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Coronavirus Pandemic

Erythrocyte morphology as a clinical disease indicator in hospitalized COVID-19 patients

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Abstract
Introduction: Most COVID-19 cases are mild, but some require hospitalization due to pneumonia, with symptoms like hypoxia and dyspnea. This has led to speculation about erythrocyte involvement in the infection. This study aimed to examine the differences in the presence of dysmorphic erythrocytes in COVID-19 patients upon admission compared to healthy subjects, as well as to assess these differences in relation to the severity of the clinical presentation of COVID-19.
Methodology: This study included 150 participants: 100 COVID-19 patients and 50 healthy subjects who formed the control group. The COVID-19 positive participants were divided into two groups based on the deterioration or improvement of their health conditions during hospitalization. Hematological parameters were analyzed, and peripheral blood smears were prepared to observe morphological changes in erythrocytes.
Results: The morphological changes observed in hospitalized COVID-19 patients included spiculated red blood cells (RBCs), spherocytes, stomatocytes, schistocytes, knizocytes, keratocytes, as well as mushroom- and cup-shaped RBCs. At admission, spiculated RBCs and spherocytes were more prevalent in patients showing improvement. Conversely, stomatocytes, knizocytes, keratocytes, and mushroom-shaped RBCs were more frequent in patients experiencing deterioration. Additionally, spiculated RBCs were more common in patients with improvement, while stomatocytes, schistocytes, knizocytes, keratocytes, mushroom-, and cup-shaped RBCs were more prevalent in deteriorating patients.
Conclusions: The complete blood count and the examination of peripheral blood smears in hospitalized patients may serve as fundamental tools to assist clinicians in differentiating disease severity and improving treatment decision-making.

Key words: SARS-CoV-2; COVID-19; red blood cells; peripheral blood smear.

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Introduction
The Coronavirus Disease 2019 (COVID-19) pandemic is an ongoing global crisis caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2). The rapid spread of SARS-CoV-2 has in a pandemic with significant impacts on all aspects of human life. The clinical manifestations of COVID-19 can vary from symptoms to severe disease, which may lead to permanent lung damage as a result of the entry of the virus into host cells. This process is accompanied by multiple systemic changes, particularly hematological changes [1,2]. Early hematological abnormalities in COVID-19 patients serve as important indicators in cases where unusual symptoms are present and where there are in molecular diagnostics [3].

Although the significance of quantitative deviations in the complete blood count is well-known, data describing the morphological changes of erythrocytes are lacking. The morphology and function of erythrocytes as oxygen transporters to tissues can be impaired in various conditions, particularly in cases involving free radicals and inflammation [4]. The fact that dysmorphic erythrocytes found in other conditions can negatively impact circulation and gas exchange underscores the importance of recognizing such changes in COVID-19 patients [5]. In the case of COVID-19, an increased degree of cellular oxidation has been observed. The SARS-CoV-2 virus affects skeletal and structural erythrocyte proteins, including the N-terminal end of the Band-3 protein, spectrin, and ankyrin [6]. This alteration in key structural proteins responsible for the biconcave shape of erythrocytes may explain the emergence of dysmorphic erythrocytes, which contribute to complications during the course of the disease.

In addition to the Band-3 protein, CD147 plays a central role in SARS-CoV-2 infection and the pathogenesis of COVID-19 [7]. The entry of the SARS-CoV-2 virus is mediated by the expression of CD147 on erythroblasts, leading to dysregulation of iron metabolism. All of these factors contribute to the formation of dysfunctional hemoglobin, which hinders adequate oxygen transport and promotes the development of severe systemic complications. For these reasons, we can conclude that systemic changes adversely affect the morphology of erythrocytes during infection [8]. Given that laboratory diagnostics require significant funding, which is unfortunately unavailable in underdeveloped and developing countries, it is crucial to develop tools that ensure high reliability, reproducibility, and economic viability [9,10]. Numerous studies have highlighted that infections cause hematological changes, making the application of laboratory diagnostics in the detection and treatment of COVID-19 a primary focus [11,12].

In this context, the peripheral blood smear is an important diagnostic tool for assessing hematological disorders, particularly the morphological changes of blood cells. However, there is an insufficient number of studies examining the association of morphological abnormalities with the severity of disease in COVID-19 [13].

According to currently available data, the described abnormalities that are not necessarily related to other diseases and observed in COVID-19 include poikilocytosis, basophilic stippling, rouleaux formation, erythrocyte aggregation, spherocytes, schistocytes, spiculated erythrocytes, bite cells (keratocytes), stomatocytes, knizocytes, cup-shaped erythrocytes, and mushroom-shaped cells. Most studies have been case reports or included a small number of subjects with varying severity of the disease [14,15]. Adequate recognition of erythrocyte aggregation may lead to a deterioration of the physiological properties of blood and the function of the vascular endothelium, which is a significant indicator for monitoring and treating severe COVID-19 conditions [16,17].

Our main aim is to examine whether there is a difference in the presence of dysmorphic erythrocytes in findings upon admission compared to healthy subjects, and subsequently in relation to the severity of the clinical picture of COVID-19. This could potentially aid in the further diagnosis and treatment of the disease.

