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The Relationship between the Levels of Serum Iron, Ferritin, and Hemoglobin in Patients Infected with Coronavirus Disease -19

BY

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Abstract

***Background**: The coronavirus disease 2019 (COVID-19) is an aggressive virus that spread worldwide and caused a pandemic infection. On March 11, 2020, the world health organization (WHO) declared COVID-19 a global pandemic. Therefore, The battle against COVID-19 is likely to be a marathon and the pandemic has a major impact on health care systems in many countries. **Objectives**: The current study aimed to evaluate the relationship between hemoglobin, serum ferritin, and iron concentrations in patients infected with coronavirus, and the prevalence of anemia in patients with coronavirus disease-19. **Materials and methods**: In this descriptive and screening study, 70 healthy individuals have been randomly chosen to be considered as a control group and 70 infected people with a Covid-19 have been randomly chosen as a participant in this study. Blood samples were collected twice (1st week & 2ed week) from all participants to be analyzed during the period of September 2021 up to July 2022. **Results**: Results showed that covid-19 infection has effect on the concentration of hemoglobin more than other RBCs indices like MCH (pg/cell) and MCHC because the difference was very low with no significant difference. There was a weak negative correlation between the change in ferritin level and percent of lymphocytes (Correlation coefficient (r)= -0.219 with P value of 0.001). Mean value of ferritin level has significantly (P value = 0.000) increased into high levels during both periods of infection. Percent of anemia among males was slightly low in comparison with females during the first week of infection (35.14% and 36.36%, respectively). **Conclusion**: Results of the current study confirmed the observations and other results revealed by the previous studies regarding the variations in hematological parameters and some other inflammatory factors in patients infected by covid-19. Therefore, further hematological studies are needed to confirm these results to help the clinicians for better understanding of COVID-19 infection and to provide more clinical treatment options.*

***Key words**: Covid-19, Hb. Concentration, Ferritin level, Serum iron, Hematological parameters, Anemia.*

1. Introduction

The novel coronavirus pneumonia (COVID-19) is an infectious acute respiratory caused by the novel coronavirus. In late 2019, an outbreak of viral pneumonia caused by a novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China; subsequently, the coronavirus 2019 disease (COVID-19) spread worldwide, and on March 11, 2020, the world health organization (WHO) declared COVID-19 a global pandemic [1]. Therefore, The battle against COVID-19 is likely to be a marathon and the pandemic has a major impact on healthcare systems in many countries.

If deteriorating, COVID-19 can lead to sepsis, septic shock, and multiple organ dysfunction syndrome, with mechanical ventilation or extracorporeal membrane oxygenation having low therapeutic efficacy [2]. The pathophysiological background underlying deterioration and low efficacy of common treatments is unclear.

Most patients with COVID-19 who require intensive care will develop an atypical form of the acute distress respiratory

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syndrome (ARDS) with preserved lung gas volume [3], suggesting hypoxia due to physiological processes other than alveolar dysfunction may play a role in the prognosis of the disease [4]. Disturbed iron metabolism may be one such affected process. Indeed, recent data show that COVID-19 patients tend to present decreased hemoglobin levels indicating the presence of anemia, and pathologically increased levels of ferritin.

It has previously been demonstrated that SARS-CoV-2 binds to hemoglobin through ACE2, CD147, Cd26, and other receptors that are present on the surface of erythrocytes. After this association, the virus attacks the beta1 chain of hemoglobin which leads to dysfunctional hemoglobin in addition to hemolysis, thereby reducing the oxygen supply to the body, causing tissue hypoxia, a remarkable characteristic of COVID-19 [5, 6].

