

## The Effects of COVID-19 Infection on Hematologic Parameters

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### ABSTRACT

**Background:** The coronavirus disease "COVID-19" was reported in 2019 as an outbreak in Wuhan, China, and categorized as a pandemic disease in 2020 with severe complications. **Objective:** This study aimed to test the effects of COVID-19 infection on blood parameters and to assess these effects with disease progress.

**Patients and Methods:** 120 patients with COVID-19 in Al-Amal Specialized Hospital for Communicable Diseases in Al-Najaf Al-Ashraf province with 30 healthy (control) individuals of both genders were included in this study. Blood parameters (complete blood count, PLT and ferritin) were measured for 3 weeks from the 1<sup>st</sup> day of hospitalization.

**Results:** The study revealed significant differences in the hematological parameters for COVID-19 patients in comparison with the control group and these variations increased with the progress and severity of the disease. No significant variations were noticed in Hb and HCT of patients compared to control, but these parameters decreased with disease progression.

**Conclusion:** A comparison of COVID-19 patients with healthy individuals revealed significant differences in hematological parameters, which became more pronounced with the progression and severity of the disease.

**Keywords:** COVID-19, Coronavirus, SARSCoV-2, Hematologic parameters

### INTRODUCTION

The world experienced a pandemic of a novel corona virus disease "COVID-19" that caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) <sup>(1)</sup>. SARS-CoV-2 is analogous to SARS-COV of about 80%; binds with angiotensin-converting enzyme2 (ACE2) receptor to invade host human cells <sup>(2)</sup>. Coronavirus-19 disease had fast prevalence worldwide with destructive consequences. Approximately 80% of COVID-19 patients were hospitalized and 60% of them came into intensive care units (ICUs), while the mortality ranged between 3-5% <sup>(3)</sup>. X

Although, the disease infects the respiratory tract, many studies have validated that it is a multi-systemic disease as it is associated with cardiovascular disorders, gastrointestinal diseases, neurological signs, as well as hematopoietic and immunity dysfunction <sup>(4,5)</sup>. The haematological abnormalities associated with COVID-19 disease are attributed to multi factors, these disorders are linked with the progress, severity and mortality of the disease. Decreased lymphocyte and thrombocyte, coagulation disorders and disseminated intravascular coagulation (DIC) are usually reported in COVID-19 patients <sup>(6)</sup>. COVID-19 infection has a respectable effect on haematopoiesis and haemostasis. Lymphopenia rate, neutrophil to lymphocyte ratio and platelet to lymphocyte ratio may have importance in prediction and determining the severity of cases <sup>(7)</sup>. Blood tests including WBCs count and characteristics such as neutrophil or lymphocyte percent have a considerable role in the early diagnosis and monitoring of the progress of the disease <sup>(8)</sup>. Frequently laboratory variations particularly hematologic abnormalities have been reported in COVID-19 patients. Leukocyte count and lymphocytes may alter with the disease progression. Moreover, thrombocytopenia is usually correlated with

disease progression. Also, several studies reported that haemoglobin levels are decreased in COVID-19 patients and this is correlated with disease severity <sup>(9)</sup>.

The haematological effects of the COVID-19 virus have to be traced up closely as this epidemic developed <sup>(10)</sup>. Haematology and inflammation tests such as CBC, CRP, ferritin, D-dimer and coagulation parameters can have an important role in the early prognosis of disease gravity, thus helping in the reduction of disease morbidity and mortality <sup>(11)</sup>.

Therefore, this study aimed to investigate the effect of the COVID-19 virus on haematological criteria and to evaluate the hematologic markers changes with disease progression.

### PATIENTS AND METHODS

This is a retrospective cross-sectional study performed in Alamal Specialized Hospital in Al-Najaf Province. Data for six months from July to December 2020 were included, a total of 120 patients and 30 healthy individuals (as control) of both genders between 35-80 years of age were studied. Blood parameters (WBC, Neu, Lym, Mon, RBCs, Hb, HCT, PLT and ferritin) were measured over 20 days from the first day of admission at the hospital <sup>(12, 13)</sup>. Studied COVID-19 patients were selected without any h

haematological or special chronic diseases that could affect the blood parameters under study <sup>(14, 15)</sup>. Complete blood count done by Sysmex KX-21N Hematology Analyzers (China). While serum ferritins don by Abbot Architect I 1000 SR (China).