Methodology

This prospective, descriptive, and analytical study included 150 subjects, comprising 100 patients who tested positive for SARS-CoV-2 and controls (seemingly healthy subjects). The subjects were patients with symptoms (cough, fever, difficulty breathing, fatigue, headache, etc.) who presented at the JZU "Health Center Brčko" from June to December 2022. The diagnosis of COVID-19 was confirmed using real-time PCR on nasopharyngeal swab samples. Demographic data and laboratory results from hematological analyses were collected using the information system of the health institution, and data processing was conducted in accordance with the Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. For each COVID-19 positive patient, a complete blood count (CBC) was obtained upon admission to the health center, along with a follow-up CBC to assess the course of the disease. Depending on the patient's symptoms and condition, interventions with antibiotics, anticoagulants, corticosteroids, and oxygen were administered, leading to an improvement in the clinical picture of the group of COVID-19 patients who showed clinical improvement.

This research was conducted after obtaining permissions from the Ethical Committee in JZU "Health Center Brčko" (No. 05-EO-002/22-5-1) and the Ethical Committee of Clinical Center University of Sarajevo (No. 06-04-9-19265), Bosnia and Herzegovina.

Criteria

The criteria for inclusion in the study were as follows: confirmed presence of the SARS-CoV-2 virus in patients, patients older than 18 years, and complete documentation. The exclusion criteria included: negative SARS-CoV-2 test results, patients 18 years of age, patients with incomplete medical documentation, pregnant women, and individuals with any diseases that can affect erythropoiesis red blood cells (such as hypertension, malignancy, type 2 diabetes mellitus, coagulopathies, and obstructive lung diseases, except for COVID-19). The control group consisted of subjects who, aside from having tested negative for SARS-CoV-2, did not have any other disorders or diseases.

Hematological analysis

Whole blood samples were collected in EDTA tubes, which serve as the preferred anticoagulant because they minimally damage cell morphology. The samples were then analyzed using a Sysmex XP-300 automated hematology analyzer. This hematology analyzer measures a complete blood count (CBC) along with a differential blood count.

The study included the total number of erythrocytes (RBC), hemoglobin concentration (Hgb), mean corpuscular volume (MCV), hematocrit (HCT), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and the coefficient of variation in erythrocyte volume distribution (RDW), as well as the total number of leukocytes (WBC) along with the absolute counts of neutrophils and lymphocytes.

The results of these parameters were monitored throughout the hospital stay to assess whether there was a deterioration or improvement in the patient's health condition, comparing them to the results at admission. Based on this assessment, the respondents were divided into two groups: those with deterioration in COVID-19 and those with improvement.

Cytomorphological analysis

For the cytomorphological analysis of the cells, peripheral blood smears from patients (at admission, during deterioration, and with improvement of the clinical picture) and the control group were prepared. Peripheral smears were made and stained using the Pappenheim method, specifically the May-Grunwald-Giemsa staining technique. The preparations of peripheral blood smears were observed and analyzed using an Olympus CX23 binocular microscope with immersion at a magnification of 1000x by an experienced specialist in medical biochemistry and a medical laboratory technologist.

The smears were examined from the thinnest to the thickest layer, covering an average of 60-80 visual fields, with an average number of erythrocytes per visual field ranging from 150 to 200. Cell images were obtained using the automated hematology analyzer Sysmex XN-3100.

Statistical analysis

After collecting the data, statistical analysis was conducted using the IBM SPSS Statistics software (version 25.0), with Microsoft Word and Excel used for preparing and displaying the results. The Kruskal-Wallis test was employed to evaluate statistically significant differences in the examined hematological parameters between groups, while Pearson's chi-square test was used to assess morphological changes. Differences between repeated measurements in each group were tested using the Wilcoxon signed-rank test. A p of less than 0.05 was considered significant for all tests.

Results

The study included 100 COVID-19 patients and 50 subjects. The control group consisted of 50 subjects, with a median age interquartile range (IQR) of 59.50 years (53.0–68.0) compared to 66.0 years (57.0–74.75) in the COVID-19 patient group. The overall gender distribution of the examined population was 96 men (64%) and 54 women (36%). In the control group, there were 34 men (68%) and 16 women (32%). Among

Table 1. Differences in the values of the hematological parameters between controls and COVID-19 patients at admission.

Parameter	Group	N	Median	IQR		Mann Whitney U	*p*
Age (years)	Controls	50	59.50	53.00	68.00	1884.500	**0.014**
	COVID-19	100	66.00	57.00	74.75		
Leukocytes (10e9/L)	Controls	50	6.90	6.12	8.00	2369.000	0.601
	COVID-19	100	7.20	5.60	10.05		
Lymphocytes (%)	Controls	50	29.35	24.32	32.77	637.000	**< 0.001**
	COVID-19	100	14.55	8.32	22.10		
Neutrophils (%)	Controls	50	60.00	57.22	65.30	657.000	**< 0.001**
	COVID-19	100	77.35	68.77	86.62		
Erythrocytes (10e12/L)	Controls	50	4.80	4.60	5.00	1489.000	**< 0.001**
	COVID-19	100	4.50	4.12	4.80		
Hemoglobin (g/dL)	Controls	50	14.50	13.97	15.02	968.500	**< 0.001**
	COVID-19	100	13.00	11.72	14.00		
Hematocrit (%)	Controls	50	43.40	41.92	44.12	998.000	**< 0.001**
	COVID-19	100	38.10	35.42	41.75		
MCV (fL)	Controls	50	90.45	86.55	91.92	1691.500	**0.001**
	COVID-19	100	87.00	83.90	90.32		
MCH (pg)	Controls	50	29.90	29.27	31.00	1655.000	**0.001**
	COVID-19	100	29.20	27.90	30.37		
MCHC (g/dL)	Controls	50	33.50	32.90	34.42	2259.000	0.336
	COVID-19	100	33.50	32.62	34.10		
RDW (%CV)	Controls	50	12.45	11.80	13.05	1544.500	**< 0.001**
	COVID-19	100	13.20	12.40	14.30		