In more details, studies have demonstrated that the amino acid sequence of the coronavirus spike protein is identical to hepcidin, a protein that acts as the main systemic regulator of iron metabolism. Therefore, this similarity between hepcidin and coronavirus spike protein can lead to a mimetic effect, suggesting that SARS-CoV-2 can increase serum hepcidin and then ferritin, and cause hyperferritinemic syndrome [7]. Therefore, the association between dysfunctional hemoglobinopathy and SARS-CoV-2-related hyperferritinemia may affect the oxygen transport capacity of erythrocytes, thereby leading to hypoxia, while causing tissue damage due to non-transferrin-bound iron (NTBI), and subsequently releasing free radicals at the inflammation sites [8].

With regard to the protein known as ferritin, it is a key mediator of immune dysregulation, especially under extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm [9]. It has been reported that fatal outcomes by COVID-19 are accompanied by cytokine storm syndrome, thereby it has been suggested that disease severity is dependent of the cytokine storm syndrome [10].

2. Objectives

The current study aimed to evaluate the relationship between hemoglobin, serum ferritin, and iron concentrations in patients infected with coronavirus, and the prevalence of anemia in patients with coronavirus disease-19.

3. Materials and Methods

3.1. Study population

Descriptive and screening study has been carried out in western region of Libya, beginning from September (2021) up to July 2022. Seventy healthy people (Males and Females) have been randomly chosen to be considered as a control group and seventy infected people with a Covid-19 (Males and Females) have been randomly chosen as a participants in this study to do all investigations determined in our objectives. PCR technique has been used to confirm the infection of Covid-19 for all patients (Table 1 and Figure 1). The mean value and the standard diffusion of age of both groups were **42.7±2.4** and **44.8±1.8** respectively. Table 2 and Figure 2 showing the distribution of age groups of all participants (Control group and Covid-19patients).

Table 1: Distribution of control group and COVID-19 patients according to gender.

Control		COVID-19 Patients	
Males	Females	Males	Females
29	41	37	33

Table 2: Distribution of COVID-19 infection subjects according to Age groups.

Age Groups (Years)	Total	%
14-25	7	10.0
26-35	12	17.1
36-45	22	31.4
46-55	12	17.1
56-65	8	11.4
66-75	9	12.9

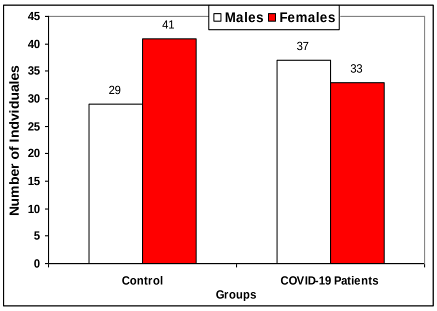

Figure 1: Distribution of control and COVID-19 infection subjects according to gender.

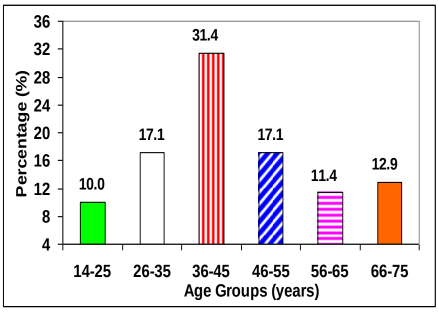

Figure 2: Distribution of control and COVID-19 infection subjects according to Age groups.

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3.2. Methods

According to the methods and the procedures used in different central laboratories either in governmental hospitals or in private laboratories (3rd and 4th levels) for analyzing blood samples to get complete blood count (CBC) and/or other laboratory investigations like serum iron and ferritin level, it's known that the following methods and procedures are usually used as a standard ways. In this context, we are going to explain those methods and procedures that had been used to achieve different investigations for all control group and Covid-19 patients to get into final results that have been recorded in patients' files

3.3.1. Sample collection

2.5ml venous blood had been collected from both groups (Control group and Covid-19 patients) in ethylene diamin tetra acitic acid (EDTA) tubes for CBC test and another 5ml venous blood in plain tubes for serum iron and serum ferritin. Directly after collection, the needed investigations have been done according to the manufacture procedures as following:

3.3.2. Complete blood count (CBC)

The haematological parameters: haemoglobin, red blood cells, white blood cells, platelets, and red blood indices, were detected by using Sysmex (KX-21N) instrument. Sysmex (KX-21) is a blood analyzer Performs rapid and accurate analysis of 17 parameters and utilizes same Direct Current detection method as Sysmex high-end systems. In details, for RBC and PLT it uses the direct Current (DC) detection method and for WBC it uses DC detection method. For Hb, it uses non-cyanide method and for HCT it uses a cumulative pulse height detection method. The total blood volume used for all 17 parameters is 50µl [11].