### Ethical considerations:

**The study concept for human studies was approved from Al-Amal Specialized Hospital for Communicable Diseases and AlKafeel Hospital by**

**The Institutional Ethics Committee. Additionally, before taking part in the study, each participant gave written, informed consent. . This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.**

**Statistical analysis**

Windows 2010 and SPSS version 23 was utilized to evaluate the study's data. Unpaired sample t-tests was used to compare two groups, and one-way ANOVA tests was performed to compare groups that had been separated based on the parameters that were assessed. SPSS version23 have been used to create each and every figure. A statistically significant threshold was set at  $P \leq 0.05$  (16, 17).

**RESULTS**

**Blood parameters**

There was a statistically significant difference in the hematological parameters of COVID-19 patients between the three weeks of infection. Table (1) showed significantly increased white blood cell (WBCs) count in COVID-19 patients ( $9.24 \pm 0.71 \times 10^3/\mu\text{l}$ ) compared to normal (control) individuals ( $5.62 \pm 0.25 \times 10^3/\mu\text{l}$ ). Also, WBCs were elevated significantly in the 2<sup>nd</sup> week ( $14.55 \pm 0.34 \times 10^3/\mu\text{l}$ ) compared to 1<sup>st</sup> week ( $9.24 \pm 0.71 \times 10^3/\mu\text{l}$ ). Whereas, in the 3<sup>rd</sup> week, WBCs decreased ( $10.42 \pm 0.9 \times 10^3/\mu\text{l}$ ) when compared to the 2<sup>nd</sup> week ( $P < 0.001$ ). For neutrophils, there was a significant increase ( $P < 0.001$ ) when infected with COVID-19 ( $75.95 \pm 1.12\%$ ) compared to the control group ( $64.68 \pm 0.64\%$ ). But there was a non-significant difference in their percent between 1<sup>st</sup> week ( $75.95 \pm 1.12\%$ ) and 2<sup>nd</sup> week ( $77.82 \pm 0.89\%$ ), while in the 3<sup>rd</sup> week they decreased significantly ( $67.92 \pm 1.54\%$ ) when compared to the 2<sup>nd</sup> week. The results of lymphocytes percentage showed significant decrease ( $P < 0.002$ ) in the COVID-19 patients in comparison with the healthy control group. Lymphocytes reached  $17.27 \pm 0.6\%$  in the 1<sup>st</sup> week and decrease significantly in the 2<sup>nd</sup> week ( $14.76 \pm 0.28\%$ ) compared to the 1<sup>st</sup> week. While, it started to increase in the 3<sup>rd</sup> week ( $18.81 \pm 0.78\%$ ) compared to the 2<sup>nd</sup> week ( $14.76 \pm 0.28\%$ ). Regarding monocytes, they decreased significantly ( $P < 0.02$ ) in the 1<sup>st</sup> week of COVID-19 infection ( $4.01 \pm 0.35\%$ ) compared to the control group ( $5.2 \pm 0.15\%$ ).

But, there was a non-significant difference between the 1<sup>st</sup> and 2<sup>nd</sup> week ( $4.01 \pm 0.35\%$  and  $4.05 \pm 0.41\%$  respectively). While, there was a significant increase ( $P < 0.02$ ) between the 2<sup>nd</sup> and 3<sup>rd</sup> week ( $7.45 \pm 0.31\%$ ) as illustrated in table (1). Also, table (1) showed that there was a significant decrease ( $P < 0.01$ ) in the RBCs count of the COVID-19 group compared to the normal group, where it was  $4.68 \pm 0.15 \times 10^6/\mu\text{l}$  in the 1<sup>st</sup> week of infection vs  $5.2 \pm 0.14 \times 10^6/\mu\text{l}$  in the control group. When comparing the RBCs count between the 1<sup>st</sup> week ( $4.68 \pm 0.15 \times 10^6/\mu\text{l}$ ) and 2<sup>nd</sup> week ( $3.56 \pm 0.09 \times 10^6/\mu\text{l}$ ), there was significant ( $P < 0.01$ ) decrease. But, there

was a non-significant difference between 2<sup>nd</sup> and 3<sup>rd</sup> week that was ( $3.54 \pm 0.07 \times 10^6/\mu\text{l}$ ).