patients with worsening COVID-19, there were 44 men (64.7%) and 24 women (35.3%), while in the group of patients with improving COVID-19, there were 18 men (56.3%) and 14 women (43.8%). The groups of healthy controls and COVID-19 patients were gender-matched, showing no significant difference in gender distribution ($p = 0.470$).

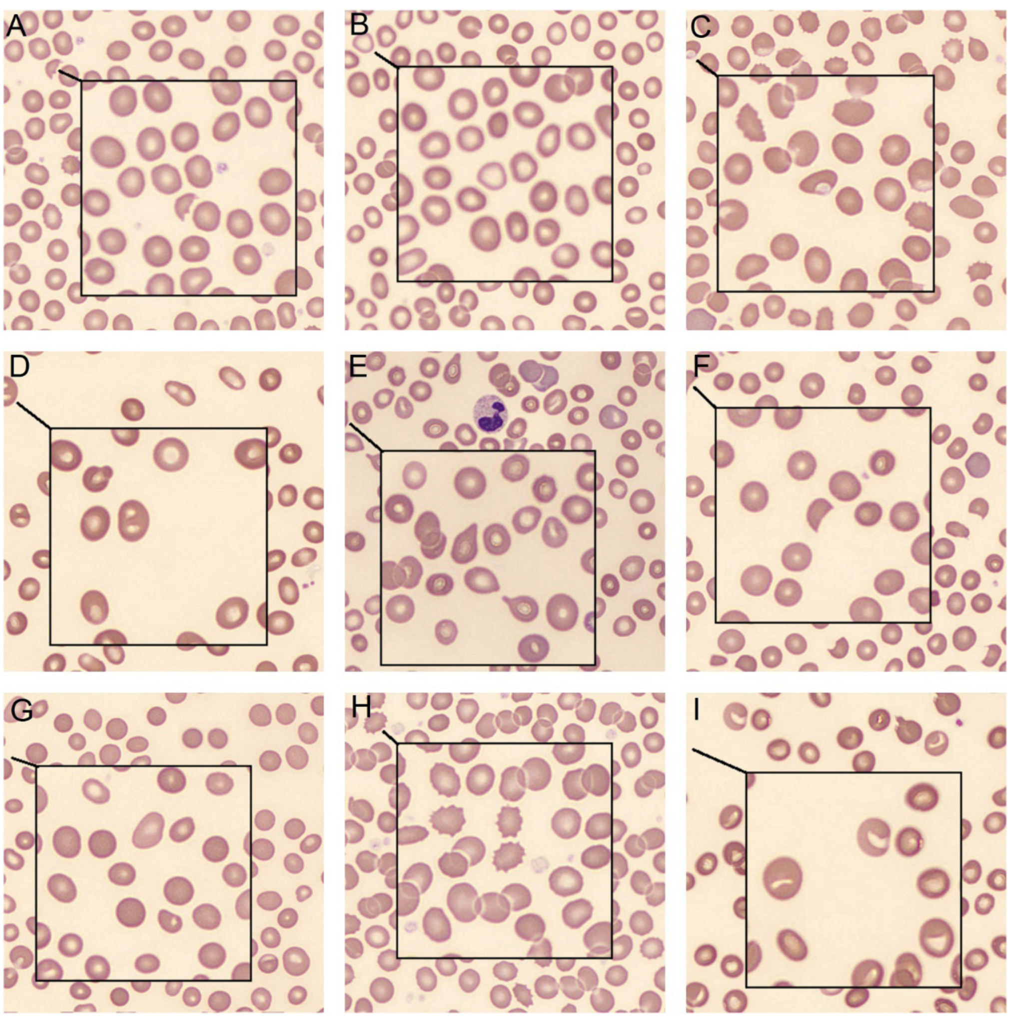
According to the Mann-Whitney U test, there is a significant difference in the values of all examined hematological parameters between the control group and COVID-19 patients, except for total leukocyte ($p = 0.601$) and mean corpuscular hemoglobin concentration (MCHC) ($p = 0.336$), as shown in Table 1. The statistical significance for all other hematological parameters was $p = 0.001$ or lower.