3.3.3. Serum iron

Serum iron has been done by using COBAS INTEGRA Iron Gen.2 (IRON2) Test IRON2, test ID 0-596. This is In vitro test for the quantitative determination of iron in human serum and plasma on COBAS INTEGRA systems.

Test principle: (FerroZine method). Under acidic conditions, iron is liberated from transferrin. Lipemic samples are clarified by the detergent. Ascorbate reduces the released Fe^{3+} ions to Fe^{2+} ions which then react with FerroZine to form a colored complex. The color intensity is directly proportional to the iron concentration. It is determined by monitoring the increase in absorbance at 552 nm [12].

3.3.4 Ferritin level

Each participant had 5 ml of venous blood drawn and quickly transported to the laboratory for the investigation performance. Ferritin level has performed by using Cobas Integra 400 methods (Roche Diagnostics, CH-6343 Rotkreuz, Switzerland). As a principle, human-driven ferritin showed agglutination with latex particles covered with anti-ferritin antibodies in the expanded particle surface immunoturbidimetric test. Precipitation was turbidimetric at 542 nm.

3.4. Ethical consideration:

Ethical approval were obtained from ethical committee of Libyan Academy of science, and from each hospital or health centre determined as a point for samples collection. Informed consent were taken from the patient who are participated in this study as a case study prior to her inclusion in this study.

3.5. Statistical analysis:

to get into the final conclusion, statistical analysis has been applied to analyse all data supposed to be collected or obtained, and then to make a final comparison using the significant value, Statistical Package for Social Science (SPSS) V.21 has been used.

4. Results

As it has mentioned above that the total number of covid-19 patients participated in this study was 70 patients divided into 37 males and 33 females compared with 70 healthy people (29 males and 41 females) as shown in Table 1. In comparison between hematology parameters in both groups (control group and covid-19 patients), especially in case of WBCs and Plts, we found that there was a big difference in those results with a high significance (P value more than 0.000).

4.1.Variation in hematological parameters

In details, mean WBCs count ($x10^3$/µl) of the control group was 6.39±0.16 whereas their count at the first week of infection has been slightly increased into 6.87±0.28 and then highly increased at the second week into 7.98±0.37 which led to the highly significant difference with F value of 8.351, (Table 3, Fig. 3).

The mean value of the mean percent of lymphocytes was 32.90±0.87 in control groups whereas their mean value has slightly decreased at the first week of covid-19 infection (30.96±1.5) and slightly increased at the second week of infection (31.52±1.47, F=0.570) with no significant difference (P value=0.566) (Table 3, Fig. 4).

The same result has been observed in case of PLTs count. As shown in Table 8 the mean value of the Plts count (PLTs $x10^3$/µl) of the control group was 236.3±5.6 whereas their count has increased at the first week of covid infection into 275.0±8.4 and at the second week of covid-19 infection their count has been again increased into 297.6±8.3 with a high significant difference of P value of (0.000) (Table 3, Fig. 5).

Table 3: Effect of COVID-19 infection on WBCs count, lymphocytes percentage, and platelets count.