Hemoglobin concentration (Hb) did not change significantly in the 1<sup>st</sup> week of infection as it was  $14.05 \pm 0.44 \text{ gm/dl}$  compared to the normal group whose Hb was  $14.57 \pm 0.14 \text{ gm/dl}$ . A significant ( $P < 0.001$ ) decrease in the Hb level was observed in the 2<sup>nd</sup> week of infection ( $10.68 \pm 0.28 \text{ gm/dl}$ ) compared to the 1<sup>st</sup> week. In contrast, when comparing the 2<sup>nd</sup> with 3<sup>rd</sup> week ( $10.61 \pm 0.22 \text{ mg/dl}$ ), there was a non-significant difference. So, HCT did not differ significantly in the primary infection with COVID-19 compared to the control group, where it was  $42.34 \pm 1.3\%$  in the 1<sup>st</sup> week of infection and  $44.73 \pm 0.45\%$  in the control group. When comparing 1<sup>st</sup> with 2<sup>nd</sup> week ( $42.34 \pm 1.3\%$  vs  $32.33 \pm 0.82\%$ ), there was a significant ( $P < 0.001$ ) decrease, while a non-significant decrease between the 2<sup>nd</sup> week and 3<sup>rd</sup> week ( $31.85 \pm 0.64\%$ ).

The count of platelets was significantly ( $P < 0.002$ ) decreased in COVID-19 patients in comparison with the normal (control), where it reached  $266.93 \pm 7.11 \times 10^3/\mu\text{l}$  in the 1<sup>st</sup> week of infection while the control group was  $295.2 \pm 4.35 \times 10^3/\mu\text{l}$ . When comparing the 1<sup>st</sup> with 2<sup>nd</sup> week, PLT showed a significant decrease ( $P < 0.002$ ) in the 2<sup>nd</sup> week ( $212.31 \pm 5.05 \times 10^3/\mu\text{l}$ ), while a non-significant change between 2<sup>nd</sup> and 3<sup>rd</sup> week ( $216.29 \pm 4.85 \times 10^3/\mu\text{l}$ ). Table (1) showed a significant elevation ( $P < 0.001$ ) in ferritin of infected individuals that reached  $487.19 \pm 8.39 \text{ ng/ml}$  in the first week of infection in comparison with the control group that was  $113 \pm 5.56 \text{ ng/ml}$ . While, there was a significant increase in 2<sup>nd</sup> week ( $569.91 \pm 8.18 \text{ ng/ml}$ ) as compared to 1<sup>st</sup> week ( $487.19 \pm 8.39 \text{ ng/ml}$ ). But there was a non-significant difference in ferritin levels in 3<sup>rd</sup> week ( $609.93 \pm 3.31 \text{ ng/ml}$ ).

**Table (1): Hematological parameters of COVID-19 patients through 3 weeks of infection**

Parameter	Mean ± SE				P-value
	Control	1 <sup>st</sup> week	2 <sup>nd</sup> week	3 <sup>rd</sup> week	
WBC ( $\times 10^3/\mu\text{l}$ )	5.62* ± 0.25	9.24* ± 0.71	14.55* ± 0.34	10.42* ± 0.9	< 0.001
Neu (%)	64.68* ± 0.64	75.95* ± 1.12	77.82+ ± 0.89	67.92+ ± 1.54	<0.001
Lym (%)	25.4* ± 0.37	17.27* ± 0.6	14.76* ± 0.28	18.81* ± 0.78	< 0.002
Mon (%)	5.2* ± 0.15	4.01* ± 0.35	4.05+ ± 0.41	7.45+ ± 0.31	< 0.02
RBC ( $\times 10^6/\mu\text{l}$ )	5.2* ± 0.14	4.68* ± 0.15	3.56* ± 0.09	3.54 ± 0.07	< 0.01
Hb (mg/dl)	14.57 ± 0.14	14.05* ± 0.44	10.68* ± 0.28	10.61 ± 0.22	< 0.001
HCT (%)	44.73 ± 0.45	42.34* ± 1.3	32.33* ± 0.82	31.85 ± 0.64	< 0.001
PLT ( $\times 10^3/\mu\text{l}$ )	295.2* ± 4.35	266.93* ± 7.11	212.31* ± 5.05	216.29 ± 4.85	< 0.002
Fer (ng/ml)	113* ± 5.56	487.19* ± 8.39	569.91* ± 8.18	609.93 ± 3.31	< 0.001

SE: Standard error, \*: Significant differences

**Coagulation indicators**

Coagulation tests of table (2) indicated that fibrinogen (FIB) and D-dimer were increased in COVID-19 patients ( $4.68 \pm 0.14$  g/l and  $0.59 \pm 1.39$  mg/ml respectively) in the 1<sup>st</sup> week of infection, and the increase was more marked in the 2<sup>nd</sup> week ( $6.56 \pm 0.07$  g/l and  $3.91 \pm 2.18$  mg/ml respectively) than in other weeks of infection.

