Original Article

The hematological changes in COVID-19 patients; its relations to outcome in a retrospective study in Makkah city

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ABSTRACT

Purpose: To detect the frequency of hematological changes in Covid-19 patients at king Abdul Aziz hospital, Makkah, Saudi Arabia; to compare the outcome of patients with or without hematological changes.

Methods: This retrospective study included 537 patients. They were 0.6% asymptomatic, 22.9% mild to moderate, 31.1% severe, and 45.4% critical. According to the hematological results, patients were divided into normal, high, and low groups.

Results: Anemia was found in 50.9%, 26%, 21.4%, and 1.7% of critical, mild to moderate, severe, and asymptomatic cases, respectively. Polycythemia was detected in 16.7% and 83.3% of mild to moderate and critical cases, respectively. Thrombocytopenia was found in 44.4%, 30%, 25.6% of critical, mild to moderate and severe cases, respectively. Neutropenia was found in 40.9%, 36.4%, and 22.7% of critical, mild to moderate and severe cases. Neutrophilia was found in 58.2%, 24.1%, and 17.7% of critical, severe, and mild to moderate cases. Lymphopenia was found in 51%, 29.3%, 19.4%, and .3%. of critical, severe, mild to moderate and asymptomatic patients. Monocytopenia was found in 55%, 30%, and 15% of critical, severe, and mild to moderate cases, respectively. Monocytosis was found in 59.3%, 25.4%, and 15.3% of critical, mild to moderate, and severe cases. The risk of death was 15.2, 2.4, 2.6, 1.9, 2.9, 2.1, 2.1 times higher in those with polycythemia, neutrophilia, monocytosis, lymphopenia, monocytopenia, diabetes, and age over 65, respectively.

Conclusion: Neutrophilia, monocytosis, lymphopenia, monocytopenia, and polycythemia, diabetic patients, and age over 65 are independent predictors for death.

Keyword: Covid-19, Neutrophilia, lymphopenia, monocytopenia, Makkah city.

Introduction

Coronavirus is a zoonotic RNA virus that can spread between animals and humans. Seven coronaviruses can infect humans, 4 of which are common pathogens of human colds, which do not cause serious illness. The remaining three coronaviruses are the severe acute respiratory syndrome coronavirus, the Middle East respiratory syndrome coronavirus, and the novel Coronavirus (SARS-COV-2), also known as COVID-19, cause severe disease to the human being. The COVID-19 was broke out in Wuhan, China, in December 2019 [1]. Then, it spreads worldwide, with 136 million confirmed cases and 2.94 million deaths [2]. The main manifestations of COVID-19 are fever,

Access this article online	
Quick Response Code:	Website: www.smh-j.com
	DOI: 10.54293/smhj.v2i2.27

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Received: 18 December 2021 | **Accepted:** 26 April 2022

Please cite this article as: moustafa AZ, S. Aldosari M, Mawlawi H, AL-Bukhari T, Reda H, Albuloshi M, Hammadallah Y, Alharbi A, A. Allohibi Y, Alzahrani F, A. Khogeer A, Al-Kulaity H, Beheiry H. The hematological changes in COVID-19 patients; its relations to outcome in a retrospective study in Makkah city: Hematological changes in COVID-19 patients and their outcome. SMHJ [Internet]. 2022;2(2):33-48. Available from: https://www.smh-j.com/smhj/article/view/27

SMHJ
Saudi Medical Horizons Journal

Dry cough, and fatigue. Severely affected patients have dyspnea and hypoxemia one week after the onset of symptoms. They may develop acute respiratory distress syndrome, septic shock, metabolic acidosis, coagulation dysfunction, and multiple organ failure [3-5]. COVID-19 primarily affects the tissues expressing high ACE2 receptors (angiotensin-converting enzyme 2), including the lungs, heart, gastrointestinal tract, lymphocytes, kidney, and adipose tissue [6]. COVID-19 has effects on the hematopoietic system. Leucopenia, lymphopenia, neutrophilia, and thrombocytopenia are found in COVID-19 patients. They were more prominent among severe cases. The lymphopenia was related to the severity of COVID-19 patients. It could use to predict the severity and prognosis of patients [7-8]. In Saudi Arabia, the coronavirus cases were 399,277, of which 6,765 (1.7%) were dead, and 384,027 were recovered cases [9]. This study aimed to detect the frequency of hematological changes in COVID-19 patients and determine its relation to the severity and outcome of the disease.

Methods

A retrospective cohort study was conducted from November 2020 to August 2021 at King Abdul Aziz Hospital, Makkah, Saudi Arabia. The institutional review board (IRB) of Makkah research approved the protocol of this study, and the approval number was H-02-K-016-0820-331. We collected the data from the laboratory and medical records of King Abdul Aziz Hospital from September 2020 to December 2020. This study includes 537 hospitalized COVID-19 patients. They were classified clinically into asymptomatic 3 (0.6%), mild to moderate 123 (22.9%), severe 167 (31.3%), and critical 244 (45.4%). We have done a longitudinal follow-up of patients at admission, one week after admission, and at discharge (either living or death). The patients were divided into three groups according to the hematological values (normal, high, and low). Inclusion criteria: both genders, any age, positive COVID-19 by PCR. Exclusion criteria: Patients with negative COVID-19

All the following data were collected from the patients: -

1- Demographic and clinical data include age, sex, nationality, weight, height, body mass index, and history of hypertension or diabetes.

2- Complete blood count (CBC). The CBC was measured on Sysmex XT-2000 (Siemens diagnostic Germany).

3- Biochemical markers were measured on Architect c 4000 clinical chemistry analyzer Abbott core laboratory.