The morphological changes of erythrocytes observed in this study included spiculated RBCs, spherocytes, stomatocytes, schistocytes, knizocytes, keratocytes, and mushroom- and cup-shaped RBCs. Only 6 (12%) of healthy controls exhibited morphologically altered erythrocytes, with spiculated RBCs present in 5 (10%) patients and spherocytes in 1 (2%) patient. Morphological changes of erythrocytes in COVID-19 patients (N = 100) at admission were significantly more frequent. Spiculated RBCs were present in 38% of COVID-19 patients, spherocytes in 39%, stomatocytes in 31%, schistocytes in 38%, knizocytes in 38%, keratocytes in 24%, mushroom-shaped RBCs in 26%, and cup-shaped RBCs in 31% of COVID-19 patients (Figure 1).

COVID-19 patients were analyzed separately as two groups, depending on the further course of the disease: patients with improvement (N = 32) and patients with deterioration (N = 68).

According to the Mann-Whitney U test, there was a significant difference only in age ($p = 0.012$) between

Figure 1. Morphological shapes of erythrocytes.



A: bite cells, B: cup-shaped erythrocytes, C: keratocytes, D: knizocytes, E: mushroom-shaped erythrocytes, F: schistocytes, G: spherocytes, H: spiculated erythrocytes, I: stomatocytes; magnification 1000x.

Table 2. Differences in the values of the hematological parameters between patients with improvement and patients with deterioration at admission.

Parameter	Group	N	Median	IQR		Mann Whitney U	*p*
Age (years)	With improvement	32	62.50	47.25	67.75	749.500	**0.012**
	With deterioration	68	67.00	62.00	77.75		
Leukocytes (10e9/L)	With improvement	32	7.50	5.25	9.75	1086.000	0.988
	With deterioration	68	6.60	5.62	10.35		
Lymphocytes (%)	With improvement	32	13.85	6.52	22.47	1059.500	0.833
	With deterioration	68	14.70	8.42	22.10		
Neutrophils (%)	With improvement	32	77.45	67.12	87.10	1065.000	0.865
	With deterioration	68	77.35	68.77	86.62		
Erythrocytes (10e12/L)	With improvement	32	4.55	4.12	4.80	1006.500	0.546
	With deterioration	68	4.45	4.12	4.80		
Hemoglobin (g/dL)	With improvement	32	13.20	11.92	13.80	1040.000	0.723
	With deterioration	68	12.95	11.62	14.07		
Hematocrit (%)	With improvement	32	38.65	36.30	41.15	996.500	0.499
	With deterioration	68	38.05	35.00	41.87		
MCV (fL)	With improvement	32	87.00	85.20	89.17	1068.500	0.885
	With deterioration	68	87.15	83.30	90.97		
MCH (pg)	With improvement	32	29.25	28.20	29.90	1084.500	0.979
	With deterioration	68	29.00	27.52	30.60		
MCHC (g/dL)	With improvement	32	33.65	32.72	33.87	1083.500	0.973
	With deterioration	68	33.45	32.60	34.10		
RDW (%CV)	With improvement	32	12.85	12.12	13.60	891.500	0.146
	With deterioration	68	13.20	12.50	14.40		

COVID-19 patients with improvement and patients with deterioration, as shown in Table 2.

The frequency of erythrocyte morphological changes at admission was significantly different between patients with improvement and those with deterioration (Table 3). Spiculated RBCs and spherocytes were more frequent in patients with improvement ($p < 0.001$ and $p = 0.015$, respectively). In contrast, stomatocytes, knizocytes, keratocytes, and mushroom-shaped RBCs were more prevalent in patients with deterioration ($p = 0.006$, $p = 0.002$, $p = 0.004$, and $p = 0.035$, respectively). There was no significant difference in the occurrence frequency of schistocytes and cup-shaped RBCs between COVID-19 patients with improvement and those with deterioration at the time of admission.

Hematological parameters, as well as morphological changes of erythrocytes, were analyzed for COVID-19 patients again 12-15 days after admission (follow-up). According to the Mann-Whitney U test, there were significant differences in the values of the examined hematological parameters between COVID-19 patients with improvement and those with deterioration at follow-up, as shown in Table 4.

Between COVID-19 patients with improvement and those with deterioration at follow-up, there were significant differences in the values of leukocytes ($p < 0.001$), lymphocytes ($p < 0.001$), neutrophils ($p < 0.001$), erythrocytes ($p = 0.008$), hemoglobin ($p = 0.012$), hematocrit ($p = 0.010$), and RDW ($p = 0.023$). The values of leukocytes, neutrophils, and RDW were higher, while the values of lymphocytes, hemoglobin, and hematocrit were lower in COVID-19 patients with deterioration.

The frequency of erythrocyte morphological changes between patients with improvement and those with deterioration at follow-up was significantly different (Table 5). Spiculated RBCs were more frequent in patients with improvement ($p = 0.002$). In contrast, stomatocytes, schistocytes, knizocytes, keratocytes, and mushroom- and cup-shaped RBCs were more common in patients with deterioration. There was no significant difference in the occurrence frequency of spherocytes between COVID-19 patients with improvement and those with deterioration at follow-up.

Table 3. Morphological changes of erythrocytes between patients with improvement and patients with deterioration at admission.