While, in the 3<sup>rd</sup> week there was a non-difference in FIB ( $5.54 \pm 0.09$  g/l) and a significant ( $P < 0.001$ ) decrease in D-dimer between the 2<sup>nd</sup> and 3<sup>rd</sup> week that became ( $1.93 \pm 1.13$  mg/ml).

**Table (2):** Coagulation parameters of COVID-19 patients during 3 weeks of infection

Parameter	Mean ± SE				P-value
	Control	1 <sup>st</sup> week	2 <sup>nd</sup> week	3 <sup>rd</sup> week	
FIB (g/l)	$2.9^* \pm 0.15$	$4.68^* \pm 0.14$	$6.56^* \pm 0.07$	$5.54 \pm 0.09$	< 0.01
D-dimer (mg/ml)	$0.213^* \pm 0.02$	$0.59^* \pm 0.04$	$3.91^* \pm 0.28$	$1.93^* \pm 0.13$	< 0.001

SE: Standard error, \*: Significant differences

**Inflammatory biomarkers**

The levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) increased significantly in most COVID-19 patients from the 1<sup>st</sup> week ( $9.07 \pm 0.45$  and  $20.05 \pm 0.34$  respectively) and increased with the progression of the disease in the 2<sup>nd</sup> week ( $16.05 \pm 0.71$  and  $46.68 \pm 0.28$  respectively). While, these levels were started dropping during the 3<sup>rd</sup> week ( $8.45 \pm 0.31$  and  $22.61 \pm 0.12$  respectively).

Also, there was a significant elevated ( $P < 0.001$ ) in the ferritin (Fer) of infected individuals that reached  $487.19 \pm 8.39$  ng/ml in the 1<sup>st</sup> week of infection in comparison with the control group. Also, there was a marked difference between 1<sup>st</sup> week and 2<sup>nd</sup> week ( $569.91 \pm 8.18$  ng/ml). But, the difference was non-significant between 2<sup>nd</sup> and 3<sup>rd</sup> week ( $609.93 \pm 3.31$  ng/ml).

**Table (3):** Inflammatory biomarkers of COVID-19 patients during 3 weeks of infection

Parameter	Mean ± SE				P-value
	Control	1 <sup>st</sup> week	2 <sup>nd</sup> week	3 <sup>rd</sup> week	
CRP (mg/l)	$4.18^* \pm 0.12$	$9.07^* \pm 0.45$	$16.05^* \pm 0.71$	$8.45^* \pm 0.31$	< 0.02
ESR (mm/hr)	$9.3^* \pm 0.24$	$20.05^* \pm 0.34$	$46.68^* \pm 0.28$	$22.61^* \pm 0.12$	< 0.001
Fer (ng/ml)	$113^* \pm 5.56$	$487.19^* \pm 8.39$	$569.91^* \pm 8.18$	$609.93^* \pm 3.31$	< 0.001

SE: Standard error, \*: Significant differences

**Serum biochemical tests**

Table (4) showed that total bilirubin (TBil), creatinine (CRE) and urea were statistically increased in infected patients ( $12.24 \pm 0.51$ ,  $75.45 \pm 0.82$  and  $4.68 \pm 0.18$  respectively) and kept increasing during 2<sup>nd</sup> week ( $20.75 \pm 0.34$ ,  $97.82 \pm 1.89$  and  $7.56 \pm 0.21$  respectively). In the 3<sup>rd</sup> week, TBil and CRE showed more increase ( $23.42 \pm 0.7$ ,  $113.92 \pm 1.5$  respectively) compared to other weeks, while urea was lowered significantly ( $5.54 \pm 0.07$  mmol/l). Lactate dehydrogenase (LDH) levels were significantly ( $P < 0.002$ ) higher than those of the control group in the 1<sup>st</sup> and 2<sup>nd</sup> weeks ( $266.3 \pm 3.11$  and  $282.5 \pm 5.02$  U/l respectively), but it began to decrease significantly in the 3<sup>rd</sup> week ( $226.2 \pm 3.81$  U/l).