4- The C reactive protein (CRP) and ferritin. The ferritin and CRP were measured by Cobas Integra 6000 analyzers and crescent diagnostics kit, K.S.A respectively.

5- Duration of staying at the hospital from admission to discharge.

6- Status of the patients at discharge, either living or death.

Statistical analysis

The statistical analysis of this study used the SPSS program version 20. The comparison between groups for the quantitative data was performed using the Student t-test, the Mann–Whitney U test, and Friedman test according to the data distribution, the number of groups, and dependent or independent sample. The chi-square test, or the Fisher exact test, and the relative risk ratio of death were used for the qualitative data. The Bivariate logistic regression model was conducted to determine the independent predictor factors for death. A two-sided p-value ≤ 0.05 was considered to represent a statistically significant difference.

Results

The results of this study were summarized from table 1 to 8. The demographic and clinical data of the patients were summarized in (Table 1). The frequency of the hematological changes at admission (Table 2). The patients were divided into groups normal, high, and low according to the variations of the hematological parameters. 63.8% had normal white blood cell count (WBC), 30.2% had high, and 6% had low count. 71.4% of males had normal hemoglobin, 1.3% had high, and 27.2% had low hemoglobin. 55.3% of females had normal hemoglobin, 0.6% had high, and 44% had low hemoglobin. The platelet count was normal in 75.6% of patients, increased in 7.6%, and low in 16.8%. The absolute neutrophil count (ANC) was normal in 48.9% of patients, elevated in 46.4% and low in 4.6%. The absolute lymphocyte count (ALC) was normal in 37% of patients, elevated in 0.8% and low in 62.2%. The absolute monocyte count (AMC) was normal in 83.3%, high in 12.5%, and low in 4.2%. The absolute eosinophil count (AEC) was normal in 99.2% and high in 0.8%. The absolute basophil count (ABC) was normal in 89.2% and high in 10.8%. The associations between hematological parameters and severity of disease at admission (Table 3). The frequency of normal WBC was 24.8%, 35%, 39.4%, and 0.9% in mild to moderate, severe, critical, and asymptomatic cases. The frequency of leukocytosis was 16%, 22.2%, 61.7%, and .0% in mild to moderate, severe, critical, and asymptomatic, respectively. The frequency of leukopenia was 37.5%, 34.3%, 28.1%, and 0% in mild to moderate, severe, critical, and asymptomatic. The frequency of normal hemoglobin was 21.5%, 36.3%, 42.2%, and 0% in mild to moderate, severe, critical, and asymptomatic. The frequency of polycythemia was 16.7%, 0%,

83.3%, and 0% in mild to moderate, severe, critical, and asymptomatic, respectively. The frequency of anemia was 26%, 21.4%, 50.9%, and 1.7% in mild to moderate, severe, critical, and asymptomatic, respectively. The frequency of normal platelets was 21.2%, 32%, 46.3%, and 0.5% in mild to moderate, severe, critical, and asymptomatic. The frequency of thrombocytosis was 24.4%, 34.1%, 39%, and 2.4% in mild to moderate, severe, critical, and asymptomatic, respectively. The frequency of thrombocytopenia was 30%, 25.6%, 44.4%, and 0% in mild to moderate, severe, critical, and asymptomatic, respectively. The frequency of normal ANC was 25%, 36.2%, 37.5%, and 1.3% in mild to moderate, severe, critical, and asymptomatic. The neutrophilia frequency was 17.7%, 24.1%, and 58.2% in mild to moderate, severe, and critical. In mild to moderate, severe, and critical cases, the frequency of neutropenia was 36.4%, 22.7%, and 40.9%. The frequency of normal lymphocyte count was 25.3%, 31%, 43.1%, and 0.6% in mild to moderate, severe, critical, and asymptomatic. The frequency of lymphocytosis was 100% in mild to moderate cases. The frequency of lymphopenia was 19.4%, 29.3%, 51%, and 0.3% in mild to moderate, severe, critical, and asymptomatic. The frequency of normal monocyte count was 22.3%, 31.5%, 45.4%, and 0.8% in mild to moderate, severe, critical, and asymptomatic. The frequency of monocytosis was 25.4%, 15.3%, and 59.3% in mild to moderate, severe, and critical. The frequency of normal eosinophil count was 21.7%, 29.9%, 48%, and 0.4% in mild to moderate, severe, critical, and asymptomatic. The frequency of eosinophilia was 50%, 0%, 25%, and 25% in mild to moderate, severe, critical, and asymptomatic. The frequency of normal basophil count was 21.6%, 30.6%, 47.2%, and 0.7% in mild to moderate, severe, critical, and asymptomatic. The frequency of basophilia was 25.5%, 21.6%, and 52.9% in mild to moderate, severe, and critical. The frequency of combined leukocytosis, neutrophilia, and lymphopenia was present in 14.3%, 20.9%, and 65.7% in mild to moderate, severe, and critical. The frequency of combined leukocytosis, neutrophilia, lymphopenia, and thrombocytopenia was present in 14.3% and 85.7% of severe and critical cases. The outcome of patients (Table 4-5): Out of 537 hospitalized patients, 67% were survivors, and 33% were non-survivor. The fatality rate of death was 0.8%, 0.6%, 71.7%, and 0% in mild to moderate, severe, critical, and asymptomatic cases, respectively. The percentage of death was 23.8%, 33.6% and 43.2% for those < 40 years, >40≤ 65 y and > 65 respectively $p<0.05$. 30.4% of males were dead versus 39% of females, with no significant difference $p>0.05$. 43.5 % of hypertensive patients have died versus 28.7% without hypertension $p<0.05$. 43.1 % of diabetic patients have died versus 27.5% without diabetes mellitus $p<0.05$. 43.3 % of obese patients died versus 30.9% non - obese $p<0.05$. For those with normal, high, and low white blood cell count, the percentage of death was 26%, 50%, and 25%, respectively, with a significant difference between the high and normal group $p<0.05$. For males with normal, high, and low hemoglobin concentration, the percentage of death was 27.8%, 80%, and 35%, respectively, with a significant difference between the high and normal group $p<0.05$. For females with normal, high, and low hemoglobin concentration, the percentage of death was 35.2%, 100%, and 42.9%, respectively, with no significant difference. For those with normal, high, and low platelets count, the percentage of death was 32.3%, 31.7%, and 36.7%, respectively, with no significant difference. For those with a normal, high, and low absolute neutrophil count, the percentage of death was 24.6%, 45.0%, and 27.3%, respectively, with a significant difference between the high and normal groups. For those with normal, high, and low absolute lymphocytes count, the percentage of death was 28.2%, 20%%, and 38.8%, with a significant difference between normal and low. For those with normal, high, and low absolute monocyte count, the percentage of death was 32.1%, 52.5%, and 55%, with a significant difference between normal and each of low and high $p<0.05$. For those with normal and high absolute eosinophils and basophil count, the percentage of death was 34.8%, versus 25% and 34.1% versus 41.2%, respectively, with no significant difference $p>0.05$. For those with leukocytosis, neutrophilia, and lymphopenia, the percentage of death was 55.2 % versus 29.8% for those without this combination. For those with leukocytosis, neutrophilia, lymphopenia, and thrombocytopenia, the death rate was 85.7 % versus 32.3% for those without this combination. There was a significant difference in both combinations. The relative risk of death using demographic, clinical data, and patient hematological parameters (Tables 4-5). The relative risk (RR) of death was significantly higher in those with hypertension, diabetes, combined hypertension, and diabetes, aged > 40 years, and obese patients when compared to those without disease and aged < 40 years $p<0.05$. The RR of death was 1.5, 1.6, 1.5, 0.7, and 0.7, respectively. The RR of death was 105 times in the critical group versus the combination of other groups, (Table 4). The RR of death showed a significant increase in those with leukocytosis, polycythemia, neutrophilia, lymphopenia, monocytosis, and monocytopenia compared to those with normal values $p<0.05$. The RR of death was 0.5, 0.3, 0.5, 0.7, 0.6 and 0.6 respectively. The relative risk of death significantly increased in those with combined leukocytosis, neutrophilia, lymphopenia or