Groups / Parameters	Control Mean±SE	First Week Mean±SE	Second Week Mean±SE	F	P-Value
WBCs Count ($x10^3$/µl)	6.39±0.16	6.87±0.28	7.98±0.37	8.351	0.000

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LYM %	32.90±0.87	30.96±1.5	31.52±1.47	0.570	0.566
PLTs Count	236.3±5.6	275.0±8.4	297.6±8.3	17.033	0.000

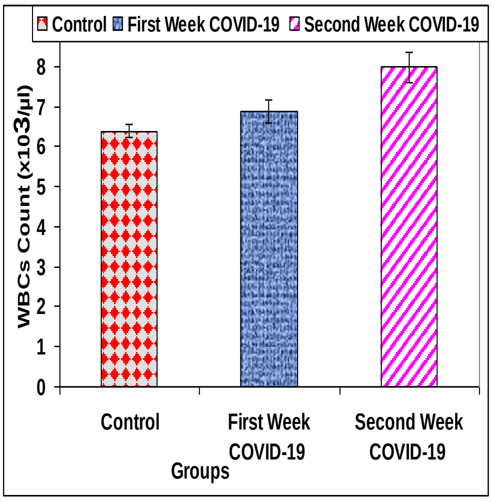

Figure 3: Effect of COVID-19 infection on WBCs count.

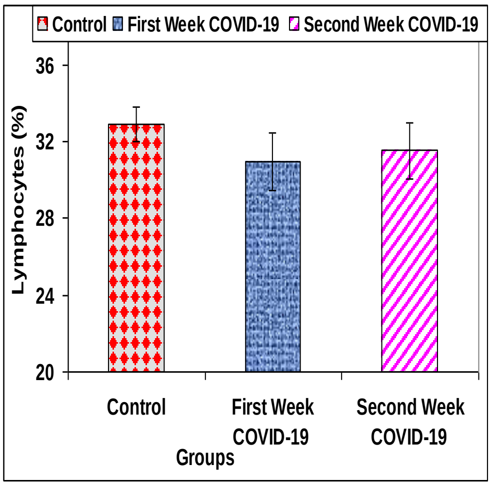

Figure 4: Effect of COVID-19 infection on lymphocytes percentage.

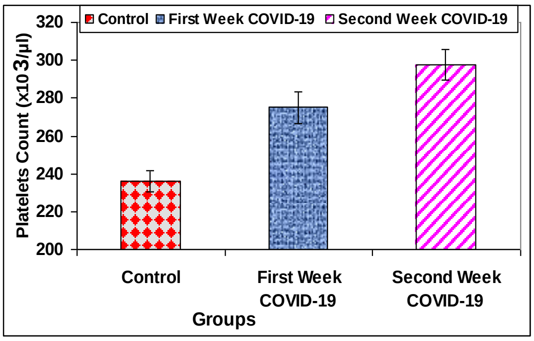

Figure 5: Effect of COVID-19 infection on platelets count.

Importantly, as shown in table 4 and figures (6-9) the comparison between the results of RBCs count (x10^6//µL) and it's indices (Hb (g/dl), HCT (%) and MCV (µm^3)) has revealed a high significant difference by a decrease in all mean values as compared with the control group. For instance, the mean value of hemoglobin concentration of the control group was 14.14±0.3 whereas it's concentration has decreased at the first week of covid-19 infection to the concentration of 13.27±0.2 and then again decreased into 12.78±0.2 at the second week of infection with a high significant difference (P value=0.000) and (F=22.533).

These results were very important to confirm that covid-19 infection effects on the concentration of hemoglobin more than other RBCs indices like MCH (pg/cell) and MCHC (g/dl) because the difference was very low with no significant difference (Fig. 10 and 11).