**Table (4):** Biochemical parameters of COVID-19 patients during 3 weeks of infection

Parameter	Mean ± SE				P-value
	Control	1 <sup>st</sup> week	2 <sup>nd</sup> week	3 <sup>rd</sup> week	
TBil (µmol/l)	$6.22^* \pm 0.25$	$12.24^* \pm 0.51$	$20.75^* \pm 0.34$	$23.42 \pm 0.7$	< 0.001
CRE (µmol/l)	$52.68^* \pm 0.34$	$75.45^* \pm 0.82$	$97.82^* \pm 1.89$	$113.92 \pm 1.5$	< 0.001
Urea (mmol/l)	$3.2^* \pm 0.14$	$4.68^* \pm 0.18$	$7.56^* \pm 0.21$	$5.54^* \pm 0.07$	< 0.001
LDH (U/l)	$125.2^* \pm 2.35$	$266.3^* \pm 3.11$	$282.5^{**} \pm 5.02$	$226.2^{**} \pm 3.81$	< 0.002

SE: Standard error, \*: Significant differences

**DISCUSSION**

Our results showed that there was a statistically significant variation in the haematological parameters of COVID-19 patients between the 1<sup>st</sup> weeks (infection week), 2<sup>nd</sup> week (a peak week) and 3<sup>rd</sup> week (healing week). Our study demonstrated that there was leucocytosis, neutrophilia and decreased lymphocytes that might be due to inflammatory responses, and these changes expanded as the disease progresses. Lymphocytopenia is frequent in patients with COVID-19, which indicates a decadence of immunity during COVID-19 infection. It is observed that the decrease of lymphocytes was below the normal range in most infected patients; this concurs with the **Gao et al.** (18) and **Zhou et al.** (19) results.

There is a clear relationship between bacterial infections and an increase of neutrophils, as well as between viral infections and lymphocyte rise, according to the neutrophil-lymphocyte ratio (NLR) of blood, which can be utilized to differentiate between infection types. Similarly, previous research showed a significant reduction in NLR of COVID-19 patients when visiting the emergency (20).

In contrast, **Liao et al.** (21) observed an increased neutrophil-lymphocyte ratio as a beneficial indicator of the severity and death of COVID-19 disease. The study also showed a lowering in patients' RBCs count compared to control group and this count decreased as

the disease progresses. Although haemoglobin and haematocrit of patients did not show an association with the disease in our study, it decreased in the peak disease (2<sup>nd</sup> week). This result concurs with findings of **Hadadi et al.** (22). These changes may be a result of the pathological effect of infection and weakness resulting from hospitalization (23).

Our study showed a significant link of PLT count with progress of the disease. The study, which is agreeing also with previous studies, revealed thrombocytopenia, leukopenia and lowering of neutrophils in COVID-19 patients.

Furthermore, **Guan et al.** (24) study showed low thrombocyte and leukocyte. Another study by **Assiri et al.** (25) and **Xu et al.** (26) noted thrombocytopenia in the patients and leukopenia in a different study. In addition, a study reported that thrombocytes decrease significantly in pneumonia patients and this reduction is proportionate with the clinical case of the patient. Several potential reasons have been suggested for thrombocytopenia in coronavirus patients as failure in thrombocyte production from classic cytokine storm in infection or attacking directly on hematopoietic stem cells, high destruction of platelet in circulating blood and decreased peripheral PLT secondary to lung damage (27). Also, serum ferritin values elevated significantly in COVID-19 patients. **Terpo et al.** (28) reported in a study from Wuhan, China, that high ferritin was a hazard factor for acute respiratory distress syndrome (ARDS), ICU backing and death.

The study by **Taj et al.** (29) concluded that leucocytosis, neutrophilia, serum ferritin and CRP are associated with the severity of COVID-19 disease.

**Erfan et al.** (30) referred to the suggested days between the COVID-19 infection and the appearance of the hematologic disorders to be ranging between 9-11 days, which are during the second week of infection. This is consistent with the results of our study, where a vast extent of hematologic differences has been shown in COVID-19 patients during the 2<sup>nd</sup> week of infection. There is an improvement in variables of haematological markers for COVID-19 patients in the 3<sup>rd</sup> week as the beginning of the healing stage. This result is in agreement with those found by **Huang et al.** (31) and **Fan et al.** (32).

## CONCLUSION

A comparison of COVID-19 patients to healthy individuals revealed significant differences in hematological parameters, which become more pronounced with the progression and severity of the disease.

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