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RESEARCH ARTICLE

The Nature of Changes in Haematological Parameters in Patients With COVID-19

Natalia Vadimov Teplova[1], Kermen Ivanovna Bairova[1], Evgeny Evsikov[2], Aldar Gabitovich Dzheksembekov[3], Vardanjan Argishti Gagikovich[1]

1 Department of Clinical Pharmacology, Pirogov Russian National Research Medical University, Moscow, Russia
2 Department of Hospital Therapy No. 1, Pirogov Russian National Research Medical University, Moscow, Russia
3 Department of the Faculty of Medicine, Pirogov Russian National Research Medical University, Moscow, Russia

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Abstract

Relevance: In the first half of 2020, reports appeared in the medical press about the presence of signs of multi-organ damage when a person is infected with COVID-19. It was suggested that hemoglobinopathies, hypoxia, and iron overload of parenchymal organ cells play an additional role in the pathogenesis of the disease. Based on these concepts and hypotheses, a system of pathogenetic therapy is formed. Clinical studies have not yet confirmed a number of hypotheses. To clarify them, additional laboratory tests are required.

Purpose and Objectives: Taking into account the available literature data and the lack of clinical data, we set the task in the study to study peripheral blood parameters and their dynamics in patients with COVID-19 who were treated with a diagnosis of viral pneumonia in a Moscow city hospital in the period April-June 2020.

Materials and Methods: All 206 patients were treated in the 3rd department (Head of MD Sokolova N. A.), including 82 men and 124 women aged from 26 to 97 years (mean age 56.8±6.1 years), 197 were discharged from the hospital, 6 were transferred to the intensive care unit, where they died, 3 died in the department. The study of peripheral blood and the calculation of the leukocyte formula were performed on the "Cobas Micro" and "Advia-21-20" analyzers (Simens, Germany). Biochemical studies were performed on a Getpremier spectrophotometer Getpremier (USA).

Results: The number of cases of anemia in patients with COVID-19 and pneumonia, when taking into account chronic diseases that precede the development of infection, did not exceed 3-9%.In the age group of patients aged 26-60 years, the number of cases with erythrocytosis was 27% higher than the proportion of patients with reduced red blood cells, which may be a consequence of the development of reactive erythrocytosis in response to respiratory and hemic hypoxia. In 37-38% of patients, a decrease in the hemoglobin content in the red blood cell was detected, which may be a manifestation of the blockade of hemoglobin synthesis by virus structures and the cause of heavier hypoxia.In 11-12% of patients with this pathology, thrombocytopenia was detected, and in 50-60%, signs of a decrease in platelet volume were detected, possibly due to their high consumption for intravascular thrombosis in the pulmonary

bloodstream and depletion of the platelet lacing process from the megakaryocyte. Most patients with COVID-19 and pneumonia were not characterized by a symptom of leukocytosis in the acute phase of the disease, except for some patients (about 20%) in the age group of 61-97 years, which may be a sign of cellular immunodeficiency. The symptom of monocytopenia was the most characteristic manifestation of changes in the granulocytic blood germ in patients, regardless of age, it was detected in 47-70% of patients, obviously reflecting the depletion of the phagocytic link of immunity, as well as lymphopenia, diagnosed in 25-52% of patients with a positive outcome of the disease.

Conclusions: The data obtained indicate a combined, multicomponent pathogenic effect of the COVID-19 virus on all three sprouts of the hematopoiesis system in patients with pneumonia: with inhibition of red blood cell saturation with hemoglobin, stimulation of erythropoiesis in some of them, changes in platelet volume, with the formation of abnormal macroforms of platelets, with the absence of reactive leukocytosis to acute inflammation, and a decrease in the number of monocytic phagocytes and lymphoid cells. It is possible that some of these changes may affect the prognosis and severity of the disease.