combined leukocytosis, neutrophilia, lymphopenia, and thrombocytopenia when compared to those without these changes. The RR of death was 1.9 and 2.7 respectively, p<.05, (Table 5). Follow up of patients using the hematological parameters in survivors and non-survivors patients (Table6): In the survivor patients, the normal group showed a significant increase in WBC, ANC, ALC, AMC, AEC, ABC, and platelet count. Also, there was a significant decrease in hemoglobin. A significant decrease of WBC, AMC, ABC, and platelets was found in the high group. In addition, the low group showed a significant increase in WBC, ALC, AMC, and platelet count. In the non-survivor patients, there was a significant increase in WBC, ANC, and ABC in the normal group. In addition, there was a significant decrease in ALC and platelet count. In the high group, there was a significant decrease in AMC, ABC, and platelets count. The low group showed a significant increase in WBC count, a significant reduction in ALC and platelet count. There was a significant decrease in hemoglobin in the three groups. Comparison between survivors and non-survivors regarding hematological, biochemical markers, demographic data, and the number of days stayed at hospital (Table 7). At presentation, there were significant increases in age, body mass index, WBC, ANC, ABC, serum creatinine, LDH, SGOT, and CRP in non-survivor patients compared to the survivor, p<0.05. At discharge, there was a significant increase in WBC, ANC, serum creatinine, LDH, SGOT, SGPT, CRP, ferritin, and the number of days stayed at the hospital. There was a significant decrease in hemoglobin concentration, platelet count, ALC, and AEC in the non-survivor versus the survivor. The effects of hematological and clinical data on the likelihood that patients with COVID-19 will die using the bivariate logistic regression model. (Table 8). The odd of death was 2.4, 2.6, and 1.9, 2.9 times greater for patients with neutrophilia, monocytosis, lymphopenia, and monocytopenia than those with normal values. The odd of death were 15.2 times greater for patients with high hemoglobin versus those with normal hemoglobin. The odd of death were 2.1 times greater for patients above 65 years of age than those under 40 years. The odd of death was 2.1 times greater for diabetic patients than non-diabetic.