RBC morphological changes	With improvement (N = 32)	With deterioration (N = 68)	Pearson x^2 value	*p*
Spiculated RBC	21 (65.6%)	17 (25%)	15.243	**< 0.001**
Spherocytes	18 (56.3%)	21 (30.9%)	5.886	**0.015**
Stomatocytes	4 (12.5%)	27 (39.7%)	7.530	**0.006**
Schistocytes	10 (31.2)	28 (41.2%)	0.910	0.340
Knizocytes	5 (15.6%)	33 (48.5%)	10.000	**0.002**
Keratocytes	2 (6.25%)	22 (32.4%)	8.129	**0.004**
Mushroom-shaped RBC	4 (12.5%)	22 (32.4%)	4.458	**0.035**
Cup-shaped RBC	6 (18.75%)	25 (36.8%)	3.301	0.069

Table 4. Differences in the values of the hematological parameters between patients with improvement and patients with deterioration at follow-up.

Parameter	Group	N	Median	IQR		Mann Whitney U	*p*
Age (years)	With improvement	32	62.50	47.25	67.75	749.500	**0.012**
	With deterioration	68	67.00	62.00	77.75		
Leukocytes (10e9/L)	With improvement	32	7.30	6.30	9.02	361.000	**< 0.001**
	With deterioration	68	11.50	8.87	15.95		
Lymphocytes (%)	With improvement	32	26.45	16.90	30.75	232.000	**< 0.001**
	With deterioration	68	8.00	4.60	14.20		
Neutrophils (%)	With improvement	32	64.30	57.27	73.82	235.500	**< 0.001**
	With deterioration	68	85.75	77.82	89.47		
Erythrocytes (10e12/L)	With improvement	32	4.45	4.10	4.70	729.000	**0.008**
	With deterioration	68	4.15	3.60	4.40		
Hemoglobin (g/dL)	With improvement	32	13.25	11.62	13.67	749.500	**0.012**
	With deterioration	68	11.90	10.92	13.17		
Hematocrit (%)	With improvement	32	39.10	34.90	40.97	740.000	**0.010**
	With deterioration	68	35.90	32.80	38.85		
MCV (fL)	With improvement	32	87.55	85.85	90.32	976.500	0.410
	With deterioration	68	88.40	84.42	93.17		
MCH (pg)	With improvement	32	29.40	28.22	30.15	1079.500	0.950
	With deterioration	68	29.40	27.77	30.97		
MCHC (g/dL)	With improvement	32	33.10	32.40	34.50	908.000	0.183
	With deterioration	68	32.95	31.92	33.67		
RDW (%CV)	With improvement	32	13.30	12.52	14.67	781.000	**0.023**
	With deterioration	68	13.75	13.10	15.97		

Table 5. Morphological changes of erythrocytes between patients with improvement and patients with deterioration at follow-up.

RBC morphological changes	With improvement (N = 32)	With deterioration (N = 68)	Pearson x^2 value	*p*
Spiculated RBC	24 (75%)	28 (41.2%)	9.974	**0.002**
Spherocytes	22 (68.8%)	34 (50%)	3.105	0.078
Stomatocytes	8 (25%)	52 (76.5%)	24.020	**< 0.001**
Schistocytes	10 (31.2%)	37 (54.4%)	4.686	**0.030**
Knizocytes	5 (15.6%)	50 (73.5%)	29.479	**< 0.001**
Keratocytes	1 (3.1%)	38 (55.9%)	25.458	**< 0.001**
Mushroom-shaped RBC	1 (3.1%)	41 (60.3%)	29.195	**< 0.001**
Cup-shaped RBC	9 (28,1%)	45 (66.2%)	12.684	**< 0.001**

Table 6. Differences in the values of the hematological parameters between measurements in patients with improvement.

Parameter	Time	Mean	SD+/-	Median	IQR		Wilcoxon signed rank Z	*p*
Age (years)	Improvement	59.37	12.56	62.50	47.25	67.75	0.000	1.000
	Admission	59.37	12.56	62.50	47.25	67.75		
Leukocytes (10e9/L)	Improvement	7.63	1.991	7.30	6.30	9.02	-0.103	0.918
	Admission	8.43	6.125	7.50	5.25	9.75		
Lymphocytes (%)	Improvement	24.76	10.244	26.45	16.90	30.75	-3.749	**< 0.001**
	Admission	16.31	11.249	13.85	6.52	22.47		
Neutrophils (%)	Improvement	65.36	12.012	64.30	57.27	73.82	-3.656	**< 0.001**
	Admission	75.74	14.654	77.45	67.12	87.10		
Erythrocytes (10e12/L)	Improvement	4.36	0.405	4.45	4.10	4.70	-1.682	0.093
	Admission	4.52	0.515	4.55	4.12	4.80		
Hemoglobin (g/dL)	Improvement	12.75	1.373	13.25	11.62	13.67	-0.990	0.322
	Admission	13.09	1.774	13.20	11.92	13.80		
Hematocrit (%)	Improvement	38.19	3.620	39.10	34.90	40.97	-1.009	0.313
	Admission	39.29	4.836	38.65	36.30	41.15		
MCV (fL)	Improvement	87.56	4.136	87.55	85.85	90.32	-1.950	0.064
	Admission	86.77	4.104	87.00	85.20	89.17		
MCH (pg)	Improvement	29.22	1.666	29.40	28.22	30.15	-2.259	**0.024**
	Admission	28.87	2.005	29.25	28.20	29.90		
MCHC (g/dL)	Improvement	33.40	2.152	33.10	32.40	34.50	-0.559	0.576
	Admission	33.26	1.331	33.65	32.72	33.87		
RDW (%CV)	Improvement	13.76	2.284	13.30	12.52	14.67	-2.403	**0.016**
	Admission	13.17	1.353	12.85	12.12	13.60		

Table 7. Morphological changes of erythrocytes between admission and follow-up in COVID-19 patients with improvement.