Table 4: Effect of COVID-19 infection on RBCs count, and its indices

Groups / Parameters	Control Mean±SE	First Week Mean±SE	Second Week Mean±SE	F	P-Value
RBCs (x10^6//µL)	4.56±0.1	4.59±0.1	4.45±0.1	7.814	0.001
Hb (g/dl)	14.14±0.3	13.27±0.2	12.78±0.2	22.533	0.000
HCT (%)	42.49±0.39	39.58±0.51	39.11±0.55	14.017	0.000
MCV (µm^3)	84.48±1.1	80.60±1.2	79.91±1.2	13.251	0.000
MCH (pg/cell)	28.48±0.7	28.34±0.7	28.17±0.7	0.043	0.958
MCHC (g/dl)	31.45±0.4	31.54±0.4	30.97±0.6	0.392	0.676

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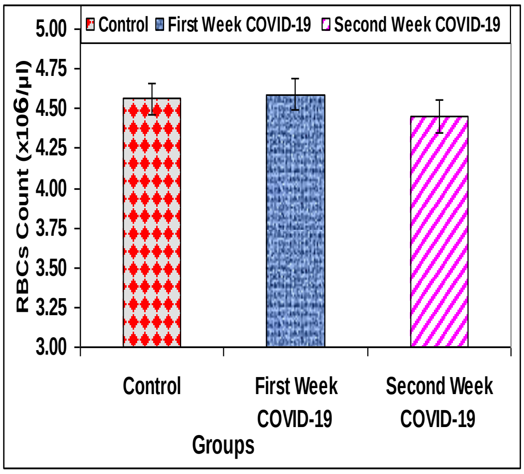

Figure 6: Effect of COVID-19 infection on RBCs count.

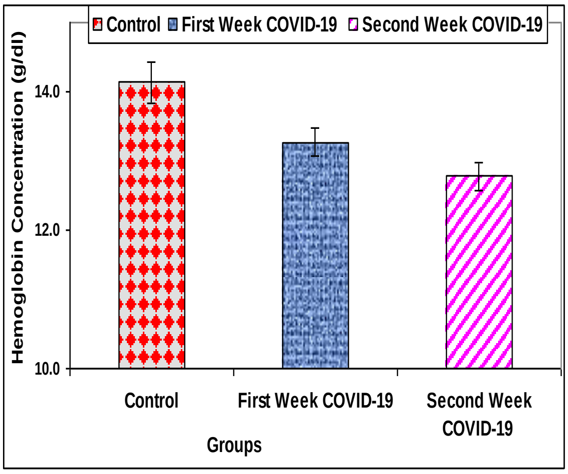

Figure 7: Effect of COVID-19 infection on hemoglobin concentration**.**

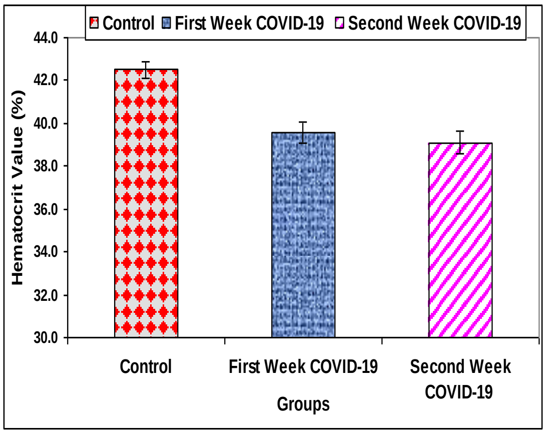

Figure 8: Effect of COVID-19 infection on hematocrit value.

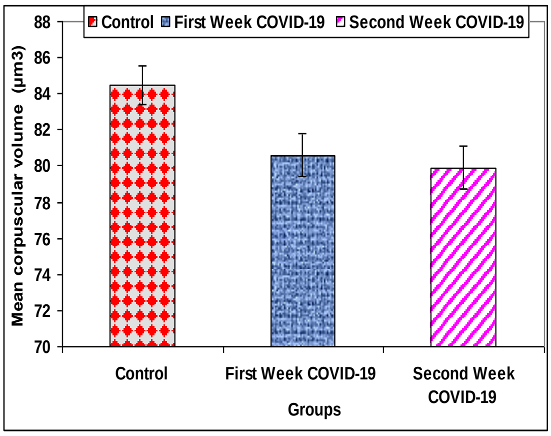

Figure 9: Effect of COVID-19 infection on mean corpuscular volume.