Discussion

The COVID-19 virus infection has an impact on the hematopoietic system. This study aimed to determine the frequency of hematological changes in COVID-19 and their relationship to patients' severity and outcome. In this work, 30.2%, 46.5%, 1%, 12.5%, 0.8%, and 10.8% had leukocytosis, neutrophilia, lymphocytosis, monocytosis, eosinophilia and basophilia respectively at admission. The white blood cells (WBC) are part of the immune system, and both the neutrophils and monocytes are the main phagocytic cells. The elevation of the WBC and its differential count in a percentage of patients at admission may be due to the increased production and mobilization of WBC from the bone marrow in response to acute infections. Or inhibition of margination [10] or hypoxia. Hypoxia inhibits neutrophil apoptosis and subsequently increases neutrophil numbers [11]. In this work, 61.7%, 58.2%, 59.3%,25%,52.9% of leukocytosis, neutrophilia, monocytosis, eosinophilia, and basophilia were present in the critical cases at presentation. The remaining percentages were distributed in mild to moderate and severe cases. In COVID-19 patients, it is known that neutrophilia predicts poor outcomes [12]. Our work confirmed this by the significant elevation of WBC and absolute neutrophil count (ANC) at admission and at discharge in the non-survivor patients compared to the survivor, table 7. In addition, a significant increase in WBC and ANC in the normal group of the non-survivor patients during the follow-up. Also, the sustained elevation of WBC and ANC in the high group of the non-survivor patients during the follow-up procedure. Moreover, the relative risk of death was significantly increased in patients with leukocytosis and neutrophilia compared to those without. Also, in bivariate regression analysis, neutrophilia was an independent predictor of death. All these results confirm the assumption that neutrophilia is a poor prognostic factor. The neutrophilia may be due to the cytokine storm or the hypoxia present in the patients [11]. In this work, 12.5% at presentation had absolute monocytosis, 59.3% were present in critical cases. This agrees with previous authors [13]. The monocytes are increased because they are part of the innate immune system [14] that participate in inflammatory responses. Also, monocytes are key contributors to cytokine storm in COVID-19 [15] via the production of IL-6. IL-6 leads to fever, granulopoiesis, hematopoiesis, and the accumulation of neutrophils at sites of infection. Our work confirmed this by the significant positive correlation between the AMC and the ANC (p<.001, r.525 data not shown). In this work, the relative risk of death was significantly increased in those with monocytosis versus the normal group. Also, in bivariate regression analysis, monocytosis had a 2.6 times risk of death than those with normal monocytes count. So, monocytosis could be used as a poor prognostic factor and independent predictor for death. In the follow-up of patients with monocytosis in the non-survivor and survivor patients. There was a significant decrease in the absolute monocytes count, which indicates a reduction in the former's immune function and recovery in the latter.

Table 1: Demographic and clinical data of the participants.

	no=537	**%**	**Nationality**	**no.**	**%**
			Afghan	8	1.5
			Ethiopian	2	.4
Age			Bangladeshi	48	8.9
Mean ±SD	52.2 ±		Burkinabe	1	.2
Median	15.7		Chinese	3	.6
Min-max	52.00		Egyptian	27	5.0
	14-93		Indian	20	3.7
Sex			Indonesian	14	2.6
male	378	70.4	Iraqi	1	.2
female	159	29.6	Jordanian	1	.2
Nationality			Malian	7	1.3
Saudi	165	30.7	Malaysian	1	.2
Non-Saudi	372	69.3	Myanmar	60	11.2
BMI			Mauritanian	2	.4
Normal	288	53.6	Moroccan	1	.2
Overweight	157	29.2	Nigerian	20	3.7
Obese	90	16.8	Pakistani	53	9.9
Underweight	2	.4	Palestinian	3	.6
Hypertension			Filipino	1	.2
Yes	154	28.7	Saudi	165	30.7
No	383	71.3	Sudanese	12	2.2
Diabetes			Syrian	12	2.2
Yes	188	35	Thai	4	.7
No	349	65	Turkish	3	.6
			Yemeni	56	10.4
DM&HTN*					
Yes	102	19			
No	435	81	Unknown	12	2.2
Severity of disease					
Asymptomatic	3	.6			
Mild to	123	22.9			
moderate	167	31.1			
Severe	244	45.4			
Critical					

*DM= diabetes mellites, HTN= hypertension

Table 2: The frequency of hematological changes in COVID-19 patients at admission.

Parameters	Frequency	Percent	Parameters	Frequency	Percent
WBC (n=537)			***ANC (n=474)***		
Normal	343	63.8	Normal	232	48.9
High	162	30.2	High	220	46.4
Low	32	6.0	Low	22	4.6
Hemoglobin[1] (n=378)			***ALC (n=473)***		
Normal	270	71.4	Normal	175	37
High	5	1.3	High	4	.8
Low	103	27.2	Low	294	62.2
Hemoglobin[2](n=159)			***AMC (n=473)***		
Normal	88	55.3	Normal	394	83.3
High	1	.6	High	59	12.5
Low	70	44	Low	20	4.2
Platelets (n=537)			***AEC (n=473)***		
Normal	406	75.6	Normal	469	99.2
High	41	7.6	High	4	0.8
Low	90	16.8	***ABC (n=473)***		
			Normal	422	89.2
			High	51	10.8

WBC= white blood cells; ANC=absolute neutrophil count; ALC= absolute lymphocyte count; AMC= absolute monocyte count; AEC= absolute eosinophil count; ABC=absolute basophil count. Hemoglobin 1= male; hemoglobin 2= female

Table 3: The associations between hematological parameters and severity of the disease at admission.

	Mild to moderate(n=123)		Severe (n=167)		Critical (n=244)		Asymptomatic (N=3)		Total no.	P-value
	no	%	no	%	no	%	no	%		
WBC										
Normal	85	24.8	120	35	135	39.4	3	.9	343	<.001
High	26	16	36	22.2	100	61.7	0	0	162	
low	12	37.5	11	34.4	9	28.1	0	0	32	
Hb										
Normal	77	21.5	130	36.3	151	42.2%	0	0	358	.001
High	1	16.7	0	0	5	83.3	0	0	6	
low	45	26	37	21.4	88	50.9	3	1.7	173	
Platelets										
Normal	86	21.2	130	32.0	188	46.3	2	.5	406	.298
High	10	24.4	14	34.1	16	39	1	2.4	41	
low	27	30	23	25.6	40	44.4	0	0	90	
ANC										
Normal	58	25	84	36.2	87	37.5	3	1.3	232	<.001
High	39	17.7	53	24.1	129	58.2	0	0	220	
low	8	36.4	5	22.7	9	40.9	0	0	22	
ALC										
Normal	44	25.3	54	31	75	43.1	1	.6	174	
High	4	100	0	0	0	0	0	0	0	.038
low	57	19.4	86	29.3	150	51	1	.3	294	
AMC										
Normal	88	22.3	124	31.5	179	45.4	3	.8	394	.220
High	15	25.4	9	15.3	35	59.3	0	0	59	
low	3	15	6	30	11	55	0	0	20	
AEC										
Normal	102	*21.7*	140	*29.9*	225	*48*	2	*.4*	469	<.001
High	2	50	0	0	1	25	1	25	4	
ABC										
Normal	91	21.6	129	30.6	199	47.2	3	.7	422	.523
High	13	25.5	11	21.6	27	52.9	0	0	51	
WBC+ANC+ALC	9	13.4	14	20.9	44	65.7	0	0	67	
WBC+ANC+ALC	0	0	1	14.3	6	85.7	0	0	7	.018
+platelets	1	33.3	0	0	2	66.7	0	0	3	
WBC+ANC+platelets	113	24.6	152	33	192	41.7	3	.7	460	
Others										

