrophils with clumped chromatin and toxic granularity (A), pseudo-Pelger anomaly of neutrophils (B and C), neutrophil with deformed nucleus (D, E, F and I, G, H); 2. lymphocytes with pale to dark blue cytoplasmic shade (A, B, and C) with lymphoplasmacytoid features (D and E); 3. abnormally shaped activated macrophages with cytoplasmic vacuolization; 4. Clusters of platelets; 5. erythrocyte with basophilic inclusion

values returning to controls' levels on the average after 7 months of hospitalisation, it being an evidence of the long-lasting effect from COVID-19 on the hematopoietic system [38]. Therefore, the results demonstrate that RT-DC can be used to track the course of COVID-19 and immune response to the disease.

In another study, peripheral blood swabs from patients with a positive COVID-19 test result were studied. The typical quantitative deviations were: anemia, followed by neutrophilia, left shift in neutrophils and lymphopenia; significant morphological changes: hypergranular neutrophil cytoplasm (dark, packed, rough, toxic) was observed in 10–89 % (in severe cases) of all blood draws. There were neutrophils with agglutinate chromatin, multiple abnormal nucleus shapes, pseudo-Pelger-Huet anomaly and indistinct neutrophils in up to 29 % of observations. Lymphoplasmacytoid cells with an eccentric nucleus, abundant dark blue cytoplasm and perinuclear type are mentioned by almost all authors; monocytes were activated with an abnormal shape and vacuolization. Figure 1 shows microimages of morphologically modified blood cells. Platelet count was adequate in a majority of patients; platelet accumulation was observed, their anisocytosis and pleomorphism were recorded in 48 % of observations. RBCs were usually normocytic and normochromic, with rough basophil inclusions of up to 77 % [39].

Few publications in this section demonstrated that cell morphology in COVID-19 changes, however, typical or specific changes are not described.

## Discussion

Despite the fact the topicality of the problem related to COVID-19 has dropped, the experience in diagnostics and management of this severe infection can be useful in the future, taking into account consequences faced by the global population during the pandemic. Specialists argue that the healthcare sector can run into an outbreak of a viral infection as new SARS-CoV-2 species appear [40]. Therefore, it is essential that every practitioner is equipped with the tools helping in forecasting the outcome of the disease and selecting an optimal management for the patient. Such tools include changes in blood values in COVID-19. Our purpose was to analyse such changes using literature and to identify key markers at the very early stages of complete blood count evaluation. Despite the absence of any specific changes, there is a certain pattern — haematological predictors of unfavourable course and outcome of the infection: increased neutrophil/lymphocyte ratio, increased RBC distribution width (RDW), reduced Hb value, thrombocytopenia, leukocytosis (often as a result of a concurrent bacterial infection), morphological changes in cells, higher ESR values [41, 42, 43]. A review of numerous studies shows that certain changes in the hematopoietic system in COVID-19 have pathogenic features, which are related to SARS-CoV-2 virus, trigger a chain of a blood-clotting disorder that differs from typical DIC syndrome, and contribute to the understanding of this pathology. It was found out that SARS-CoV-2 virus itself cannot cause blood-clotting disorders. Progressively rising D-dimer levels (up to 1500 ng/mL and over) in COVID-19 reflect disease severity and clotting activation because of viremia and cytokine storm, endothelial damage, as well as organ superinfection and dysfunction [28, 34, 35, 36].

Of note, the combination of hemoglobinopathies and iron dysmetabolism can significantly affect the ability of erythrocytes to transport $O_2$ with hypoxia, initiating tissue modifications associated with hyperferritinaemia (over 500–600 ng/mL) in COVID-19 [1]. Development of hemolytic anemia because of oxidative damage by a free iron ion can affect functioning of many other organs, and hypoxemia, ischemia, multi-organ failure can develop and promote hypercoagulation progression [18]. Free iron has toxic effect over alveolar cells and an inflammation develops which looks like a ground-glass pattern on images, also because of chemically induced pneumonitis, and not only viral pneumonia. Therefore, up-to-date anaemic syndrome correction will make it possible to reduce the risk of thrombotic complications [16].

COVID-19-caused mechanisms of thrombocytopenia can differ [18]. It is also assumed that platelets are consumed for production of respiratory clots in order to prevent the spread of the virus with blood flow [14]. An increased number of new and large circulating platelets is a compensatory reaction of the body to thrombocytopenia; they are more functional, and it can be another mechanism to boost blood clotting in COVID-19 [21-24].

