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Orgınal Article

Relationship between Coronavirus Disease and Erythrocyte Morphology Parameters

Koronavirüs Hastalığı ile Eritrosit Morfoloji Parametreleri ile İlişkisi

İbrahim Halil YASAK[1*], Mustafa YILMAZ[2], Eyyup Sabri SEYHANLI[3], Ataman GÖNEL[4]

[1] 1Harran University Faculty of Medicine, Department of Emergency Medicine, Sanliurfa / TURKİYE

[2] Fırat University Faculty of Medicine, Department of Emergency Medicine, Elazığ / TURKİYE

[3] Health Science University, Mehmet Akif İnan Research and Training Hospital, Emergency Department, Sanliurfa / TURKİYE

[4]Hasan Kalyoncu University, Department of Nutrition and Dietetics, Gaziantep,

**Corresponding author:*

Dr. İbrahim Halil YASAK (MD)

Adress: Harran University Faculty of Medicine, Department of Emergency Medicine, 63300, Sanliurfa / TURKİYE

Phone: +90 414 344 44 44 / 1378

Email: dr_ihy@hotmail.com

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Highlights

- Coronavirus Disease causes changes in erythrocyte morphology
- Microcytosis value may help in diagnosing coronavirus disease

Abstract

Background: To determine the rates of Microcytosis (%), Macrocytosis (%), Hypochromia (%), and Hyperchromia (%) as erythrocyte morphological parameters in Coronavirus Disease 2019 **(**COVID-19) infection, using a new-generation hematological autoanalyser, and to evaluate the use of these parameters for diagnostic purposes. **Material and Methods:** This retrospective study included 66 patients (F:41, M:25) with COVID-19 infection confirmed by real-time Polymerase Chain Reaction (PCR) test positivity, and 67 age and gender-matched healthy individuals (F:40, M:27) as a control group. The COVID-19 patients were separated into two groups as those with pulmonary infiltration (n=35, F/M:20/15) and those without (n=31, F/M:21/10). The hematological parameters measured on the autoanalyzer were analyzed and compared between the groups. **Results:** Age and gender distribution were similar in both study groups (p=0.619, p=0.457). The White Blood Cell (p=0.040) Neutrophil (p<0.001), Lymphocyte (p<0.001), and Platelet (p <0.001) levels were statistically significantly lower in the COVID-19 patients compared to the control group and C-Reactive Protein (CRP) levels were significantly increased (p<0.001). In the comparisons of the erythrocyte morphology parameters, Microcytosis % (p=0.011) was significantly greater, and Macrocytosis % (p=0.009) and Hypochromia % (p=0.032) were significantly lower in the COVID-19 patients. An increase was determined in Hyperchromia %, but not at a statistically significant level (p=0.059).**Conclusion:** From the erythrocyte morphological findings determined with the new-generation devices, the Microcytosis percentage was determined to be significantly increased in COVID-19-positive patients, and this parameter was found to have 78.79% sensitivity and 50.75% specificity in the differentiation of COVID-19 patients from healthy individuals.

Keywords: COVID-19, Microcytosis, Macrocytosis, Hypochromia, Hyperchromia

ÖZ

Amaç: Yeni nesil hematolojik oto analizör cihazı ile tespit edilen eritrosit morfolojik parametreleri olan Microcytosis (%), Macrocytosis (%), Hypochromia (%), Hyperchromia (%) 'nin Koronavirüs Hastalığı 2019 (Covid-19) hastalığındaki oranları ve tanı amaçlı kullanılmasının tespiti amaçland.

Gereç ve Yöntem: Retrospektif olarak tasarlanan çalışmamıza real time- Polimeraz Zincir Reaksiyonu (PCR) testi pozitif olan 66 (K/E: 41/25) hasta ile yaş ve cinsiyet olarak benzer 67 (K/E: 40/27) sağlıklı birey alındı. Covid-19 hastaları daha sonra, akciğerde infiltasyon olanlar (n=35, K/E: 20/15) ve infiltrasyon olmayanlar (n= 31, 21/10) olarak iki gruba ayrıldı. Hastaların otoanalizatör cihazda ölçülen hematolojik parametreleri analiz edildi.