Corresponding author: Teplova Natalia Vadimovna, teplova.nv@yandex.ru

Relevance

In the first half of 2020, reports appeared in the medical press about the presence of signs of multi-organ damage when a person is infected with COVID-19. It was suggested that hemoglobinopathies, hypoxia, and iron overload of parenchymal organ cells play an additional role in the pathogenesis of the disease. Scientific studies by Chinese authors have identified two potential pathophysiological mechanisms: 1) severe acute respiratory syndrome-Tori-coronavirus-2 (SARS-CoV-2) interaction with the hemoglobin molecule via CD147, CD26 and other receptors located on the red blood cell and / or blood cell precursors; 2) hepcidin-mimetic effect of the viral spike protein that induces blocking of the ferroportin protein[1][2]. It is assumed that the development of hemoglobin denaturation and impaired iron metabolism can be the causes of:

a) decrease in the level of functioning hemoglobin; c) overload of cells / tissues with iron ions (hyper-ferritinemia); c) release of free toxic circulating heme; d) hypoxemia and systemic hypoxia; e) restoration of nitric oxide; f) activation of blood clotting; g) ferroptosis with activation of oxidative stress and lipoperoxidation; hmitochondrial degeneration and apoptosis. These disorders can cause several clinical syndromes, such as pulmonary edema due to arterial vasospasm and thrombosis, narrowing and alteration of the alveolar-capillary bed barrier, sideroblast-like anemia, endothelial damage, vasospastic acrosyndrome, and arteriovenous thromboembolism[3].

It was suggested that the positive effect of antimalarial drugs in COVID-19 is due to the fact that hydroxychloroquine and flaviprivir inhibit the binding of the virus envelope protein to the porphyrin ring molecule.However, some later controlled studies on this issue did not show any benefit from treatment with chloroquine and hydroxychloroquine, and the authors suggested that they may even be harmful[4]. In the group with high dosages of drugs, there was an increased number of

deaths[5].

The study of the problem in the clinic did not confirm some of the hypotheses put forward. In clinical studies, it was found that patients with severe disease had more pronounced laboratory disorders, including changes in bone marrow granulocytic growth (including lymphocytopenia and leukopenia)[6][7]. These deviations suggested that COVID-19 infection may be associated with cellular immunodeficiency, activation of coagulation, and damage to the myocardium, liver, and kidneys. In patients who did not survive, the number of neutrophils, D-dimer, urea, and creatinine levels in the blood continued to increase, and the number of lymphocytes continued to decrease until death[8]. Neutrophilia, according to researchers, may be associated with a cytokine storm caused by a viral infection[3]. In the general blood test with the white blood cell formula in COVID-19, the number of patients who did not survive continued to increase.In 2019, the authors observed the following changes:

- Lymphocytopenia - in 83.2% of patients
- Thrombocytopenia in 36.2% of patients
- Leukopenia – in 33.7%[6].

At the same time, researchers considered lymphocytopeniato be a decrease in the number of lymphocytes in absolute values in the general blood test below 1.0 thousand / μl. But some researchers believe that the consequences of lymphocytopenia are already observed when the number of lymphocytes is lower 1,5 * 10^9/L. Thrombocytopenia in COVID-19 is a common condition characterised by a decrease in the number of platelets below 150x10^{109}/l, which can be accompanied by increased bleeding and problems with stopping bleeding. Leukopenia should be considered a decrease in the number of white blood cells per unit volume of blood (less than 4000 in 1 μl), while motor activity ("lazy white blood cell syndrome") of mature neutrophils is disrupted and their exit from the bone marrow into the blood. *There* are significantly fewer studies on changes in the bone marrow erythroid germ and their results are contradictory[6][9].

Purpose and Objectives of the Study

Taking into account the available literature data and the lack of clinical data, we set the task in the study to study peripheral blood parameters and their dynamics in patients with COVID-19 who were treated with a diagnosis of viral pneumonia in a Moscow city hospital in the period April-June 2020.

