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The Effect of SARS-COV-2 Infection on the Hematological Markers

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ABSTRACT

Background and Aim: The novel coronavirus 2019 can lead to a vast range of respiratory complications, from mild to severe, driving to acute respiratory distress syndrome (ARDS). Common symptoms of COVID-19 include fever, fatigue, and dry cough, which can lead to complications, such as gastrointestinal disorders, and liver, cardiac, and renal dysfunctions. Alteration in the hematological markers is one of the COVID-19 diseases evaluated by our study.

Materials and Methods: In this study, hematological markers, including the levels of ESR, BS, Hb, HCT, MCV, MCH, MCHC, platelet, WBC, RBC, neutrophil, and lymphocyte, have been assessed and compared in both case and control groups. Furthermore, we assessed the associations between hematological parameters, clinical manifestations, and underlying medical conditions.

Results: Our data showed that RBC, HCT, and ESR were significantly associated with the novel coronavirus 2019 infection according to the disease progression. ESR (P= 0.022), Hb (P= 0.032), and BS (P= 0.01) levels in male people infected by SARS-CoV-2 proved to have a significant relationship with the control group. Moreover, BS, Hb, HCT, ESR, and neutrophil showed significant variations in diabetic individuals suffering from SARS-CoV-2 infection.

Conclusion: The dropping of the hematological markers in COVID-19 is linked with a noticeably increased mortality rate, while high neutrophil and BS levels are related to aggravation of the disease. Monitoring the hematological markers can contribute significantly to selecting the proper treatment and hamper of disease worsening.

Keywords: COVID-19, SARS-CoV-2, Hematological, Marker

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1. Introduction

In December 2019, a group of people was diagnosed with pneumonia of unknown origin in Wuhan, China. Currently, the disease is known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and caused hospitalization and death to the life of millions throughout the world **(1, 2)**. Most of the people infected by SARS-CoV-2 demonstrate no severe symptoms and suffer from mild clinical manifestations. At the same time in some patients, it can drive to life-threatening complications such as acute respiratory failure, septic shock, and dysfunction in multiple organs **(3, 4)**.

During the initial stages of coronavirus disease 2019 (COVID-19), when the symptoms are nonspecific, the number of leukocytes and lymphocytes in peripheral blood is normal or slightly declined. After the viremia and increasing complications, substantial leukopenia and lymphopenia will occur **(5, 6)**. SARS-CoV-2 can infect T lymphocytes through the interaction with CD147 and promotes the dysfunction of these cells **(7, 8)**. Lymphopenia is more frequent in deceased patients compared with survived ones **(9)**. Moreover, cytokine storm can be distinguished due to the elevation of interleukin levels, particularly IL-2, IL-6, IL-7, MCP-1, MIP1-a, and TNFα, which might drive to apoptosis of lymphocytes **(10-12)**. The inflammatory responses affect the respiratory system, ultimately followed by respiratory distress **(13, 14)**.

A decline in Hb count and a significant increase of the levels of serum ferritin, albumin, ESR, CRP and LDH are seen in many COVID-19 patients. These studies confirm that concurrent with diminishing the Hb levels, the levels of iron ions face an increase leading to the accumulation of iron and, ultimately, inflammation in multiple organs **(15-17)**.

One of the hematological parameters associating with COVID-19 is platelet count, which can give us prognostic information regarding a patient's condition. Thrombocytopenia has been reported in 55% of COVID-19 patients during the acute respiratory syndrome (SARS) outbreak and was detected as a huge risk factor for mortality **(18, 19)**.

As suffering from COVID-19 can affect hematological parameters, monitoring and analyzing these factors can contribute substantially to more sufficient therapies. The current study aims to assess the hematological parameters, including the levels of ESR, BS, Hb and HCT, MCV, MCH, MCHC, WBC, RBC, platelet, neutrophil, and lymphocyte in COVID-19 patients and compare them with healthy cases. Given the significance of them in human health and their vast roles in causing health disorders, monitoring these factors can lead to a better understanding of patient conditions and more efficient treatments.

2. Materials and Methods

Subjects and Methods

Our study population comprises 200 individuals from the Shohadaye Ashayer Hospital of Khorramabad, Iran, between 20 March 2021 and 20 June 2021 who underwent laboratory tests and CT scans for COVID-19 diagnostic purposes. Ultimately, 100 individuals owning negative COVID-19 tests (control group) and 100 confirmed COVID-19 inpatients (case group) were chosen randomly and compared concerning the hematological profile. The risk factors of smoking, drug use, chronic blood and lung diseases, and asthma were investigated in two groups, which none of the people had a history of them.