Bulgular: Çalışma gruplarının yaş (p=0.619) ve cinsiyet (p=0.457) olarak benzerdi. Covid-19 hastalarının; White Blood Cell (p=0.040) Neutrophil (p<0.001), Lymphocyte (p<0.001), Platelet (p <0.001) düzeylerinin sağlıklı kontrol grubuna gore anlamlı oranda azaldığı fakat C-Reaktif Protein (CRP) düzeylerinin ise anlamlı oranda arttığı tespit edildi (p <0.001). Ayrıca eritrosit morfolojilerinin karşılaştırıldığında Covid-19 hastalarında Microcytosis yüzdesinin (p=0.011) anlamlı oranda fazla, Macrocytosis yüzdesinin (p=0.009) ve Hypochromia yüzdesinin (p=0.032) ise anlamlı oranda az olduğu, Hyperchromia yüzdesinin ise arttığı fakat bu artisan istatistiksel olarak anlamlı olmadığı (p=0.059) tespit edildi **Sonuç:** Yeni nesil cihazlar ile tespit edilen eritrosit morfolojik bulgularından ise Microcytosis yüzdesinin Covid pozitif hastalarda anlamlı oranda arttığı ve Covid-19 hastalarını, sağlıklı bireylerden ayırt etmede sensitivitesinin %78.79 ve specificitesinin ise % 50.75 olduğu tespit edildi.

Anahtar kelimeler: COVID-19, Microcytosis, Macrocytosis, Hypochromia, Hyperchromia

Introduction

COVID-19 infection, caused by the SARS-CoV-2 virus, is a disease affecting many organ systems, which develops with a wide range of clinical signs and symptoms from asymptomatic infection to acute respiratory distress syndrome, multiple organ failure, and death. The clinical symptoms of COVID-19 are very similar to those of various other viral infections (1-3). The SARS-CoV-2 virus is known to enter the host cells by binding to angiotensin-converting enzyme 2 (ACE2) receptors (4). Studies have reported that ACE2 is expressed in type 1 and 2 alveolar epithelial cells, in myocytes, in vascular endothelial cells, and some other cells including hematopoietic stem cells and progenitors (4, 5). It has been suggested that this may be related to a change in oxygen intake and/or oxygen binding and /or oxygen expression of red blood cells (RBC) in COVID-19 patients. A change in the hematological profile, and changes in RBC morphology, structure, and function that can occur during the acute phase of infection may explain the symptoms that emerge (6, 7). These changes may be related to damage in the beta chain of hemoglobin or to the formation of increasing methemoglobin which increases the oxygen affinity of undamaged hemoglobin (8). It has been shown in several studies that hematological parameters are changed in COVID-19 infection and may be associated with mortality (9,10). However, there is a limited number of studies related to the morphological changes in the blood cells of COVID-19 patients, and most of the publications are case reports (11, 12).

Peripheral blood smear analysis is an important diagnostic tool in RBC deteriorations, but there are very few studies giving detailed information about RBC morphology in COVID-19 patients (13). Hemoglobin (Hb) concentration tends to gradually reduce during the course of the disease. Both sepsis and hypoxia have profound effects on RBC morphology, rheology, and survival, and probably contribute to the complex pathogenesis of COVID-19 anemia (13).

New-generation hematology devices can provide neew data about erythrocyte morphology. In emergency situations, the hypochromia percentage (%), hyperchromia %, macrocytosis %, and microcytosis % can be sensitively measured automatically (14,15).

The hemogram autoanalyzer assesses the volume of erythrocytes of <60 fL as Microcytosis (%), >120 fL as Macrocytosis (%), and erythrocytes with hemoglobin concentrations of >42 pg and <17 pg as Hyperchromia (%) and Hypochromia (%), respectively).

The aim of this study was to compare the erythrocyte morphological parameters measured with a hemogram autoanalyzer in the Emergency Department between patients diagnosed with COVID-19 and healthy individuals, and to compare the COVID-19 patients with and without infiltrative involvement determined on thorax computed tomography.

Material and Methods

This case-control study included 67 patients diagnosed with COVID-19 infection confirmed by real-time PCR test positivity and 67 healthy individuals as a control group. The study was conducted in the Emergency Department of a University Faculty of Medicine Hospital in accordance with the Helsinki Declaration. Approval for the study was granted by the university Ethics Committee. Signed informed consent was obtained from all the study participants. After sample size was established, inclusion and exclusion criteria were defined. Patients were excluded if they were aged <18 years, had any hematological malignancy, or chronic lung disease. Non-Contrast Thorax Computed Tomography (CT) (Aquilion Prime SP, Canon Medical Systems, 9750 Irvine, USA) was performed on PCR positive patients. CT images were described using standard terminology using terms such as ground glass opacity, crazy-paving pattern, and consolidation(16).