Material and Methods

The analysis was carried out according to the examination and treatment of 206 patients who were admitted to the hospital 15 of the O. M. Filatov State Clinical Hospital after re-profiling in the period from 29.04.2020 to 01.06.2020 and were treated in 3 departments with diagnoses: U07. 1 U07. 1 Coronavirus infection caused by the COVID-19 virus, the virus was identified (confirmed by laboratory testing regardless of the severity of clinical signs or symptoms); U07. 2 U07. 2 Coronavirus infection caused by the COVID-19 virus, the virus has not been identified (COVID-19 is diagnosed clinically

or epidemiologically, but laboratory tests are inconclusive or unavailable. J12. 9 J12. 9 Community-acquired pneumonia. The patients' data were archived in the city computer system DZM KIS EMIAS.All 206 patients were treated in the 3rd department (Head of MD Sokolova N. A.), including 82 men and 124 women aged from 26 to 97 years (mean age 56.8±6.1 years), 197 were discharged from the hospital, 6 were transferred to the intensive care unit, where they died, 3 died in the department. The study of peripheral blood and the calculation of the leukocyte formula were performed on the "Cobas Micro" and "Advia-21-20" analyzers (Simens, Germany). Biochemical studies were performed on a Getpremier spectrophotometer (USA).

Research Design

From the data of the general group of patients, two comparison subgroups of different ages were distinguished: 1st – 78 patients aged 26-60 years (average-48.6 years), men 31, women 47, ratio 1:1.52; 2nd-128 patients aged 61-97 years (average 74.2 years), men-51, women-77, ratio 1:1.51, between which were used to compare the obtained data. C верифицированным There were 56 (71.3%) patients with verified COVID-19 in the 1st group, 88 (68.7%) in the second group. Differences were considered significant at ($p < 0.05$).

Results

In patients with COVID-19 and pneumonia, we detected significant changes in the indicators of erythroid, megakaryocytic and granulocytic blood sprouts. By comparing anamnestic data on the nature of blood pathology in infected patients prior to actual hospitalization and evaluating the dynamics of their laboratory parameters in the hospital, we were able to come closer to understanding the main trends in hematological changes under the influence of COVID-19.The most significant detected change in the erythroid germ of such patients was a decrease in the concentration of hemoglobin in the red blood cell – in 37-38% of patients.Taking into account the fact that 7-10% of patients had these changes at the prehospital stage, we can assume that the decrease in the indicator associated with COVID-19 pneumonia occurred in 27-28% of patients (Table 1). The tendency to increase the number of red blood cells in the blood was most pronounced in the group of younger patients. In the first group, the difference between the frequency of detection of abnormally high and pathologically low values of the content of red blood cells in peripheral blood was 26.9% ($p< 0.02$, significantly). The difference in the level of hemoglobin concentration in the 1st group of patients was similar, by 19.2% ($p< 0.05$).

It can be assumed that with the development of respiratory disorders and a decrease in the oxygen content in the pulmonary and systemic blood flow of these patients, a compensatory increase in erythropoiesis in the bone marrow occurs, which is most intense in patients under the age of 60 years.When analyzing changes in the megakaryocytic germ, we noted a pronounced tendency to reduce the number of normal-sized platelets and increase macrocytic forms in 50-60% of patients.This may be a sign of increased cell binding to the processes of intravascular thrombosis and increased lacing of young forms of small volume from the megakaryocyte.

Table 1. Erythrocytes, platelets and venous hematocrit in two groups of patients with COVID-19 and pneumonia of different age ranges (average values, maximum deviations of the indicator, the number of abnormal values and their frequency in percent)