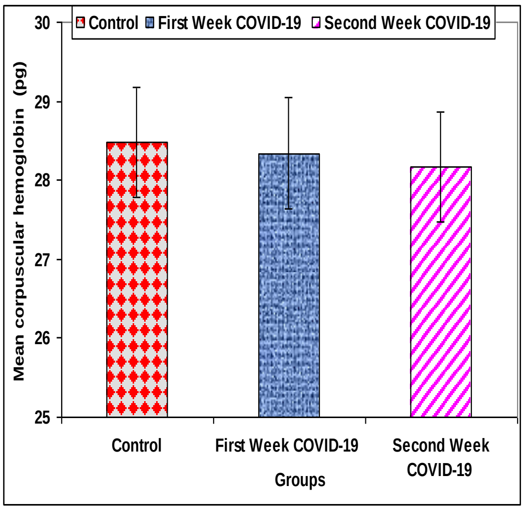

Figure 10: Effect of COVID-19 infection on mean corpuscular hemoglobin**.**

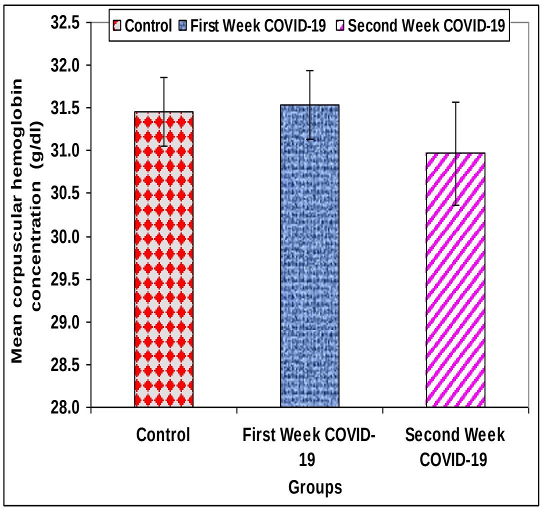

Figure 11: Effect of COVID-19 infection on mean corpuscular hemoglobin concentration.

3.2. Changes in the serum iron and ferritin level

On the other hand, this study had revealed the fact that covid-19 infection has big effect on the serum iron (mcg/dL) and the same effect on the ferritin level (ng/mL) as shown in Table 5. In more details, the mean value of serum iron of the control group was

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93.69±3.9 whereas it's value has decreased into 71.84±3.0 at the first week of covid-19 infection then it has slightly increased to the mean value of 72.23±2.9 at the second week of infection (Fig 12).

Conversely, with regard to the ferritin level, this study has confirmed the same results of many other published studies about the effect of covid-19 infection on the level of serum ferritin. As it has been observed in Table 10 that the mean value of ferritin level (ng/mL) has increased into high levels during both periods (first and second period) with a value of (336.6±33.1 and 459.8±38) and high significant difference (P value = 0.000) respectively (Figure 13).

Table 5: Effect of COVID-19 infection on Serum Iron and Ferritin levels.

Parameters / Groups	Control Mean±SE	First Week Mean±SE	Second Week Mean±SE	F	P-Value
Serum Iron (mcg/dL)	93.69±3.9	71.84±3.0	72.23±2.9	51.754	0.000
Serum Ferritin (ng/mL)	51.2±3.4	336.6±33.1	459.8±38	14.249	0.000

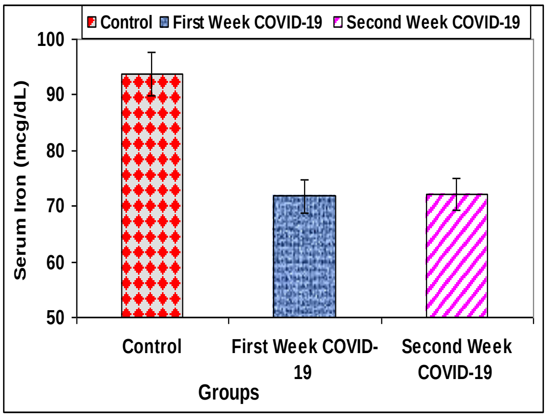

Figure 12: Effect of COVID-19 infection on serum iron levels.