Biochemical Analysis

Venous blood samples were taken from the patients presenting at the Emergency Department and from the control group subjects. The samples were analyzed using standard laboratory methods.The hemogram parameters of Microcytosis (%), Macrocytosis (%), Hypochromia (%), Hyperchromia (%), White Blood Cell (10e3/µL), Neutrophil (10e3/µL), Lymphocyte (10e3/µL), Monocyte (10e3/µL), Hemoglobin (g/dL), Hematocrit (%), Mean Corpuscular Volume (fL), Mean Corpuscular Hemoglobin (pg), Mean Corpuscular Hemoglobin Concentration (g/dL), Red Blood Cell Distribution Width , Platelet (10e3/µL), Mean Platelet Volume (fL), and Platelet Distribution Width (fL) were examined using an Alinity HQ (Abbott, USA) full automatic hemogram autoanalyzer. The biochemical parameters (Glucose (mg/dl), Urea (mg/dl), Creatine (mg/dl), C-Reactive Protein (mg/dL)) were examined using an Architect c16000 (Abbott, USA) full automatic biochemistry autoanalyzer.

Statistical Analysis

Data were analysed using SPSS 21.0 (IBM Corporation, Armonk, NY, USA) and MedCalc (Version 10.1.6.0, Ostend, Belgium) packaged software. Numerical data were expressed as median (IQR) values, and qualitative data as number (n) and percentage (%). The Shapiro–Wilk test was used to examine the conformity of

continuous variables to normal distribution. Comparisons were made using the Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. Receiver operating characteristic (ROC) curve analysis was performed using the erythrocyte parameters for the differentiation of control subjects and COVID-19 patients. The ROC curve analysis results were given as % specificity, and % sensitivity [area under the ROC curve (AUC), p-value, 95% confidence interval (CI)]. A value of $p<0.05$ was accepted as the level of statistical significance.

Results

Evaluation was made of 66 patients with COVID-19 confirmed by real-time PCR test positivity and 67 healthy individuals. Age and gender distribution were similar in both groups (p=0.619, p=0.457, respectively). The White Blood Cell (p=0.040) Neutrophil (p<0.001), Lymphocyte (p<0.001), and Platelet (p <0.001) levels were statistically significantly lower in the COVID-19 patients compared to the control group and CRP levels were significantly increased (p<0.001). The basic data of the study groups are shown in Table 1.

Table 1. The basic data of the study groups.

Variabales	COVID-19 group	Control group	p
N (F/M)	66 (41/25)	67 (40/27)	0.457
Age (years)	46.00 (29.50-60.25)	45.00 (29.00-64.00)	0.619
White Blood Cell* (10e3/µL)	6.35 (5.55-9.05)	7.53 (6.65-8.52)	0.040
Neutrophil* (10e3/µL)	3.50 (2.16-4.43)	4.76 (3.68-5.28)	<0.001
Lymphocyte* (10e3/µL)	1.47 (1.03-1.84)	2.10 (1.68-2.64)	<0.001
Monocyte* (10e3/µL)	0.50 (0.42-0.68)	0.60 (0.48-0.71)	0.075
Hemoglobin* (g/dL)	13.80 (12.78-15.43)	14.00 (12.60-15.50)	0.993
Hematocrit* (%)	42.60 (39.40-47.43)	44.00 (39.00-46.50)	0.845
Mean Corpuscular Volume* (fL)	89.60 (86.18-92.75)	90.30 (86.20-93.80)	0.685
Mean Corpuscular Hemoglobin* (pg)	29.15 (28.20-30.23)	29.40 (28.00-30.20)	0.633
Mean Corpuscular Hemoglobin Concentration* (g/dL)	32.40 (32.00-32.83)	32.40 (31.80-32.90)	0.914
Red Blood Cell Distribution Width	12.55 (12.18-13.33)	12.80 (12.30-13.70)	0.084
Platelet* (10e3/µL)	229.50(190.75-262.25)	288.00 (226.00-335.00)	<0.001
Mean Platelet Volume* (fL)	8.20 (7.63-8.90)	8.11 (7.55-8.74)	0.253
Platelet Distribution Width* (fL)	13.40 (12.90-13.73)	13.20 (12.80-13.50)	0.187
Glucose (mg/dl)	93.00 (84.75-113.00)	96.00 (86.00-115.00)	0.369
Urea (mg/dl)	25.68 (21.40-29.96)	25.68 (19.26-32.10)	0.964
Creatine (mg/dl)	0.70 (0.59-0.89)	0.70 (0.50-0.80)	0.055
C-Reactive Protein* (mg/dL)	0.92 (0.43-2.50)	0.11 (0.05-0.31)	<0.001

* Median (IQR)

In the comparisons of the erythrocyte morphology parameters, Microcytosis % (p=0.011) was significantly greater, and Macrocytosis % (p=0.009) and Hypochromia % (p=0.032) were significantly lower in the COVID-19 patients. An increase was determined in Hyperchromia %, but not at a statistically significant level (p=0.059) (Table 2).