According to clinical guidelines, there are 4 forms (degrees of severity) of COVID-19: mild, moderate, severe and extremely severe. If judging only by changes in blood values, then analysis of erythrocytes of patients with mild coronavirus infection did not reveal any significant changes, while in severe cases a lower RBC count (with large RDW-SD) and Hb can be a sign of comorbidity or severity of the underlying disease. It was found out that leukocyte count does not reflect severity of the disease; however, a reduction in lymphocyte count below $1.0\times10^9$/L and a higher neutrophil count, as well as an increase in the ratio of these indicators is a predictor of a more severe infection. Also, these values can evidence an insufficient resource of body's adaptive mechanisms in acute inflammation, pointing out to unfavourable changes in the overall reactivity of patients with coronavirus infection, and this is a significant prognostic factor. Changes in platelet count were observed in patients with a severe infection (≤ 120–$180\times10^9$/L). Severity of the disease will be also reflected by an increased ferritin level of over 500 ng/mL, CRP of 10 and over 75 mg/L, D-dimmers of over 1000 ng/mL, procalcitonin and ESR as markers of an inflammation process [41, 44].

Peripheral blood cell morphology in COVID-19 changes, however, there are no typical or specific changes. Significant reduction in lymphocyte hardness, increased monocyte size, identification of smaller and less deformed RBCs and large, deformed, activated neutrophils can be taken into account. These changes persist

even in 7 months, evidencing the long-lasting effect of COVID-19 on the hematopoietic system [37].

## Conclusion

Therefore, this review on changes in blood values in the novel coronavirus infection COVID-19 describes some new pathogenic mechanisms, mentions a combined multiple effect of SARS-CoV-2 on all three components of the hemapoiesis system: inhibition of erythrocyte saturation with Hb; development of hemolytic anemia in some of them with bone marrow regeneration with incomplete erythropoiesis; thrombocytopenia associated with pathological process progression and changes in platelet volume; absence of reactive leukocytosis in response to acute inflammation; reduced lymphoid cell count. All these qualitative and quantitative changes in hematopoiesis are involved in COVID-19 pathogenesis, they stimulate hypercoagulation and, thus, can affect prognosis and severity of the disease.

**Вклад авторов:**

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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**Список литературы/References:**

1. Wenzhong L., Hualan L. COVID-19: Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism. Biological and Medicinal Chemistry. 2020 Mar; v5:38 Preprint. doi.:10.26434/chemrxiv. 11938173.
2. Ehsani S. COVID-19 and iron dysregulation: distant sequence similarity between hepcidin and the novel coronavirus spike glycoprotein. Biology Direct. 2020;15 (19):1-13. Doi:10.1186/s13062-020-00275-2
3. Hirschhorn T, Stockwell BR. The development of the concept of ferroptosis. Free Radic Biol Med 2019 Mar; 133: 130-143. doi: 10.1016/j.freeradbiomed.2018.09.043.
4. Евтюгина Н.Г., Санникова С.С., Пешкова А.Д. и др. Количественные и качественные изменения клеток крови при COV ID-19. Казанский мед. ж. 2021; 102 (2): 141–155. DOI: 10.17816/KMJ2021-14.
Yevtyugina N.G., Sannikova S.S., Peshkova A.D., et al. Quantitative and qualitative changes of blood cells in COV ID-19. Kazan medical journal. 2021; 102 (2): 141-155. DOI: 10.17816/KMJ2021-14. [in Russian]
5. Zhao J., Yang Y., Huang H. et al. Relationship between the ABO Blood Group and the COVID-19 Susceptibility. Clinical Infectious Diseases 2021;.73(2):328-331, doi:10.1093/cid/ciaa1150
6. Задумина Д.Н., Скворцов В.В. Изменение гематологических показателей при COVID-19. Лечащий Врач. 2022; 11(25): 30-36. DOI: 10.51793/OS.2022.25.11.005.
Zadomina D.N., Skvortsov V.V. Change of hematological parameters in COVID-19. Lechaschi Vrach. 2022; 11 (25): 30-36. DOI: 10.51793/OS.2022.25.11.005. [in Russian]
7. Liu Y, Sun W, Guo Y, et al. Association between platelet parameters and mortality in coronavirus disease 2019: Retrospective cohort study. Platelets. 2020 May 18; 31(4): 490-496. doi: 10.1080/09537104.2020.1754383.
8. Zhang Y, Zeng X, Jiao Y, et al. Mechanisms involved in the development of thrombocytopenia in patients with COVID-19. Thromb Res. 2020 Sep; 193: 110-115. doi: 10.1016/j.thromres.2020.06.008.
9. Guan WJ, Ni ZY, Hu Y, et al. China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30; 382(18): 1708-1720. doi: 10.1056/NEJMoa2002032.
10. Yang X, Yang Q, Wang Y, et al. Thrombocytopenia and its association with mortality in patients with COVID-19. J ThrombHaemost. 2020 Jun; 18(6): 1469-1472. doi: 10.1111/jth.14848. Epub 2020 May 4. PMID: 32302435.
11. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020 Jun; 7(6): e438-e440. doi: 10.1016/S2352-3026(20)30145-9. Epub 2020 May 11. PMID: 32407672; PMCID: PMC7213964.
12. Thachil J. What do monitor platelet counts in COVID-19 teach us? J Thromb Haemost. 2020 Aug;18(8): 2071-2072. doi: 10.1111/jth.14879.
13. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. ClinChimActa.2020 Jul; 506: 145-148. doi: 10.1016/j.cca.2020.03.022.
14. Henry BM, de Oliveira MHS, Benoit S, Plebani M, et al. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020 Jun 25; 58(7): 1021-1028. doi: 10.1515/cclm-2020-0369.
15. Bomhof G, Mutsaers PGNJ, Leebeek FWG, et al. COVID-19-associated immune thrombocytopenia. Br J Haematol. 2020 Jul; 190(2): e61-e64. doi: 10.1111/bjh.16850.
16. Chabert A, Hamzeh-Cognasse H, Pozzetto B, et al. Human platelets and their capacity of binding viruses: meaning and challenges? BMC Immunol.2015 Apr 28; 16: 26. doi: 10.1186/s12865-015-0092-1.
17. Assinger A. Platelets and infection — an emerging role of platelets in viral infection.. Frontiers in immunology. 2014, Dec 18; vol. 5: 649. doi:10.3389/fimmu.2014.00649
18. Seyoum M, Enawgaw B, Melku M. Human blood platelets and viruses: defense mechanism and role in the removal of viral pathogens. Thromb J. 2018 Jul 17; 16: 16. doi: 10.1186/s12959-018-0170-8.