RBC morphological changes	Admission (32)	Improvement (32)	Pearson x^2 value	*p*
Spiculated RBC	21	24	0.674	0.412
Spherocytes	18	22	1.067	0.302
Stomatocytes	4	8	1.641	0.200
Schistocytes	10	10	0.000	1.000
Knizocytes	5	5	0.000	1.000
Keratocytes	2	1	0.350	0.554
Mushroom-shaped RBC	4	1	1.953	0.162
Cup-shaped RBC	6	9	0.784	0.376

In addition to analyzing groups of COVID-19 patients based on the course of the disease (improvement versus deterioration), we also examined differences in hematological parameters and RBC morphological changes within each group between admission and follow-up.

According to the Wilcoxon signed-rank Z test, differences in the values of the hematological parameters between measurements in COVID-19 patients with improvement were significant (Table 6). Lymphocytes, mean corpuscular hemoglobin (MCH), and RDW were lower at admission compared to follow-up ($p < 0.001$, $p = 0.024$, $p = 0.016$, respectively), while neutrophils were higher ($p < 0.001$).

Frequency of erythrocyte morphological changes between measurements in patients with improvement did not differ significantly for any of the forms, as shown in Table 7.

According to the Wilcoxon signed-rank Z test, differences in the values of hematological parameters between measurements in COVID-19 patients with deterioration were significant (Table 8). Leukocytes, neutrophils, mean corpuscular volume (MCV), and red cell distribution width (RDW) were lower at admission compared to follow-up ($p < 0.001$ for all), while lymphocytes, erythrocytes, hemoglobin, hematocrit, and mean corpuscular hemoglobin concentration (MCHC) were higher ($p < 0.001$ for all).

The frequency of erythrocyte morphological changes between measurements in patients with deterioration significantly differed for all forms except schistocytes, as shown in Table 9. The frequency of these morphological changes increased at follow-up for all forms.

Discussion

COVID-19 causes several changes in hematological parameters. These blood abnormalities, if carefully monitored, can help manage the progression of the disease. Research has shown that such blood changes are significantly more frequent and pronounced in patients with severe forms of COVID-19 and are related to the progression and severity of the infection. While lymphopenia and other abnormalities in peripheral blood are well described in the literature, little is known about changes in circulating blood cells in COVID-19. Therefore, monitoring these hematological changes in patients with COVID-19 can

Table 8. Differences in the values of the hematological parameters between measurements in patients with deterioration.

	Time	Mean	SD+/-	Median	IQR		Wilcoxon signed rank Z	*p*
Age (years)	Deterioration	66.85	13.842	67.00	62.00	77.75	0.000	1.000
	Admission	66.85	13.842	67.00	62.00	77.75		
Leukocytes (10e9/L)	Deterioration	12.796	5.2200	11.500	8.875	15.950	-6.370	**< 0.001**
	Admission	9.146	9.4105	6.600	5.625	10.350		
Lymphocytes (%)	Deterioration	9.819	5.8092	8.000	4.600	14.200	-5.897	**< 0.001**
	Admission	15.853	9.0645	14.700	8.425	22.100		
Neutrophils (%)	Deterioration	83.865	7.4390	85.750	77.825	89.475	-5.393	**< 0.001**
	Admission	76.537	11.5347	77.350	68.775	86.625		
Erythrocytes (10e12/L)	Deterioration	4.032	.7097	4.150	3.600	4.400	-6.026	**< 0.001**
	Admission	4.443	.6750	4.450	4.125	4.800		
Hemoglobin (g/dL)	Deterioration	13.860	12.6498	11.900	10.925	13.175	-5.575	**< 0.001**
	Admission	13.999	10.0090	12.950	11.625	14.075		
Hematocrit (%)	Deterioration	35.275	5.6301	35.900	32.800	38.850	-5.732	**< 0.001**
	Admission	38.366	5.4436	38.050	35.000	41.875		
MCV (fL)	Deterioration	88.407	6.8796	88.400	84.425	93.175	-5.507	**< 0.001**
	Admission	86.701	6.7466	87.150	83.300	90.975		
MCH (pg)	Deterioration	32.341	27.2130	29.400	27.775	30.975	-0.324	0.746
	Admission	28.868	3.1005	29.000	27.525	30.600		
MCHC (g/dL)	Deterioration	32.738	1.6802	32.950	31.925	33.675	-3.711	**< 0.001**
	Admission	33.237	1.5806	33.450	32.600	34.100		
RDW (%CV)	Deterioration	14.693	2.4356	13.750	13.100	15.975	-5.804	**< 0.001**
	Admission	13.740	2.1289	13.200	12.500	14.400		

Table 9. Morphological changes of erythrocytes between admission and follow-up in COVID-19 patients with deterioration.