WBC=leukocytosis, ANC=neutrophilia, ALC= lymphopenia, Platelets=thrombocytopenia

Table 4: The relative risk of death using demographic and clinical data of patients using Chi-Square test.

	Living no / (%)	Death no / (%)	Total no.	RRE of death	Significance
Age					
<40 y (G1)	109 (76.2)	34 (23.8)	143	.708 [a]	0.038[a]
>40≤ 65 (G2)	188 (66.4)	95(33.6)	283	.550 [b]	0.001[b]
> 65 (G3)	63 (56.8)	48 (43.2)	111	.776 [c]	.072 [c]
Sex					
Male	263(69.6)	115(30.4)	378	.780	.054
Female	97 (61)	62 (39)	159		
Hypertension					
Yes	87 (56.5)	67 (43.5)	154	1.515	.001
No	273 (71.3)	110 (28.7)	383		
Diabetes					
Yes	107(56.9)	81(43.1)	188	1.566	<.001
No	253 (72.5)	96 (27.5)	349		
DM&HTN					
Yes	55 (53.9)	47 (46.1)	102	1.542	.002
No	305 (70.1)	130 (29.9)	435		
BMI					
Non obese	309(69.1)	138(30.9)	447	.712	.027
Obese	51(56.7)	39(43.3)	90		
Severity of disease					
Asymptomatic	3(100)	0(0)	3(.6)		<.001
Mild to moderate	122(99.2)	1(.8)	123(22.9)	*105.0	
Severe	166 (99.4)	1(.6)	167(31.1)		
Critical	69(28.3)	175(71.7)	244(45.4)		

a G1 versus G2; b G1 versus G3; c G2 versus G3; DM= diabetes; HTN= hypertension.
*between critical group versus the combination of other groups

Table 5: The relative risk of death using the hematological parameters.

	Living no / (%)	Death no / (%)	Total no.	RR of death	P value
WBC					
Normal/high	255 (*74.3*)/ 81(*50*)	88(*25.7*)/81 (*50*)	343/162	**.521**	**<.001**
Normal /low	255 (*74.3*)/ 24 (*75*)	88(25.7)/8 (*25*)	343/32	.868	1.026
High/low	81 (50)/24(75)	81(50)/8(25)	162/32	**2.0**	**.010**
Hemoglobin[1]					
Normal/high	195(72.2)/1(20)	75(27.8)/4(80)	270/5	**.347**	**.025**
Normal /low	195(72.2)/67(65)	75(27.8)/36(35)	270/103	.795	.175
High/low	1(20)/ 67(65)	4(80)/ 36(35)	5/103	2.289	.062
Hemoglobin[2]					
Normal/high	57(64.8)/0(0)	31(35.2)/1(100)	88/1	.352	.360
Normal /low	57(64.8)/40(57.1)	31(35.2)/30(42.9)	88/70	.822	.328
High/low	0(0)/ 40(57.1)	1(100)/ 30(42.9)	1/70	2.333	.437
Platelets					
Normal/high	275(67.7)/ 28 (68.3)	131(32.3)/ 13 (31.7)	406/41	1.018	.942
Normal /low	275 (67.7)/ 57 (63.3)	131 (32.3)/ 33 (36.7)	406/90	.880	.422
High/low	28 (68.3)/ 57 (63.3)	13 (31.7)/ 33 (36.7)	41/90	.865	.581
ANC					
Normal/high	175(75.4)/121(55)	57(24.6)/99(45.0)	232/221	**.546**	**<.001**
Normal /low	175(75.4)/ 16(72.7)	57(24.6)/6(27.3)	232/22	.901	.779
High/low	121(55)/ 16(72.7)	99(45.0)/ 6(27.3)	221/22	1.659	.105
ALC					
Normal/High	125(71.8)/4(80)	49(28.2)/1(20)	174/5	1.4	.688
Normal /Low	125(71.8)/ 180(61.2)	49(28.2)/ 114(38.8)	174/294	**.726**	**.020**
High/Low	4(80)/ 180(61.2)	1(20)/ 114(38.8)	5/294	.516	.392
AMC					
Normal/High	272(69)/28(47.5)	122(32.1)/31(52.5)	394/59	**.589**	**.002**
Normal /low	272(69)/9(45)	122(32.1)/11(55)	394/20	**.563**	**.025**
High/low	272(69)/28(47.5)	31(52.5)/ 11(55)	59/20	.955	.849
AEC					
Normal/High	306(65.2)/3(75)	163(34.8)/1(25)	469/4	1.4	.683
ABC					
Normal/High	278 (65.9)/30(58.8)	144 (34.1)/21(41.2)	422/51	.829	.318
leukocytosis +neutrophilia+ lymphopenia Yes/No	30 (44.8)/330 (70.2)	37 (55.2)/140(29.8)	67/460	**1.9**	**<0.001**
leukocytosis +neutrophilia+ lymphopenia + thrombocytopenia Yes/No	1 (14.3)/359(67.7)	6 (85.7)/171 (32.3)	7/530	**2.657**	**.003**

Hemoglobin[1]= male, Hemoglobin[2] = female, ANC= absolute neutrophil count,ALC= absolute lymphocyte count ;AMC= absolute monocyte count; AEC= absolute eosinophil count.