19. Lador A, Leshem-Lev D, Spectre G, et al. Characterization of surface antigens of reticulated immature platelets. J Thromb Thrombolysis. 2017 Oct; 44(3): 291-297. doi: 10.1007/s11239-017-1533-x.
20. Handtke S, Steil L, Palankar R, et al. Role of Platelet Size Revisited-Function and Protein Composition of Large and Small Platelets. ThrombHaemost. 2019 Mar; 119(3): 407-420. doi: 10.1055/s-0039-1677875.
21. Hille L, Lenz M, Vlachos A, et al. Ultrastructural, transcriptional, and functional differences between human reticulated and non-reticulated platelets. J ThrombHaemost. 2020 Aug; 18(8): 2034-2046. doi: 10.1111/jth.14895.
22. Handtke S, Thiele T. Large and small platelets-(When) do they differ? J ThrombHaemost. 2020 Jun; 18(6): 1256-1267. doi: 10.1111/jth.14788.
23. Zhang S, Liu Y, Wang X, et al. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. J HematolOncol. 2020 Sep 4; 13(1): 120. doi: 10.1186/s13045-020-00954-7.
24. Hottz ED, Azevedo-Quintanilha IG, Palhinha L, et al. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. Blood. 2020 Sep 10; 136(11): 1330-1341. doi: 10.1182/blood.2020007252.
25. Manne BK, Denorme F, Middleton EA, et al. Platelet gene expression and function in patients with COVID-19. Blood. 2020 Sep 10; 136(11): 1317-1329. doi: 10.1182/blood.2020007214.
26. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation.Blood. 2020 Jun 4; 135(23): 2033-2040. doi: 10.1182/blood.2020006000.
27. Spyropoulos AC, Levy JH, Ageno W, et al; Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis. Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J ThrombHaemost. 2020 Aug; 18(8): 1859-1865. doi: 10.1111/jth.14929.
28. Helms J, Tacquard C, Severac F, et al; CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis). High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020 Jun; 46(6): 1089-1098. doi: 10.1007/s00134-020-06062-x.
29. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med. 2020 Jun 25; 58(7): 1116-1120. doi: 10.1515/cclm-2020-0188.
30. Li, Q., Cao, Y., Chen, L. et al. Hematological features of persons with COVID-19. Leukemia. 2020.34:2163–2172 doi:10.1038/s41375-020-0910-1
31. Thachil J, Cushman M, Srivastava A. A proposal for staging COVID-19 coagulopathy.Res PractThrombHaemost. 2020; 4(5): 731-736. Published 2020 Jul 6. doi:10.1002/rth2.12372
32. Escher R, Breakey N, Lämmle B. Severe COVID-19 infection associated with endothelial activation. Thromb Res. 2020 Jun; 190: 62. doi: 10.1016/j.thromres.2020.04.014.
33. Othman M, Labelle A, Mazzetti I, et al. Adenovirus-induced thrombocytopenia: the role of von Willebrand factor and P-selectin in mediating accelerated platelet clearance. Blood. 2007 Apr 1; 109(7): 2832-9. doi: 10.1182/blood-2006-06-032524. PMID: 17148587.
34. Escher R, Breakey N, Lämmle B. ADAMTS13 activity, von Willebrand factor, factor VIII and D-dimers in COVID-19 inpatients. Thromb Res. 2020 Aug; 192: 174-175. doi: 10.1016/j.thromres.2020.05.032.
35. Martinelli N, Montagnana M, Pizzolo F, et al. A relative ADAMTS13 deficiency supports the presence of a secondary microangiopathy in COVID 19. Thromb Res. 2020 Sep; 193: 170-172. doi: 10.1016/j.thromres.2020.07.034.