RBC morphological changes	Admission (68)	Deterioration (68)	Pearson x^2 value	*p*
Spiculated RBC	17	28	4.019	**0.045**
Spherocytes	21	34	5.159	**0.023**
Stomatocytes	27	52	18.876	**< 0.001**
Schistocytes	28	37	2.387	0.122
Knizocytes	33	50	8.935	**0.003**
Keratocytes	22	38	7.635	**0.006**
Mushroom-shaped RBC	22	41	10.675	**0.001**
Cup-shaped RBC	25	45	11.775	**0.001**

play an important role in disease management and in preventing the risk of severe disease outcomes.

The research included a total of 150 subjects, of which 100 tested positive for COVID-19, while 50 patients comprised the control group (apparently healthy subjects). The control group had a median age of 59.50 years, compared to 66.0 years in COVID-19 patients. The gender distribution of the total examined population consisted of 96 men (64%) and 54 women (36%). The groups of healthy controls and COVID-19 patients were gender-matched, showing no significant difference in gender distribution ($p = 0.470$).

In our study, there was a significant difference in the values of all examined hematological parameters between the control group and COVID-19 patients ($p = 0.001$ or lower for all), except for white blood cell (WBC) counts ($p = 0.601$) and mean corpuscular hemoglobin concentration (MCHC) ($p = 0.336$). Patients with COVID-19 pneumonia may present with normal, low, or high WBC counts, as shown in numerous studies [18-21], particularly in the early stage of COVID-19, where predicting disease severity remains a challenge. We found that the average values of erythrocytes, hemoglobin, hematocrit, and mean corpuscular hemoglobin (MCH) were significantly lower in patients with COVID-19 compared to the control group, while the average values of red cell distribution width (RDW) were higher. The results of this research align with those of Elderdery *et al.* [22], and another study reported a rapid decline in hemoglobin and erythrocyte levels among patients with COVID-19 [23].

In the case of COVID-19, lymphopenia and neutrophilia are common findings in blood counts [24-26]. As the disease progresses to a severe stage, lymphopenia continues to worsen. Some studies propose the number of lymphocytes as an indicator for classifying the severity of the disease [27]. This provided a guideline for our study in determining whether the health condition of COVID-19 patients worsened or improved during their hospital stay. Based on this, we established COVID-19 patient groups in our research and monitored changes in the red blood cell parameters.

Depending on the further course of the disease, COVID-19 patients were analyzed as those with improvement (N = 32) and those with deterioration (N = 68). At the time of admission, there was no significant difference in the values of leukocyte, lymphocyte, neutrophil, and erythrocyte counts between patients with improvement and those with deterioration, nor in the values of hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW).

On the other hand, the frequency of erythrocyte morphological changes between patients with improvement and those with deterioration at admission was significantly different. At the time of admission, spiculated RBCs and spherocytes were more frequent in patients with improvement ($p < 0.001$ and $p = 0.015$, respectively), whereas stomatocytes, knizocytes, keratocytes, and mushroom-shaped RBCs were more frequent in patients with deterioration ($p = 0.006$, $p = 0.002$, $p = 0.004$, and $p = 0.035$, respectively).

Compared to healthy controls, anemia with low hemoglobin levels in COVID-19 patients indicates a disturbance in the transport of oxygen to the organs, leading to hypoxia, which can result in multi-organ dysfunction. All of these factors contribute to the severe outcomes commonly seen in cases of severe COVID-19. Initial assessment and prospective monitoring of these parameters seems advisable in patients with SARS-CoV-2 infection, as a progressive decrease in their concentrations may indicate worse clinical progression. However, these parameters have limited diagnostic value in predicting the course of the disease in COVID-19 patients during the initial phase of the illness [28].

In our study, hematological parameters as well as morphological changes of erythrocytes were analyzed again for COVID-19 patients 12-15 days after admission (follow-up).

At follow-up, significant differences were observed between COVID-19 patients with improvement and those with deterioration in the values of leukocyte, lymphocyte, neutrophil, and erythrocyte counts, as well as in the values of hemoglobin, hematocrit, and red cell distribution width (RDW).

Although the average levels of erythrocytes, hemoglobin, and hematocrit tend to decrease in both groups of COVID-19 patients (those with deterioration and those with improvement), this decrease is more pronounced in patients with a deteriorating health status. While no previous research has divided subjects into groups in this way, a study was conducted in which COVID-19-positive patients were categorized into three groups based on the severity of the disease [29].

Our study demonstrated that COVID-19 patients with deterioration had lower values for red blood cells (RBC) and hemoglobin. Patients with severe COVID-19 exhibited significantly lower hemoglobin levels than those with mild or moderate COVID-19 [30,31]. This finding aligns with the research of Yuan *et al*., who reported that severely and critically ill patients had significantly reduced RBC counts and hemoglobin [32].

Additionally, higher RDW in patients with deterioration is consistent with the data from Lee *et al*., who found that nearly half (49.7%) of patients hospitalized for COVID-19 had elevated RDW values [29]. Wang *et al*. also identified that RDW-CV and RDW-SD parameters were significantly higher in the group with severe COVID-19. Their analysis revealed that increased RDW was associated with nine-fold greater odds of severe COVID-19 [33].