After receiving the informed consent from all participants (Ethic code: IR.LUMS.REC.1399.332), we collected 5 mL venous blood for EDTA-containing tubes and 5 mL without EDTA. Then, blood samples containing EDTA were utilized for the ESR test by the Westergren method and blood cell count by a Sysmex cell counter. The serum isolated from the EDTA-free blood sample was employed to measure the BS by blood sugar test kit (Man Company, Iran) and the AutoAnalyzer.

The COVID-19 positive cases were diagnosed using qRT-PCR method (Sansure Nucleic Acid Diagnostic Kit).

Statistical Analysis

The collected data were analyzed using SPSS 26 (SPSS Inc., Chicago, Ill., USA) and the descriptive data are presented for nominal and quantitative data. The Chi-squared and Fisher's exact tests were used to analyze the nominal data. All the quantitative data was primarily analyzed for the normal distribution using the Kolmogorov-Smirnov normality test. The independent t-test was used for quantitative data with normal distribution, and P values under 0.05 were considered statistically significant.

3. Results

In our study, 107 individuals were males creating 53.5% of the total (46 individuals were diagnosed with SARS-CoV-2, and 61 were negative). The median age of infected and healthy men was 54.33 and 49.61, respectively. During the current study, 93 individuals were female, comprising 46.5% of the total (54 individuals were diagnosed with SARS-CoV-2, and 39 individuals were negative). The median age of infected and healthy women was 56.11 and 54.77, respectively.

The clinical manifestations such as fever, cough, muscle aches, diminished level of consciousness, headache, dizziness, abdominal pain, and diarrhea were compared the control and case groups (Table 1).

Table 1. Clinical manifestations of the control and case groups.

Clinical manifestations		Groups		P-value*
		Control n(%)	Case n(%)	
Fever	No	100(100)	51(51)	<0.001
	Yes	0(0.00)	49(49)	
Cough	No	100(100)	51(51)	<0.001
	Yes	0(0.00)	49(49)	
Muscle pain	No	100(100)	74(74)	<0.001
	Yes	0(0.00)	26(26)	
Diminished level of consciousness	No	100(100)	97(97)	0.246
	Yes	0(0.00)	3(3)	
Headache	No	100(100)	98(98)	0.497
	Yes	0(0.00)	2(2)	
Dizziness	No	100(100)	99(99)	1.000
	Yes	0(0.00)	1(1)	
Abdominal pain	No	100(100)	99(99)	1.000
	Yes	0(0.00)	1(1)	
Diarrhea	No	100(100)	99(99)	1.000
	Yes	0(0.00)	1(1)	

* Fisher Exact Test

According to Table 1, there is a significant difference between the clinical manifestations, including fever (P<0.001), cough (P<0.001), and muscle pain (P<0.001) of patients and healthy individuals. There is a diminished level of consciousness (3 cases), headache (2 cases), dizziness (1 case), abdominal pain (1 case), and diarrhea (1 case) in the patient's group. In contrast, none of them was observed in the control group. Moreover, we found that neither participant in both group showed anosmia, dysgeusia, convulsions, limb paralysis, dermal lesion, nausea, vomiting, and anorexia.

Hematological parameters and their comparisons between both groups are indicated in Table 2.

Table 2. Hematological parameters of the control and case groups.

Variables	Group	N	Mean	SD	P value*
ESR	Control	61	26.16	21.576	0.003
	Case	73	37.75	25.022	
BS	Control	65	131.66	81.322	0.4
	Case	64	126.06	62.756	
WBC	Control	99	8.624	8.7085	0.393
	Case	98	7.772	4.3896	
RBC	Control	99	4.709	.8748	0.026
	Case	98	4.455	.7001	
Hb	Control	99	14.265	2.9957	0.060
	Case	98	13.577	2.0016	
HCT	Control	99	40.470	6.9397	0.017
	Case	98	38.321	5.5032	

Variables	Group	N	Mean	SD	P value*
MCV	Control	99	86.479	6.8003	0.956
	Case	98	86.433	4.7087	
MCH	Control	99	30.607	3.0451	0.825
	Case	98	30.521	2.3233	
MCHC	Control	99	35.387	2.0143	0.847
	Case	98	35.333	1.9249	
Platelet	Control	99	208.11	78.685	0.302
	Case	98	196.19	82.887	
Neutrophil	Control	97	62.51	24.094	0.154
	Case	98	67.28	22.389	
Lymphocytes	Control	97	24.52	12.450	0.188
	Case	98	22.05	13.586	

* Independent t-test.