Table 2. Comparisons of the erythrocyte morphology parameters of the study groups

Variables	COVID-19 group	Control group	p
Microcytosis* (%)	1.35 (1.01-1.35)	1.00 (0.68-1.73)	0.011
Macrocytosis *(%)	0.66 (0.33-1.63)	1.21 (0.60-2.41)	0.009
Hypochromia* (%)	0.51 (0.34-0.96)	0.82 (0.44-1.62)	0.032
Hyperchromia* (%)	0.12 (0.06-0.16)	0.07 (0.03-0.16)	0.059

* Median (IQR)

According to the ROC curve analysis performed to evaluate the use of erythrocyte morphology parameters in the differentiation of COVID-19 patients from healthy control subjects, a cutoff value of >0.998 for the Microcytosis percentage was determined to have 78.79% sensitivity and 50.75% specificity. A cutoff value of >0.0666 for the Hyperchromia percentage was determined to have 72.73% sensitivity and 49.25% specificity (Table 3, Figure 1).

Table 3: ROC Curve analysis results for the differentiation of COVID-19 patients from healthy individuals

Varaibles	Cut Off	AUC	95% CI	Sensitivity	Specificity	PPV	NPV	P
Microcytosis* (%)	>0.998	0.628	0.540 - 0.711	78.79	50.75	61.2	70.8	0.008
Macrocytosis *(%)	≤0.727	0.632	0.544 - 0.713	54.55	70.15	64.3	61.0	0.007
Hypochromia* (%)	≤0.797	0.608	0.519 - 0.691	71.21	52.24	59.5	64.8	0.031
Hyperchromia* %)	>0.066	0.595	0.506 - 0.679	72.73	49.25	58.5	64.7	0.058

* Median (IQR)