Indicators	Group 1 (26-60 years) (n= 78)	Group 2 (61-97 years old) (n=128)	Difference in	%Reliability
of Hemoglobin (g / l):	133,0,±8,7,7	130,6±6,9	1,8%	nd
including	(86-154)	(104-158)		
A > 120	9(11,5%)	15(19,2%)	7,7%	nd
V < 140	24(30,7%)*	15(19,2%)	11,5%	nd
Red blood cells (million in µl):	4,57±0,42	4,38±0,36	4,1%	nd
including	(2,5-6,4)	(3,5-5,2)		
A > 3.9	3(3,8%)	12(15,4%)	11,6%	nd
V < 4,7	24(30,7%)*	19(24,3%)	6,4%	nd
Hematocrit (in %):	39,6±1,7	39,0±1,2	1,5%	nd
including	(26-49)	(32-46)		
A > 36V	12(15,4%)	16(20,5%)	5,1%	nd
< 42	21(26,9%)	12(15,4%)	11,5%	nd
Average red blood cell volume (fl):	87,1±6,8	89,4±8,1	2,6%	nd
including	(61-104)	(79-105)		
A > 80	6(7,7%)	3(3,8%)	3,9%	nd
V < 100	3(3,8%)	3(3,8%)	0	nd
Average hemoglobin concentration in the red blood cell(g / l): including	338±35	337±48	0,7%	nd
	(287-403)	(320-377)		
A > 330	30(38,5%)*	29(37,2%)*	1,3%	nd
V < 380	6(7,7%)	0	7,7%	nd
Platelets (thousand in µl): including	232±64	253±72	8,3%	nd
	(135-429)	(110-476)		
A > 150	9(11,5%)	10(12,8%)	1,3%	nd
V < 450	0	7(9%)	7%	nd

Average platelet volume (pl): including	7,52±0,78 (5,9-9,7)	7,31 ±0,49 (5,9-10,2)	2,8%	nd
A > 7.6	39(50%)*	47(60,2%)*	10,2%	nd
B < 10,8	0	0	0	nd

Note: nd-the differences in the groups are unreliable.

** - significant difference in subgroups A and B.*

The results of the analysis of the nature of changes in peripheral blood leukocytes in patients with COVID-19 and pneumonia allowed us to establish that cases of leukopenia were detected in groups 1-2 infrequently – in 2-15% of patients, more often in younger patients (Table 2). On the contrary, leukocytosis was more often detected in patients over the age of 60 years.The difference between the incidence of leukopenia and leukocytosis in group 2 was 21.9% and was significant ($p < 0.05$). Signs of lymphopenia were detected significantly more often than cases with lymphocytosis in the first group, by 20.5% ($p < 0.05$, significantly), when assessing relative lymphocytosis.In absolute terms of blood cell concentration, this difference was pronounced and significant in both groups, and the frequency of detection of lymphopenia was 25-52%.Even more often, patients with COVID-19 and pneumonia showed signs of a decrease in the number of the largest and most lysosomal phagocytes of the granulocyte series – monocytes.

Table 2. Indicators of the study in peripheral blood of leukocytes and leukocyte formula in two groups of patients with COVID-19 and pneumonia of different age intervals (average values, maximum deviations of the indicator, the number of abnormal values and their frequency in percent)

Indicators	Group 1 (26 -60 years) (n= 78)	Group 2 (61-97 years old) (n=128)	Difference in	%Reliability
White blood cells (thousand in µl.): including	6,28±1,03 (2,3-20)	6,87±1,14 (3,8-12,8)	8.6%	nd
A > 4.0	12(15,3%)	3(2,3%)	13%	nd
in < 9,0	12(15,3%)	31(24,2%)*	8.9%	nd
Granulocytes (in %): including	65,6± 8,2 (47,7-83,1)	66,6±7,4 (41,8-84)	1.5%	nd
A > 48	6(7,7%)	5(3,9%)	3.8%	nd
B < 80	3(3,8%)	5(3,9%)	0.1%	nd
	4,38±0,85	4,49±0,92	2,4%	nd

Granulocytes (abs .ths. in mkl): including	(1,5-8,5)	(2,3-8,4)		
A > 2	3(3,8%)	0	3,8%	nd
V < 6,5	6(7,7%)	20((15,6%)	7,9%	nd
Lymphocytes (in %): including	24,4±2,74	27,7±3,4	11,9%	nd
	(6-39,1)	(10,2-52,6)		
A > 19	25(32%)*	31(24,2%)	7,8%	nd
V < 37	9(11,5%)	20(15,6%)	4,1%	nd
Lymphocytes (abs. thousand in µl): including	1,25±0,27	1,83±0,53	31,7%	p< 0.01
	(0,43-2,3)	(0,8-4,4)		
A > 1.2	41(52,6%)*	33(25,8%)*	26,8%	p< 0.02
V < 3	0	10(7,8%)	7,8%	nd
Monocytes (in %): including	3,81±0,86	4,71±0,92	19,1%	p< 0.05
	(1,7-8,2)	(2,1-9,5)		
A > 3	26(33,3%)*	31(24,2%)*	9,1%	nd
V < 12	0	0	0	nd
Monocytes (abs. thousand in µl.): including	0,240±0,025	0,261±0,016	8%	nd
	(0-2,8)	(0,1-0,7)		
A > 0.3	55(70,5%)*	61(47,6%)*	22,9%	p< 0.05
V < 1,1	3(3,8%)	0	3,8%	nd