Table 6: Follow up of patients using the hematological parameters in survivors and non-survivors.

Survivor	Normal(median)					High(median)					Low(median)				
	no	1st	2nd	3rd	P	no	1st	2nd	3rd	P	no	1st	2nd	3rd	P
WBC	222	7.0	8.1	8.5	<.001	73	15.4	13.3	11.1	<.001	19	3.2	4.0	4.8	<.001
ANC	51	4.4	6.4	8.1	<.001	42	9.3	10.5	8.6	.242	16	.934	1.9	1.4	.135
ALC	39	1.8	1.4	1.9	.015	3	6.7	3.2	3.2	.148	59	.94	1.04	1.22	.002
AMC	90	.500	.622	.654	.002	28	1.3	1.1	.719	.019	3	.0930	.150	.173	.050
AEC	96	.0040	.0125	.0305	.038	1	.420	.290	.840	-------					
ABC	91	.0340	.0560	.0680	<.001	30	.145	.0600	.0790	.044					
Platelets	233	237.6	295.6	314.0	<.001	26	477.4	432.3	458.2	.016	57	123.6	169.7	217.3	<.001
Hb male	187	145.8	140.1	136.4	<.001	1	186.5	184.2	165.0	-------	63	114.8	115.0	113.0	.289
Hb female	51	130	126.0	129.8	.02	0	0	0	0	0	37	107.0	101.0	100.0	.865
Non-survivor	Normal(median)					High(median)					Low(median)				
WBC	87	7.0	13.4	14.6	<.001	80	15	17.2	16.4	.549	6	3.3	9.0	10.4	.04
ANC	35	5.0	12.7	12.66	<.001	43	11.9	14.9	14.7	.231	6	1.6	7.1	12.3	.097
ALC	25	2.0	1.2	.91	<.001	0	0	0	0	0		1.04	.55	.75	.039
AMC	65	.444	.493	.568	1.0	31	1.37	.665	.381	.013	4	.0900	.513	.421	.174
AEC	81	.0020	.0070	.0100	.068	0	0	0	0	0					
ABC	69	.0300	.0580	.0630	<.001	21	.145	.0545	.0535	.001					
Platelets	131	238.7	263.7	190.8	<.001	12	490.7	330.1	257.1	.002	30	123	136.7	93.2	.048
Hb male	74	146.5	126.5	112.9	<.001	4	184.3	146.7	105.9	.039	36	114.9	100.2	96.0	.003
Hb female	31	130.6	105.7	90.0	<.001	1	164.4	124.0	111.0	-------	28	103.6	90.3	88.1	.02

Table 7: Comparison between survivors and non-survivors with regards to hematological parameters, biochemical markers, and days stayed in the hospital at presentation and discharge.

	Participants	N	Median at presentation	Median at discharge	P value
WBC	Survivors	360	7.7	9	***P1< .001***
	Non-survivors	177	10.2	14.9	P2<.001
Hemoglobin	Survivors	360	136.3	129.7	P1.161
	Non-survivors	177	132	95.6	P2<.001
Platelets	Survivors	360	227.4	304.3	P1.519
	Non-survivors	177	226.5	174.6	P2<.001
Neutrophil*	Survivors	312	5.7	***7.2***	***P1< .001***
	Non-survivors	164	8.6	13.3	P2<.001
Lymphocytes*	Survivors	309	1.3	1.5	P1.133
	Non-survivors	164	1.2	.773	P2<.001
Monocytes*	Survivors	310	.48	.640	P1.082
	Non-survivors	164	.52	.590	P2=.278
Eosinophils *	Survivors	309	.0040	.032	P1.438
	Non-survivors	164	.0030	.0100	P2<.001
Basophils*	Survivors	308	.0300	.0660	P1.029
	Non-survivors	164	.0385	.0630	P2=.404
Creatinine	Survivors	355	83.5	70.5	***P1< .001***
	Non-survivors	176	105.8	162.4	***P2< .001***
LDH	Survivors	292	404	319.5	***P1< .001***
	Non-survivors	161	470	525	***P2< .001***
SGOT	Survivors	353	53	38	***P1.029***
	Non-survivors	174	63.5	65	***P2< .001***
SGPT	Survivors	355	39	47	P1.308
	Non-survivors	176	35.5	62	P2=.002
CRP	Survivors	232	48	24	***P1.031***
	Non-survivors	132	48	48	P2=.022
Ferritin	Survivors	244	593	791.7	P1.168
	Non-survivors	134	739	1318	P2=.003
Days in hospital	Survivors	360	----------	10	***P2<.001***
	Non-survivors	177	----------	15	
Age	Survivors	360	50	----------	P1<.001
	Non-survivors	177	58	----------	
BMI	Survivors	360	24.6	----------	P1=.008
	Non-survivors	177	25.4	----------	

p1= at presentation, p2= at discharge

Table 8: Bivariate regression analysis of the hematological and clinical parameters.