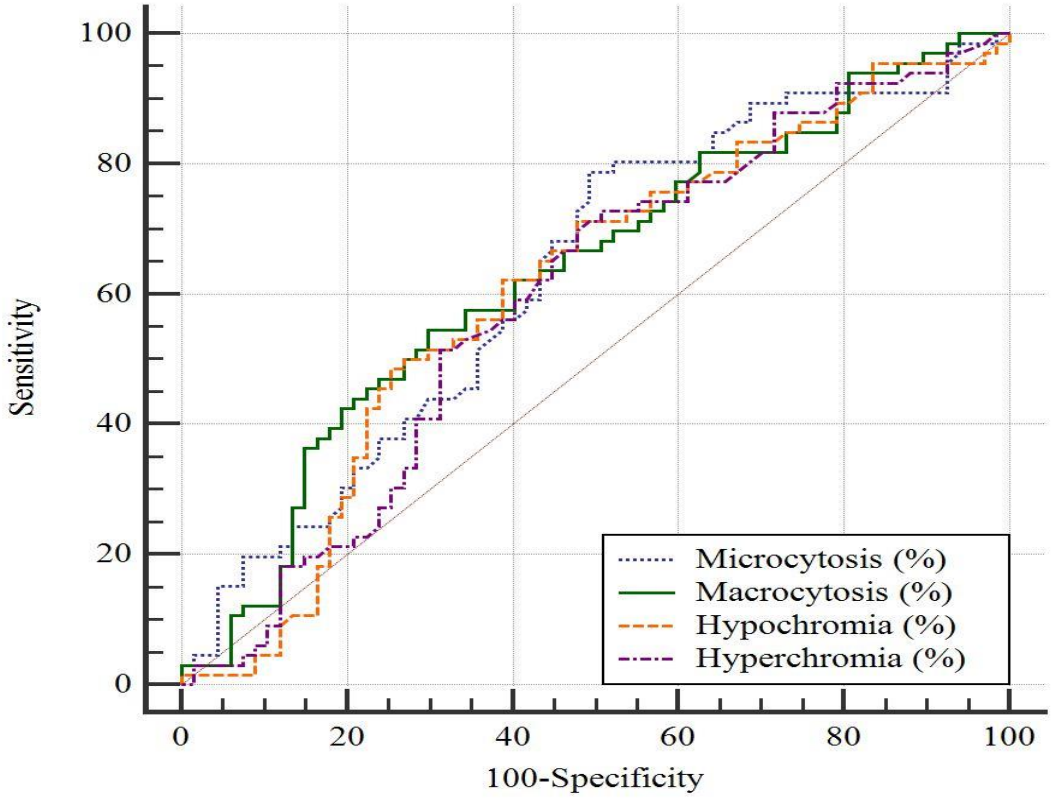

Figure 1: ROC curve analysis for the differentiation of COVID-19 patients from healthy control subjects

When the patients diagnosed with COVID-19 were separated into two groups as cases with and without infiltration on thorax CT, the age (p=0.001), WBC (p=0.043), glucose (p=0.008), urea (p=0.017), creatinine (p=0.010), and CRP (p<0.001) levels were determined to be significantly higher in the patients with infiltration on thorax CT, and the lymphocyte count was significantly lower (p=0.021). No significant difference was determined between the groups in respect of the erythrocyte morphological data (Table 4).

Table 4: Comparisons of the COVID-19 patients with and without infiltration on thorax CT

Thorax CT infiltration	Present	Absent	P
N (F/M)	35 (20/15)	31 (21/10)	0.264
Age (years)	48.00 (41-66)	32.00 (22-51)	0.001
Microcytosis* (%)	1.66 (1.04-2.17)	1.22 (0.88-2.78)	0.492
Macrocytosis *(%)	0.56 (0.29-1.46)	0.78 (0.35-1.71)	0.352
Hypochromia* (%)	0.58 (0.35-1.23)	0.46 (0.34-0.73)	0.225
Hyperchromia* (%)	0.11 (0.05-0.15)	0.12 (0.06-0.19)	0.581
White Blood Cell* (10e3/µL)	6.95 (5.82-9.23)	6.10 (5.05-7.53)	0.043
Neutrophil* (10e3/µL)	3.72 (2.19-4.67)	3.21 (2.05-4.34)	0.240
Lymphocyte* (10e3/µL)	1.36 (0.92-1.61)	1.66 (1.28-1.93)	0.021
Monocyte* (10e3/µL)	0.49 (0.40-0.75)	0.58 (0.46-0.67)	0.329
Hemoglobin* (g/dL)	13.70 (13.00-15.20)	13.90 (12.50-15.50)	0.729
Hematocrit* (%)	42.80 (40.20-46.70)	42.20 (38.50-48.40)	0.817
Mean Corpuscular Volume* (fL)	89.00 (85.80-91.90)	90.60 (86.30-93.80)	0.232
Mean Corpuscular Hemoglobin* (pg)	28.90 (27.90-29.60)	29.40 (28.30-30.50)	0.136
Mean Corpuscular Hemoglobin Concentration* (g/dL)	32.20 (31.80-32.70)	32.40 (32.10-32.90)	0.347
Red Blood Cell Distribution Width	12.80 (12.20-13.50)	12.40 (12.10-13.00)	0.234
Platelet* (10e3/µL)	223.00 (181.00-256.00)	241.00(198.00-275.00)	0.165
Mean Platelet Volume* (fL)	8.16 (7.59-8.91)	8.25 (7.64-8.83)	0.995
Platelet Distribution Width* (fL)	13.50 (13.00-13.80)	13.20 (12.70-13.60)	0.070
Glucose (mg/dl)	100.00 (88.00-120.00)	87.00 (80.00-97.00)	0.008
Urea (mg/dl)	27.82 (21.40-38.52)	23.54 (19.26-27.82)	0.017
Creatine (mg/dl)	0.83 (0.64-0.99)	0.62 (0.54-0.75)	0.010
C-Reactive Protein* (mg/dL)	1.73 (0.82-5.48)	0.60 (0.24-1.00)	0.001

* Median (IQR)

Discussion

The results of this study demonstrated that of the classic hematological parameters, the lymphocyte and platelet counts were significantly reduced in COVID-19-positive patients, and the CRP level was significantly increased. From the erythrocyte morphology findings determined with a new-generation device, the Microcytosis% was determined to be significantly increased in the COVID-19-positive patients, the Macrocytosis% and Hypochromia% were significantly reduced, and there was no significant difference between the patient and control groups in respect of the Hyperchromia%. The Microcytosis % was determined to have 78.79% sensitivity and 50.75% specificity in the differentiation of COVID-19 patients from healthy individuals. No significant difference was determined between the patients with and without infiltration on thorax CT in respect of the erythrocyte morphological findings.