When calculating the number of these cells as a percentage of all leukocytes, signs of their deficiency were detected in 24-33% of patients, and in absolute values-in 47-70%, all differences are significant. Analysis of data on the premorbid "hematological" background in the studied patients with COVID-19 and pneumonia allowed us to establish that in the group of younger patients, changes were mainly associated with erythroid growth: in two cases with chronic post-hemorrhagic anemia, in one case with CKD, with acute leukemia and polychemotherapy, with iron deficiency unknown origin (Table 3).

Table 3. Anamnestic data on diseases with hematological changes in the group of patients with COVID-19 and pneumonia aged 26-60 years

Diseases and syndromes	Group 1 (26-60 years) (n= 78) (6 of them 78 - 7.6%)	Nature of hematological changes
1. Iron deficiency anemia	male	Normochromic, normocytic anemia of moderate severity.
2. CKD 4 tbsp.	Female	gender microcytic anemia, hypochromic, iron deficiency, mild course
3. Acute leukemia, myelodysplastic syndrome. Condition after polychemotherapy	Female gender	Normochromic, normocytic anemia of moderate severity.
4. Post-hemorrhagic anemia. Acute erosive gastritis.	Gender female	Anemia normochromic, normocytic, with a normal level of serum iron
5.Post-hemorrhagic anemia. Uterine bleeding	Gender female	Anemia normochromic, normocytic, mild
6. Brain tumor. Removal of the tumor.Polychemotherapy.	Gender Female	leukocytosis

In the group of elderly patients, four cases of anemia were associated with chronic blood loss, 8 cases with oncopathology and its pathogenetic treatment, and one with systemic collagen disease Table 4.

Table 4. Anamnestic data on diseases with hematological changes in the group of patients with COVID-19 and pneumonia aged 26-60 years

Diseases and syndromes	Group 2 (61-97 years) (n= 128) (13 out of 128 – 10.1%)	The nature of hematological changes
1. Tumor of the right lung	Male	gender Anemia hypochromic, normocytic, severe
2. Bladder cancer TUR operation.	Male	gender normochromic anemia, normocytic, mild
3. Erosive gastritis	Female gender	normochromic anemia, normocytic, mild.Normal serum iron levels.
4. Systemic lupus erythematosus	female gender	hypochromic anemia, microcytic, mild course.
5. Chronic gastritis	male	gender Anemia normochromic, normocytic, mild course.Reduced concentration In_{12}
6. Kidney cancer cells. Nephrectomy.	Gender female	Anemia normochromic, normocytic, mild course.Normal serum iron levels
7. Stomach cancer. Gastric resection	Female gender	normochromic anemia, normocytic, mild course.Normal level of serum iron
8. Prostate cancer with sprouting into the colon	Male	sex Anemia normochromic, normocytic, moderate-severe course.Normal serum levels
9. of Scalp cancer. 4 courses of	polychemotherapy Female gender	normochromic anemia, normocytic anemia, mild
10. Cancer of the right kidney.Nephrectomy.	Gender female	Anemia is hyperchromic, macrocytic, moderate-severe, iron-deficient.
11. Chronic erosive gastritis	Male	gender microcytic anemia, normochromic, iron deficiency
12. Erosive bulbitis	Female gender	normochromic anemia, normocytic, mild
13. Stomach cancer. Gastrectomy	Male	sex macrocytic anemia, normochromic,$_{B12}$-deficient

Thus, the most characteristic hematological changes identified by us during inpatient examination of patients with COVID-19 and pneumonia were a decrease in the level of monocytes and lymphocytes in peripheral blood, frequent development

of leukocytosis in patients over the age of 60, a decrease in the average platelet volume, a decrease in the average hemoglobin concentration in the red blood cell, an increase in the number of red blood cells and hemoglobin in the blood of some of the younger patients.