	B	Wald	Sig.	Exp(B)	95% C.I.for EXP(B)	
					Lower	Upper
Hb groups		5.6	.06			
normal vs high	2.806	5.599	**.020**	**15.2**	1.549	149.6
normal vs low	.013	.017	.896	1.032	.645	1.649
Platelets groups		5.656	.059			
normal vs high	-.884	3.817	.070	.446	.186	1.003
normal vs low	. .477	2.397	.139	1.611	.881	2.947
Neutrophil groups		13.5	.001			
normal vs high	.857	12.8	.000	2.4	1.473	3.768
normal vs low	-.565	.594	.819	1.179	.288	4.828
Lymphocytes groups		7.5	**.023**			
normal vs high	-.200	.032	.857	.806	.077	8.401.
normal vs low	.661	7.565	**.006**	**1.9**	1.324	3.496
Monocytes groups		11.0	**.004**			
normal vs high	.775	4.406	**.008**	**2.6**	1.053	4.471
normal vs low	1.459	5.890	**.046**	**2.9**	1.324	13.982
Eosinophil groups	-1.084	.641	.423	.338	.024	4.805
Basophils groups	.184	.224	.636	1.203	.561	2.579
Age groups		4.819	.090			
<40 y vs >40≤ 65	.256	.868	.346	1.292	.758	2.202
<40 y vs > 65	.722	4.816	**.028**	**2.058**	1.013	3.707
Sex (female Vs male)	.469	3.638	.056	1.598	.987	2.588
Obese vs non -obese	.265	.852	.356	1.304	.742	2.289
Hypertension*(yes vs no)*	.294	1.332	.248	1.341	.815	2.208
Diabetes*(yes vs no)*	.746	6.416	**.011**	**2.108**	1.184	3.753
DM &HTN (yes vs no)	-.578	1.301	.254	.561	.208	1.515

Eosinophilia and basophilia were present at admission in 0.8% and 10.8 of patients, respectively. Eosinophils and basophils are phagocytic cells, and this is the cause for their increase. The basophilia present in both survivor and the non-survivor group showed a significant decrease in the follow-up procedure. This decrease indicates recovery in the survivor and decreased immune function in the non-survivor patients. Patients with eosinophilia were not followed up. In this work, both eosinophilia and basophilia do not affect the relative risk of death or prediction of death. Significant eosinopenia was found in non-survivor patients at discharge compared to survivor patients, indicating immune suppression. This is in accordance with previous authors who reported eosinopenia and linked it to poor outcomes [16]. In this work, 4 cases (0.8%) had absolute lymphocytosis. All of them were mild to moderate cases who were recovered with return of the absolute lymphocytes count (ALC) to normal but without significance table 6. The lack of significance is due to the small number of patients. This is the first report about lymphocytosis in COVID-19 patients. The increase in the absolute lymphocyte count may be due to increased CD4 T helper cells that fight infection. In this study, at presentation 6%,4.6%,62.2%, and 4% had leukopenia, neutropenia, lymphopenia and monocytopenia. It is suggested that COVID-19 inhibits hematopoiesis in the bone marrow and promotes apoptosis, leading to decreased cell production with subsequent leukopenia. In addition, the sequestration of different WBC into infected organs or direct infection of WBC by SARS-CoV2 [17-18]. Our work found the highest leukopenia cases in mild to moderate, 37.5%, then severe, 34.4%, then the critical cases, 22.7%. However, the highest neutropenic cases were found in critical cases, 40.9%, then mild to moderate, 36.4%, and severe cases 22.7%. This is in accordance with previous results [19-21]. Both leukopenia and neutropenia did not affect the relative risk of death or the prediction of death in our work. The leukopenic and neutropenic patients in both survivor and the non-survivor group showed an increase in the WBC and neutrophils count. The rise of WBC was significant, while the increase in neutrophils was not significant. The increase in the survivor group was towards the normal values, which indicate recovery. While in the non-survivor, it was above normal values, suggesting the cytokine storm table 6. Physicians must be alret about the cytokine storm and avoid the use of granulocyte colony-stimulating factor for the leukopenia and neutropenia associated with SARS CoV-2 as it may worsen the condition with the early development of acute respiratory distress syndrome. In this study, 62.8% of our patients had lymphopenia at admission, and after one week, it increased to 68.2% (data not shown). This is in accordance with previous authors [18, 22, 23]. Multiple factors are contributing to lymphopenia. It may be due to direct lysis via the virus as lymphocytes have ACE2 receptors on their surface [8]. Or sequestration of the lymphocyte in the lung and gastrointestinal tract, or suppressing hematopoietic stem cells, or the cytokine-mediated disruption of lymphocyte trafficking [24]. The highest proportion of lymphopenia was found in the critical cases 51%, then severe 29.3%, then mild to moderate 19.4%, then the asymptomatic .3%. This agrees with previous authors who reported a correlation between the disease severity and lymphopenia [25-26]. Lymphopenia causes immunosuppression and promotes cytokine storm, which leads to viral persistence, viral replication, multi-organ failure, and eventually death. In this work, the relative risk of death was significantly increased in those with lymphopenia versus the normal group. Also, in bivariate regression analysis, lymphopenia had a 1.9 times risk of death than normal lymphocyte count. So, lymphopenia could be used as a poor prognostic factor and independent predictor for death. In the follow-up of patients with lymphopenia in the non-survivor and survivor patients. There was a significant decrease and a significant increase in the absolute lymphocytes count, respectively. The former indicates more immunosuppression, and the latter indicates recovery. This agrees with previous findings [27]. So, serial assessment of the absolute lymphocyte count is essential. In this study, 4% of our patients had monocytopenia, of which 55% were present in critical cases, 30% in severe, and 15% in mild to moderate. This monocytopenia is consistent with previous results but against their finding that monocytopenia is present in diabetic patients only [28]. In our work, it is present in 35% of diabetics and 65% of non-diabetic. In this work, the relative risk of death was significantly increased in those with monocytopenia versus the normal group. Also, in bivariate regression analysis, monocytopenia had a 2.9 times risk of death than those with normal monocytes count. So, monocytopenia could be used as a poor prognostic factor and an independent predictor of death. The follow-up procedure of patients with monocytopenia showed a significant increase in the survivor patients, which indicates recovery. The non -survivor showed no significant difference, suggesting more impairment in the immune function table 6. The monocytopenia in our work is more aggressive than monocytosis as in bivariate regression analysis, the odds ratio of death was 2.9 and 2.2 in those with monocytopenia and monocytosis, respectively. This makes us give more attention to those with monocytopenia in COVID-19 patients. In this study, 7.6% and 16.8% of patients had thrombocytosis and thrombocytopenia, respectively. The highest frequency of thrombocytosis and