Mean corpuscular volume (MCV) is defined as <80 fL (17). A small size of red blood cells is due to deficient hemoglobin production. The causes of microcytic anemia can be observed in vitamin B6 deficiency and in various diseases, including the absence of iron transmission to the group (iron deficiency anemia), the absence of the synthesis of α-globin or b-globin (thalassemia minor or major), limited iron transmission to the group (liver disease, chronic kidney disease, chronic inflammatory disease, tuberculosis, chronic inflammation) and defects in the synthesis of the hem group (sideroblastic anemias). It is also known that it may be related to race or causes of false positivity (hyponatremia, excessive EDTA) (18-22).

Pulmonary involvement of COVID-19 infection and the change in hematological parameters depends on the interaction between host cell receptors and proteases. The SARS-CoV-2 virus can enter into interaction with different molecules (furins, TMPRSS2, ACE2, cyclophils, hemoglobin) and erythrocyte receptors, and there has also been reported to be interaction with CD147 receptors in erythrocytes (23). Therefore, it has been claimed that COVID-19 could be evaluated as an oxygen deficient blood disease in addition to pneumonia. The SARS-CoV-2 virus binds to cell receptors using proteins and can enter cells by differentiating proteases and polypeptides. A compensatory increase in the number of erythrocyte receptors (CD147) associated with oxygen deficiency can cause more binding of the virus and a greater effect of the erythrocytes. There are

different and complex mechanisms affecting hematological parameters in COVID-19 patients. Impaired iron metabolism can be one type of process affected. There are known to be low hemoglobin levels and pathologically increased ferritin levels showing the presence of anemia in COVID-19 patients (9). The innate immune response can restrict the availability of iron during infections with deprivation from the pathogen, and this is a mechanism which can lead to anemia. Previous studies have reported a prevalence of iron deficiency of up to 59% in patients with heart failure who are not anemic. The iron status, independently of hemoglobin levels, has also been determined to be associated with a decrease in exercise capacity, diminished quality of life and death, and an increased risk of (re-) admission to hospital (24). Hematological abnormalites in COVID-19 patients are generally thought to occur because of iron deficiency, hypoxia, and inflammation.

Berzuini et al. evaluated the erythrocyte morphological appearance of peripheral blood smears of 20 patients with anemia who required blood transfusion, and the blood smears were determinedwith RBC shape abnormality (spherocyte and schistocyte), consistent with hemolytic mechanisms (13). These show that hematological changes in COVID-19 patients are a complex event occurring with the activation of many different mechanisms. The fact that there was no change in the hemoglobin levels in the patient and healthy control groups in the current study, and that there was an increase in the microcytosis level in patients without anemia could probably be due to the onset of a change in erythrocyte morphology because of the cellular response given before anemia develops.

Although the microcytosis level shows an increase in COVID-19 patients, the sensitivity and specificity have been determined to be very low for diagnostic use. In addition, the fact that there was no difference between patients with and without pulmonary infiltration in repect of erythrocyte morphology, suggests that these changes that occur could be related more to receptor interaction than to hypoxia.

Study Limitations

The primary limitation of this study is that it was conducted in a single centre. Another limitation could be said to be that no advanced laboratory tests were made to determine the reasons for the Microcytosis (%), Macrocytosis (%), Hypochromia (%), and Hyperchromia (%) values of the patients determined on new-generation devices. Nevertheless, it can be considered that this preliminary study will be of guidance for future prospective studies.

Conclusion

From the erythrocyte morphological findings determined with the new-generation devices, the Microcytosis percentage was determined to be significantly increased in COVID-19-positive patients, and this parameter was found to have 78.79% sensitivity and 50.75% specificity in the differentiation of COVID-19 patients from healthy individuals.

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***Ethical Approval**: Ethical approval was taken from the Bursa Uludag University, Faculty of Medicine, Clinical Research Ethics Committee (Date 17 August 2020; Number: HRU/20.14.18). We conducted this study according to the principles of the Declaration of Helsinki. Informed consent was obtained from all the participants.*

***Author Contributions:** Concept:İHY. Literature Review:İHY,MY. Design: ESŞ,AÖ. Data acquisition:İHY,AÖ. Analysis and interpretation: MY, ESŞ. Writing manuscript:İHY,MY. Critical revision of manuscript:ESŞ,AÖ.*

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