According to Table 2, infection with SARS-CoV-2 demonstrates a significant correlation with ESR (*P*=0.003), RBC (*P*=0.026), and HCT (*P*=0.017) levels. Furthermore, the Hb level in the case group was decreased compared to the control group, although the difference was not significant (*P*>0.05).

Hematological parameters in the case and control groups are presented in Figures 1 and 2.

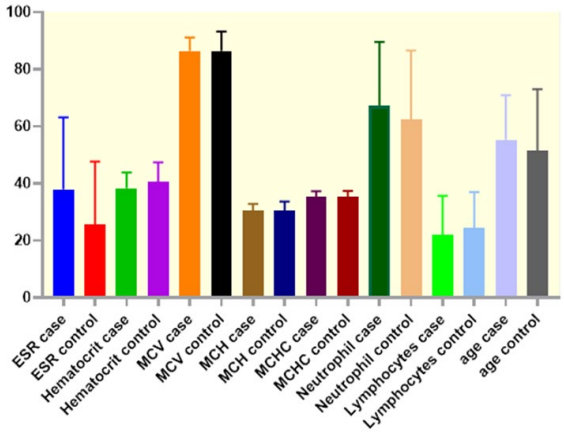

Figure 1. ESR, HCT, MCV, MCH, MCHC, Neutrophi, and Lymphocytes counts in the case and control groups.

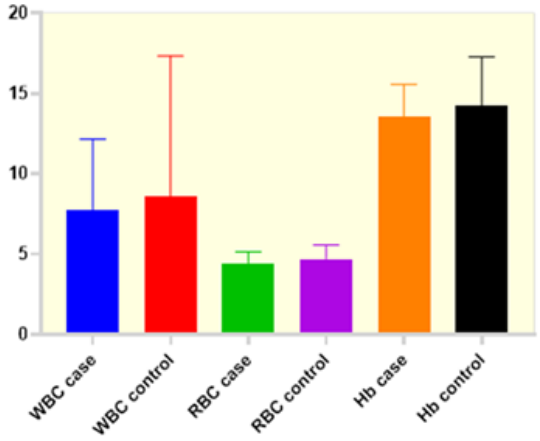

Figure 2. WBC, RBC and Hb counts in the case and control groups.

Hematological parameters and their comparisons between females and males belonging to the case and control groups are demonstrated in Table 3.

According to Table 3, there is a significant correlation between the infection with SARS-CoV-2 and the levels of ESR (P=0.022), BS (P=0.010), and Hb (P=0.032) in male patients. Unlike the total comparison (Table 2), there was no significant correlation between RBC levels with genders (P>0.05). Furthermore, we found no significant correlation between infection with SARS-CoV-2 and gender of the patients.

Table 3. Hematological parameters of female and male participants.

		Female				Male			
ESR	Control	24	26.83	22.327	0.066	37	25.73	21.376	0.022
	Case	34	37.32	25.205		39	38.13	25.184	
BS	Control	26	126.92	106.443	0.211	39	134.82	60.485	0.010
	Case	37	142.73	76.985		27	103.22	19.989	
WBC	Control	39	7.738	4.3031	0.504	60	9.200	10.6388	0.841

		Female				Male			
RBC	Case	53	7.285	3.7502	0.273	45	8.347	5.0234	0.146
	Control	39	4.515	.8978		60	4.835	.8433	
Hb	Case	53	4.328	.6500	0.745	45	4.604	.7342	0.032
	Control	39	13.026	2.9415		60	15.070	2.7676	
Hematocrit	Case	53	13.204	1.9856	0.457	45	14.016	1.9515	0.050
	Control	39	38.354	6.7886		60	41.845	6.7401	
MCV	Case	53	37.406	5.3931	0.287	45	39.400	5.4946	0.294
	Control	39	85.700	7.1675		60	86.985	6.5622	
MCH	Case	53	87.008	4.5169	0.105	45	85.756	4.8888	0.142
	Control	39	29.597	3.1452		60	31.263	2.8141	
MCHC	Case	53	30.528	2.3049	0.174	45	30.513	2.3708	0.396
	Control	39	34.556	1.9125		60	35.927	1.9056	
Platelet	Case	53	35.104	1.8829	0.590	45	35.602	1.9599	0.405
	Control	39	204.97	82.296		60	210.15	76.883	
Neutrophil	Case	53	196.13	73.870	0.393	45	196.27	93.258	0.055
	Control	38	57.95	25.780		59	65.44	22.684	
Lymphocytes	Case	53	62.72	26.439	0.085	45	72.64	14.982	0.580
	Control	38	27.55	11.505		59	22.56	12.735	
	Case	53	22.85	13.501		45	21.11	13.778	

Table 4. A comparison between the hematological parameters in diabetic patients afflicted by COVID-19.