At follow-up, the frequency of erythrocyte morphological changes between patients with improvement and those with deterioration was significantly different. Spiculated RBCs were more frequent in patients with improvement (p = 0.002), while stomatocytes, schistocytes, knizocytes, keratocytes, and mushroom- and cup-shaped RBCs were more prevalent in patients with deterioration.

When there are numerical changes in the number of red blood cells, analyzing a peripheral blood smear becomes an important diagnostic tool. Despite the advancements in genetic and molecular techniques for diagnosing various diseases, examining cell morphology in blood smears remains valuable for uncovering the causes of vague symptoms and signs [34].

Our study identified several morphological changes in erythrocytes across different examined groups. Notably, in COVID-19 patients showing improvement, we found spiculated erythrocytes with overlapping characteristics of echinocytes and acanthocytes in 75% of the cases. Additionally, spherocytes were observed in 68.8% of these patients, marking them as the most common findings.

The frequency of erythrocyte morphological changes in COVID-19 patients with deterioration was notably lower, with spiculated erythrocytes observed in 41.2% of cases and spherocytes in 50%. The most prevalent finding in deteriorating COVID-19 patients was stomatocytes, which occurred in 76.5% of cases, followed closely by knizocytes at 73.5%. Additionally, there was a high incidence of mushroom and cup-shaped red blood cells (RBCs), observed in 60.3% and 66.2% of cases, respectively; these changes were rare in patients whose conditions improved.

Similar results were reported by Marchi *et al*., who identified spiculated erythrocytes as a typical finding in their research. This was also echoed in the work of Khakwani *et al*. [35]. COVID-19 patients experiencing deterioration exhibited higher rates of stomatocytes, schistocytes, knizocytes, keratocytes, as well as mushroom and cup-shaped RBCs. Conversely, a lower percentage of morphological changes was observed in patients with improved health status. Nevertheless, our data indicate that even after improvement, morphological abnormalities can persist for an extended period.

These findings may enhance understanding of the mechanisms underlying long-term symptoms that some patients experience for months after viral infection [36]. Berzuini *et al.* focused on seriously ill COVID-19 patients, highlighting a prolonged hospital stay and significant drops in hemoglobin levels, which correlated with the prevalence of stomatocytes, knizocytes, and cup-shaped erythrocytes [23]. Pezeshki *et al.* also noted the presence of schistocytes in peripheral blood smears of COVID-19-positive patients [37].

Interestingly, the discovery of mushroom-shaped erythrocytes, reported by Gerard *et al.* and Dienstmann *et al.* [38,39], was corroborated in our study. Another unusual observation was the presence of keratocytes, or bite cells, noted in the peripheral blood smears of deteriorating COVID-19 patients - a phenomenon documented in only one previous study.

Based on the results obtained, we can hypothesize that the presence of spiculated cells and spherocytes may reflect milder changes in the composition of the erythrocyte membrane caused by SARS-CoV-2 infection. In contrast, the presence of stomatocytes, knizocytes, schizocytes, keratocytes, as well as mushroom-shaped and cup-shaped erythrocytes, likely indicates more advanced damage characterized by a loss of erythrocyte elastic properties.

The study conducted by Ćosić *et al.* demonstrated the interaction between the Band-3 protein and the SARS-CoV-2 virus using a biophysical model. This finding may be significant for understanding the reduced oxygen transport associated with COVID-19, as well as the morphological changes observed in erythrocytes; however, further extensive studies are required to validate this hypothesis [40].

In addition to the Band-3 protein, CD147 plays a central role in SARS-CoV-2 infection and the subsequent pathogenesis of COVID-19. The entry of the virus is mediated by the expression of CD147 on erythroblasts, which can lead to dysregulation in iron metabolism [7].

These erythrocyte morphological abnormalities ultimately disrupt oxygen delivery to tissues. Studies have indicated that SARS-CoV-2 can also target erythrocytes via the interaction of its spike protein with both CD147 and the Band-3 protein, suggesting that this interaction may drive the observed morphological changes. Dysfunctional erythrocytes may struggle to navigate through narrow blood vessels, potentially weakening circulation and inducing hypoxemia [7,41,42].

Our study has several limitations. Firstly, it is a single-center study conducted at one health center. Secondly, the small sample size, compared to other studies, limits the generalizability of our results to the broader population. Future research should aim to include a larger number of patients, which could be achieved through collaboration among multiple health centers and institutions.

Conclusions

This study evaluated standard laboratory parameters that are regularly performed, as well as morphological changes in erythrocytes that may aid in the identification and differentiation of COVID-19 cases, thereby assisting in the care and treatment of patients. Limitations of the study include the small sample size and the unclear causal mechanisms underlying the morphological changes observed in erythrocytes. Nonetheless, this research represents a significant step toward understanding the hematological manifestations of COVID-19.

Changes in hematological parameters among COVID-19 patients can be beneficial for diagnosing the disease, assessing its severity, and prognosticating outcomes in hospitalized cases. A comprehensive understanding of the numerical and morphological changes in red blood cells within peripheral blood, if corroborated by larger studies, could enhance diagnostic accuracy for COVID-19. Additionally, a complete blood count and examination of the peripheral blood smear in hospitalized patients could serve as essential tools for clinicians in differentiating disease severity and improving treatment decision-making.

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Conflict of interests

No conflict of interests is declared.

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