thrombocytopenia was present in critical cases, then severe, then mild to moderate. The thrombocytosis may occur as a reaction of the bone marrow against viral infection. The thrombocytopenia occurs because of inhibition of hematopoiesis by the virus or secondary hemophagocytic or increased levels of autoantibodies and immune complexes, resulting in the specific destruction of platelets. Pulmonary endothelial cells may activate platelets in the lungs, resulting in aggregation and formation of microthrombi, which increases platelet consumption [29]. The follow-up of the thrombocytosis patients in both survivor and non-survivor showed a significant decrease in the platelet count. On the other hand, the follow-up of the thrombocytopenic patients showed a significant increase in the platelets count in the survivor, indicating recovery and a significant decrease in the non-survivor, which suggests an increase in the severity and complication of the disease [30]. In this work, both thrombocytosis and thrombocytopenia did not affect the relative risk of death. However, the combination of thrombocytopenia with leukocytosis, neutrophilia, and lymphopenia, showed a 2.7 times increase in death than those without, (Table5). So, thrombocytopenia can be used as a marker of poor prognosis in combination with leukocytosis, neutrophilia, and lymphopenia. In this work, in male patients at admission, 71.4%, 1.3%, and 27.2% had normal, high, and low hemoglobin, respectively. In females, 55.3%, 0.6%, and 44% had normal, high, and low hemoglobin at admission. The critical cases in this work showed the highest polycythemia and anemia, 83.3% and 50.9%, respectively. The relative risk of death significantly increased in males with polycythemia versus the normal group. Also, in bivariate regression analysis, polycythemia patients had a 15.2 times risk of death than those with normal hemoglobin. So, polycythemia could be used as a poor prognostic factor and independent predictor for death. The follow-up of patients with polycythemia showed a significant decrease of hemoglobin in the non-survivor patients and the development of anemia, which is associated with the cytokine storm and indicates poor prognosis [31] (Table 6). In this study, the follow-up of anemic patients who survived showed no significant difference in hemoglobin concentration. In contrast, the anemic non-survivor patients showed a significant decrease in hemoglobin, which also is due to the cytokine storm. The follow-up of the normal group of survivor patients showed a significant increase in WBC and its components and the platelet count. The increase in most of the parameters was within the normal values. This denotes the response of the bone marrow and indicates the recovery of patients. In the non-survivor patients, there was a significant increase of WBC and ANC above normal values, a significant decrease of ALC and platelet count. All these changes indicate cytokine storms. The hemoglobin concentration in both survivor and non-survivor patients showed a significant reduction, indicating the occurrence of anemia. The comparison between survivor and non -survivor patients at admission showed significant leukocytosis, neutrophilia, basophilia, increased each of s creatinine, LDH, SGOT, CRP, age, and body mass index at admission in non-survivor when compared to the survivor. This agrees with previous authors [32-33]. At discharge, the comparison between both groups showed persistence of leukocytosis, neutrophilia, high levels of each of s creatinine, LDH, SGOT, CRP, and an increase in the number of days stayed in the hospital. In addition, there was loss of basophilia and acquisition of high SGPT, high ferritin, anemia, thrombocytopenia, lymphopenia, and eosinopenia. The persistence of significant changes in some parameters and new changes in other parameters indicates cytokine storm with an increase in the severity of the disease and an increase in the immune suppression (Table7). In this study, 28.7%, 35%, 19%, 16.8% were hypertensive, diabetic, combined diabetes, and hypertension, and obese. These comorbidities may affect vascular health and lower the ability of the body to tolerate systemic cytokines. At presentation, hypertension, diabetes, age > 40 <65, age >65, combined diabetes and hypertension, and obese patients were statistically significantly related to morality in the Chi-Square test. However, in the bivariate analysis, they were lost except for diabetes and age >65 y.

Limitation of the study

This study was conducted at one hospital. It may have included disproportionately more patients with poor outcomes. There were no data on post-hospitalization outcomes. Also, some data did not find during collection. There is no measurement of other viruses that cause lymphocytosis in the 4 COVID-19 cases. We could not confirm the cause of leukopenia, neutropenia, lymphopenia, and monocytopenia among the different subjects; either it is due to suppression or sequestration or a combination of both.

Conclusion

Patients with COVID-19 infection may have normal, low, or high values of the different parameters of the complete blood count. The relative risk of death is increased in patients with leukocytosis, neutrophilia, monocytosis, polycythemia, lymphopenia, and monocytopenia. Patients with a combination of leukocytosis, neutrophilia, lymphopenia, and thrombocytopenia have a 2.6 risk of death than others. The independent predictors for death are neutrophilia, monocytosis, lymphopenia, monocytopenia,

polycythemia, diabetic patients, and age over 65. The follow-up of COVID-19 patients with the complete blood count is recommended to detect early patient changes and early management.

Conflict of Interest

None

Funding

None

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