Variables	Diabetes	N	Mean	SD	P value
ESR	Yes	8	65.25	24.973	0.001
	No	65	34.37	23.021	
BS	Yes	5	194.40	104.598	0.010
	No	59	120.27	55.557	
WBC	Yes	10	9.360	4.7331	0.229
	No	88	7.592	4.3409	
RBC	Yes	10	4.050	.8462	0.053
	No	88	4.501	.6718	
Hb	Yes	10	12.280	2.5041	0.030
	No	88	13.724	1.8982	
Hematocrit	Yes	10	34.980	6.6476	0.042
	No	88	38.701	5.2693	
MCV	Yes	10	86.680	5.1346	0.862
	No	88	86.405	4.6888	
MCH	Yes	10	30.300	1.5506	0.752
	No	88	30.547	2.4006	
MCHC	Yes	10	35.010	1.6003	0.579
	No	88	35.369	1.9629	
Platelet	Yes	10	224.40	101.996	0.258
	No	88	192.99	80.511	
Neutrophil	Yes	10	80.50	10.845	0.048
	No	88	65.77	22.898	
Lymphocytes	Yes	10	15.20	10.337	0.093
	No	88	22.83	13.738	

According to Table 4, such parameters, including ESR levels (*P*=0.001), BS (*P*=0.010), Hb (*P*=0.030), HCT (*P*=0.042), and neutrophil (*P*=0.048), demonstrate a significant correlation with SARS-CoV-2 infection in diabetic patients. Moreover, lymphocyte levels face a substantial decline, but no significant correlation exists (*P*=0.093).

There was a significant correlation between RBC values (*P*=0.025), Hb (*P*=0.005), HCT (*P*=0.020), and the requirement to the intubation. Patients requiring intubation experienced lower levels of all mentioned hematological characteristics. Lymphocyte level indicated no significant correlation, although it was diminished dramatically in patients requiring intubation (9%).

Moreover, our data analysis indicated a significant correlation of BS (P=0.021) with respiratory distress in COVID-19 patients (comprising 52% of total cases). The levels of lymphocyte and platelet were slightly lower in patients affected by respiratory distress, although differences were not significant (p>0.05). Furthermore, neutrophil levels faced a slight increase in these patients (70.81 vs. 63.28%).

4. Discussion

According to previous studies, clinical manifestations of COVID-19 patients mainly comprise fever, dry cough, and fatigue **(20-22)**. During the current study, we have recorded these clinical manifestations frequently in the patients affected by SARS-CoV-2. Moreover, other clinical presentations, such as diminished levels of consciousness, headache, dizziness, abdominal pain, diarrhea, anosmia, dysgeusia, convulsions, limb paralysis, dermal lesion, nausea, vomiting, and anorexia, have been analyzed in both the control and COVID-19 affected patients. Our results indicated no significant correlation between the clinical manifestations of these two groups. Although, by worsening the disease, some of these clinical manifestations, including diminished levels of consciousness, headache, dizziness, abdominal pain, and diarrhea, have been experienced in some patients. The severity of these manifestations indicates a correlation with the severity of the disease. In this study, we observed that the dominant strains of virus are alpha (B.1.1.7) variants. Also, we conducted a study and compared the laboratory findings and clinical manifestations of patients affected by the SARS-CoV-2 and healthy participants.

A slight WBC decline was observed in the case group, but it led to no significant correlation. However, augmenting the severity of the disease led to a further drop in the WBC level. In respect of this drop, encountering some viruses, including SARS-CoV, MERS-CoV, and SARS-CoV-2, can result in lymphopenia due to the active roles of lymphocytes against the viruses **(23-25)**. The results acquired from the autopsy of the patients afflicted by the SARS-CoV-2 illustrated the necrosis of lymphatic tissues (including spleen and lymph nodes) and diminished bone marrow hematopoiesis levels **(26)**. We found that patients with less WBC decline own a greater chance of recovery. Previous studies have elucidated that deceased patients have experienced more significant lymphopenia than surviving ones **(20)**, and the ratio of lymphocyte/WBCs of patients afflicted by severe COVID-19 demonstrates a decline compared to recovered patients **(27, 28)**. Also, the increase of lymphocytes has been reported seven days after the outset of symptoms in recovered individuals, contrary to deceased ones **(29)**. Therefore, constant monitoring of lymphocyte counts may play a substantial role as an influential prognostic factor for the disease outcomes. A model based on lymphocyte counts has been proposed by Tan et al. whereby patients owning less than 20% and 5% lymphocyte during 10-12 days and 17-19 days of symptoms outset, respectively, demonstrate the worst prognosis **(30)**.