36. Blasi A, von Meijenfeldt FA, Adelmeijer J, et al. In vitro hypercoagulability and ongoing in vivo activation of coagulation and fibrinolysis in COVID-19 patients on anticoagulation.J ThrombHaemost. 2020 Oct; 18(10): 2646-2653. doi: 10.1111/jth.15043.
37. O. Otto, P. Rosendahl, et al., J. Guck Real-time deformability cytometry: on-the-fly cell mechanical phenotyping/ Nature Methods, 2015, 12: 199-202 doi: 10.1038/nmeth/3181.
38. Kubánková M, Hohberger B, Hoffmanns J, et al. Physical phenotype of blood cells is altered in COVID-19. Biophys J. 2021 Jul 20; 120(14): 2838-2847. doi: 10.1016/j.bpj.2021.05.025.
39. Kaur G, Sandeep F, Olayinka O, et al. Morphologic Changes in Circulating Blood Cells of COVID-19 Patients. Cureus. 2021 Feb 18; 13(2): 13416. doi: 10.7759/cureus.13416. PMID: 33758711; PMCID: PMC7978157
40. Багненко, С. Ф., Рассохин, В. В., Трофимова и др. Эволюция пандемии COVID-19. Балтийский медицинский образовательный центр. 2021. 410 с.
Bagnenko, S.F., Rassokhin, V.V., Trofimova et al. Evolution of the COVID-19 pandemic. Baltic Medical Education Center. 2021: 410p [in Russian]
41. Министерство здравоохранения Российской Федерации. Временные методические рекомендации: Профилактика, диагностика и лечение новой коронавирусной инфекции (COVID-19). 2022. Версия 16 : 249с.
Ministry of Health of the Russian Federation. Temporary methodological recommendations: Prevention, Diagnosis and Treatment of New Coronavirus Infection (COVID-19). 2022, Version 16 :249. [in Russian]
42. Садретдинов М.А., Тимербулатов Ш.В., Валишин Д.А., и др. Диагностика COVID-19: неиспользованные технологии — возможности общего анализа крови. Медицинский вестник Башкортостана. 2020. Т. 15, № 3(87). С. 31-34. .
Sadretdinov M.A., Timerbulatov Sh.V., Valishin D.A., et al. COVID-19 diagnostics: Unused technologies — General blood analysis capabilities // Bashkortostan Medical Journal. 2020. vol. 15, . 3(87): 31-34. [in Russian]
43. Тимофеева Н.Ю., Кострова О.Ю., Стоменская И.С., и др. Изменения показателей общего анализа крови и коагулограммы при легком течении коронавирусной инфекции. Евразийский мед. журнал. 2021. № 2. С. 44-49. DOI: 10.47026/2413-4864-2021-2-44-49.
Timofeeva N.Yu., Kostrova O.Yu., Stomenskaya I.S., et al. Changes in the indicators of the general blood test and coagulogram in the mild course of coronavirus infection. Acta medica Eurasica. 2021. 2: 44-49. DOI: 10.47026/2413-4864-2021-2-44-49. [in Russian]
44. Губенко Н.С., Будко А.А., Плисюк А.Г. и др. Связь показателей общего анализа крови с тяжестью течения COVID-19 у госпитализированных пациентов. Южно-Российский журнал терапевтической практики. 2021; 2(1): 90-101. doi.10.21886/2712-8156-2021-2-1-90-101.
Gubenko N.S., Budko A.A., Plisyuk A.G. et al. The relationship of the indicators of the general blood test with the severity of COVID-19 in hospitalized patients. South-Russian Journal of Therapeutic Practice. 2021; 2(1): 90-101. doi.10.21886/2712-8156-2021-2-1-90-101. [in Russian]