Discussion of the Results

Data from the study show that in some patients with COVID-19 and pneumonia,**the concentration of hemoglobin in red blood cells significantly decreases. Some of these patients are large and, according to our data, account for 37-38%.**

Researchers Wenzhong Liu and Hualan Li found that viral proteins penetrate hemoglobin molecules and block the binding of iron to the porphyrin ring. Four detected proteins interfere with oxygen transport: orf1ab, ORF10, ORF3a, and ORF8, which is only superficially involved. Hemoglobin with a low iron content is no longer able to perform its main function – to transport oxygen[1][2]. Theoretically, an increase in the concentration of iron – utilizing protein ferritin in the systemic circulation, an increase in serum iron, and hemosiderosis of parenchymal organs can be observed.We did not find any clinical data on the existence of such a mechanism in patients with COVID-19 and pneumonia in the available international medical resources.

According to our data, the diameter of red blood cells did not change much in the studied patients with COVID-19 and pneumonia, which is typical for chronic iron deficiency anemia, but we detected signs of macrocytosis in another non – nuclear cell-the platelet of these patients. In our study, when analyzing changes in the megakaryocytic germ, we noted a pronounced tendency to reduce the number of normal-sized platelets and an increase in macrocytic forms in 50-60% of patients, which may be a sign of increased cell consumption for intravascular thrombosis and replacement of small-volume young forms of megakaryocyte lacing when the plates are deficient.

We have not found data on a decrease in platelet volume in COVID-19 in the available literature. Signs of excessive thrombosis and an increase in the fibrinogen D-dimer metabolite in this pathology were noted earlier and described in several clinical studies[6][7].

Based on the results of our studies of granulocytic blood sprouts, we noted that the immune system of COVID-19 patients only in a part of patients (24%), mainly aged over 60 years, reacted to pneumonia with leukocytosis, which may indicate its significant depression, even during the period of maximum inflammatory changes in the lung tissue. The main type of changes in the leukocyte formula of patients was monocytopenia-in 47-70% and lymphopenia - in 25-52%.

According to the literature,imphopenia among COVID-19 patients is the most common type of leukocyte changes and occurs in approximately 83 % of cases[6]. In cases with a fatal outcome, lymphopenia became more severe over time, up to death[8]. In addition to lymphopenia, neutrophilia, increased blood pressure, and increased blood pressure can also be associated with a severe course of the with a severe course of the disease нейтрофилия, повышенный уровень .serum alanine aminotransferase and aspartate aminotransferase levels, elevated lactate dehydrogenaselevels, high C-reactive

protein levels, and high ferritin levels [6]. Elevated D-dimer levels and lymphopenia are associated with fatal outcomes[10][11][9].

In human blood, there is a pool of monocytes circulating through the bloodstream and a marginal pool adjacent to the vascular wall, it is 3.5 times larger than the circulating one. In peripheral blood, monocytes make up 1-10% of all white blood cells, the absolute number in adults is 80-600 cells per 1 mm3. Monocytes have a pronounced phagocytic function. These are the largest peripheral blood cells, they are macrophages, that is, they can absorb relatively large particles and cells or a large number of small particles and, as a rule, do not die after phagocytication (monocyte death is possible if the phagocytic material has any cytotoxic properties for the monocyte). In this way, they differ from microphages-neutrophils and eosinophils, which can absorb only relatively small particles and, as a rule, die after phagocytication[12].

The data obtained by us indicate a combined, multicomponent pathogenic effect of the COVID-19 virus on all three sprouts of the hematopoiesis system in patients with pneumonia: with inhibition of red blood cell saturation with hemoglobin, stimulation of erythropoiesis in some of them, changes in platelet volume, with the formation of abnormal macroforms of platelets, with the absence of reactive leukocytosis to acute inflammation, and a decrease in the number of monocytic cells. phagocytes and lymphoid cells. It is possible that some of these changes may affect the prognosis and severity of the disease.