According to the study conducted by Guan et al. concerning the clinical presentations of 1099 COVID-19 patients, approximately 83% of patients were diagnosed with lymphocytopenia, 36.2% with thrombocytopenia, and 33.7% with leukopenia. These percentages reach 96.1%, 57.7%, and 61.1%, respectively in patients experiencing severe clinical presentations **(21)**.

It has been revealed that the risk of ARDS is directly correlated with increased and diminished counts of neutrophils and lymphocytes, respectively, and expanding the number of neutrophils is associated with an increased mortality rate **(9)**. In the current study, despite no significant correlation between neutrophil and lymphocyte percentage in the patients experiencing ARDS compared to those without ARDS, the lower median of lymphocytes in ARDS-affected individuals (20.44) compared with individuals without this clinical manifestation (23.87) was recorded. Furthermore, the median of neutrophils was increased in ARDS-affected individuals (70.81) compared to those suffering from no ARDS (63.28). We have recorded no significant correlation between respiratory distress and platelet. However, the median was lower in patients suffering from respiratory distress (184.85 vs. 209.02). Therefore, the current study confirms that the levels of disease severity correlate with diminished levels of platelet and lymphocyte and the expanded number of neutrophils. In our study, ARDS was significantly correlated with BS levels in COVID-19 patients. Other

studies confirm lymphocytopenia and mild thrombocytopenia in 69 and 20% of COVID-19 patients, respectively **(31, 32)**.

Fan et al. have discovered that lymphocyte count was dramatically diminished in patients requiring intensive care unit (ICU) support at baseline **(31)**. In another study comprising 52 patients suffering from severe COVID-19 in Wuhan, lymphopenia was reported in 85% of patients **(33)**. During the current study, patients requiring intubation and ICU admission experienced declined levels of lymphocyte. However, there was not a significant correlation in comparison with patients who did not need intubation. The mean lymphocyte level was 9.00 and 22.46 in intubated and non-intubated individuals, respectively. Also, there was no significant correlation between the neutrophil level and intubation. We have found a significant correlation between intubation and the levels of RBC, BS, Hb, and HCT; except BS, which faced a significant increase, other mentioned hematological parameters have declined in individuals who underwent intubation.

In the current study, a significant correlation was detected between the presence of diabetes in COVID-19 patients and the levels of ESR, BS, Hb, neutrophil, and HCT. Diabetes can elevate the risk of infection and mortality in acute infections. Previous studies have revealed that the possibility of developing severe COVID-19 in diabetic patients ranges between 14 and 32% **(9, 20, 21, 34-37)**. A study of 138 COVID-19 patients conducted by Wang et al. has illustrated that 72% of diabetic patients required ICU admission **(20)**. During the current study, diabetic patients experienced a severe type of disease and required ICU admission.

The expression of ACE2 on the cells of pancreatic islets attracts the SARS-CoV-1 virus and raises the BS in nondiabetic individuals **(38)**. Thus SARS-CoV-2 may also infect these cells since it has similar receptors as SARS-CoV-1 and drives to the disruption and increase of BS regulation.

5. Conclusion

The infection by COVID-19 would be followed by diverse clinical manifestations, including fever, cough, fatigue, muscle aches, diarrhea, vomiting, and others. However, these clinical manifestations will not be detected in all patients. Profound changes in hematological parameters are detectable, which would be augmented by COVID-19 progress. Drastic decreases of hematological parameters such as lymphocyte, RBC, WBC, platelet, Hb, and HCT elevate the mortality rate substantially. In contrast, the increased levels of neutrophil and BS are associated with the severity of the disease. Diabetes, the required intubation, and respiratory manifestations such as ARDS are correlated with vast alterations of some hematological parameters. Assessing of underlying medical conditions, clinical manifestations, and hematological parameters can significantly select the right and sufficient therapeutic directions at the disease's outset. During their treatment, they can also enhance the current therapeutic methods and be employed as a valuable prognostic factor of patient condition.

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Ethics Approval

This study was accepted by the ethical committee of the Lorestan University of Medical Sciences, and written informed consent was obtained from all subjects (Ethic code: IR.LUMS.REC.1399.332).

Authors' Contribution

Conception and design: Mehdi Ajorloo; data collection: Seyed Majid Fatahi, Annahita Ghalandarian; statistical analyses: Rasool Mohammadi, Sayyad Khanizadeh; writing of manuscript: Seyed Majid Fatahi, Ali Safarzadeh, Ashkan Alamdary, Hadi Razavi Nikoo; revising the article for important intellectual content; and final approval: all authors

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Conflict of Interest

The authors declare that they have no competing interests.

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