Conclusions

1. The number of cases of anemia in patients with COVID-19 and pneumonia, when taking into account chronic diseases preceding the development of infection, did not exceed 3-9%.In the age group of patients aged 26-60 years, the number of cases with erythrocytosis was 27% higher than the proportion of patients with reduced red blood cells, which may be a consequence of the development of reactive erythrocytosis in response to respiratory and hemic hypoxia. In 37-38% of patients, a decrease in the hemoglobin content in the red blood cell was detected, which may be a manifestation of the blockade of hemoglobin synthesis by virus structures and the cause of heavier hypoxia.
2. In 11-12% of patients with this pathology, thrombocytopenia was detected, and in 50-60% there were signs of a decrease in platelet volume, possibly due to their high consumption for intravascular thrombosis in the pulmonary bloodstream and depletion of the platelet lacing process from the megakaryocyte.
3. Most patients with COVID-19 and pneumonia were not characterized by a symptom of leukocytosis in the acute phase of the disease, except for some patients (about 20%) in the age group of 61-97 years, which may be a sign of cellular immunodeficiency. The symptom of monocytopenia was the most characteristic manifestation of changes in the granulocytic blood germ in patients, regardless of age, it was detected in 47-70% of patients, obviously reflecting the depletion of the phagocytic link of immunity, as well as lymphopenia, diagnosed in 25-52% of patients with a positive outcome of the disease.

References

1. [a, b]*Wenzhong L, Hualan L. COVID-19Disease: ORF8 and surface glycoproteininhibit heme metabolism by binding to porphyrin. ChemRxiv 2020; Preprint. doi:10.26434/chemrxiv.11938173.v3.*
2. [a, b]*Wenzhong L, Hualan L. COVID-19: Attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. ChemRxiv 2020. Preprint. doi:10.26434/chemrxiv.11938173.v8.*
3. [a, b]*Cavezzi A, Troiani E, Salvatore Corrao S. COVID-19: hemoglobin, iron, and hypoxia beyond inflammation. A narrative review. Clinics and Practice. 2020; V.10:1271.*
4. [^]*Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. JAMA. 2020; 24 April (vol. 3, iss. 4.23): e208857–e208857. doi:10.1001/jamanetworkopen.2020.8857.*
5. [^]*Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. The Lancet. Elsevier, 2020. Published online May 22. doi:10.1016/S0140-6736(20)31180-6.*
6. [a, b, c, d, e, f]*CDC. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). Coronavirus Disease 2019 (COVID-19). U. S. Centers for Disease Control and Prevention (11 February 2020). Accessed March 31, 2020.*
7. [a, b]*Wang D, Hu B, Hu C, Zhu F, Liu X. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020; 7 February. doi:10.1001/jama.2020.1585. Wang D. et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020.*
8. [a, b]*https://cdlab.info/izmeneniya-pokazateley-krovi-pri-koronaviruse-COVID-19.html cdlab.info. Changes in blood counts for the COVID-19 coronavirus. cdlab.info.2020/04/17 website.*
9. [a, b]*Belyakov NA, Rassokhin VV, Yastrebova EB. Coronavirus infection COVID-19: nature of the virus, pathogenesis, clinical manifestations. Message 1. HIV Infect Immunosuppress. 2020;12(1):7-21.*
10. [^]*Paschenkov MV, Khaitov MR. Immune response against epidemic coronaviruses. 2020;41(1):5-19.*
11. [^]*Kostinov MP. Immunopathogenic properties of SARS-CoV-2 as a basis for choosing pathogenetic therapy. Immunology. 2020;41(1):83-91.*
12. [^]*Chesnokova NP, Ponukalina EV, Nevvazhay TA. Features of the structure, function and metabolism of blood monocytes and mononuclear-phagocytic system of tissues. Saratov State Med Univ Razumovsky. 2015;(4-2):290-2.*