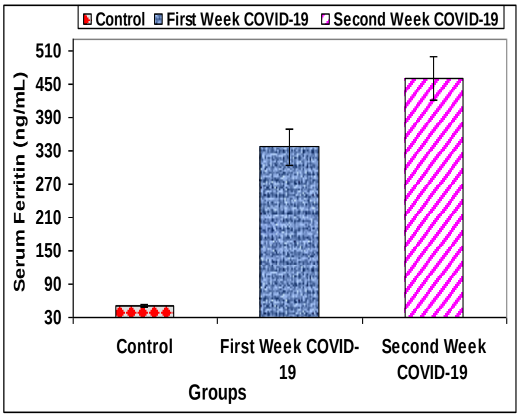

Figure 13: Effect of COVID-19 infection on serum ferritin levels.

4.3. Correlation between serum iron and Ferritin levels and hematological parameters in COVID-19 infected patients.

As it has been shown in table 6; there was no correlation between the changes in both parameters (Ferritin level and serum iron) and the total count of WBCs in patients infected with covid-19. This result confirms the slightly change in WBCs count as we have seen in Table 3, especially at the first week of infection.

Conversely, there was a weak negative correlation between the change in ferritin level and percent of lymphocytes (Correlation coefficient (r)= -0.219 with P value of 0.001).

On the other hand, with regard to the correlation between both parameters (ferritin level and serum iron) and RBCs count as well as it's indices; the study has confirmed the presence of low positive correlation in case of RBCs count and hemoglobin concentration with the change in serum iron-as it had been expected- (Correlation coefficient (r)= 0.286 and 0.326 with P value of 0.000) respectively. Additionally, with regard to the PLTs count; the correlation was very low (positive) with the change in ferritin level (Correlation coefficient (r)= 0.191 and P value = 0.005) with no effect of the change in serum iron on this parameter.

Table 6: Correlation between serum iron and Ferritin levels and hematological parameters in COVID-19 infected patients.

Hematological Parameters	Serum Ferritin		Serum Iron	
	Correlation coefficient (r)	P- Value	Correlation coefficient (r)	P- Value)
WBCs count	-0.049	0.477	-0.100	0.200
Lymphocytes %	-0.219-**	0.001	0.035	0.610
RBCs count	0.008	0.904	0.286**	0.000
Hb	-0.100	0.150	0.326**	0.000
Hct	-0.044	0.526	0.122	0.078
MCH	-0.042	0.545	.145*	0.037
MCHC	0.095	0.171	0.091	0.192
PLT count	0.191**	0.005	-0.169-*	0.014

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4.4. Effect of covid-19 infection on the prevalence of anemia

According to many of published studies in this context that the prevalence of anemia among covid-19 patients was not common (as clarified in the literature review). In details, although the hemoglobin level was lower than the normal range, but generally percent of anemia was an independent risk factor associated with severe illness in COVID-19 infection.

In this study, in order to determine the percent of anemia prevalence we considered the hemoglobin concentration in both males and females as (Hb <13g/dl and Hb <12g/dl) respectively. Accordingly, as shown in Table 12 percent of anemia among males was slightly low in comparison with females during the first week of infection (35.14% and 36.36%) respectively. Generally, this result means that the anemic patients of females were higher than the anemic patients of males with a general percent of 35.71% for both genders out of 70 covid-19 infected patients. Dependently, the percent of non anemic patients during the first week of covid-19 infection represents 64.29%.

Conversely, the prevalence of anemia during the second week of infection has changed as it is clear in tables (7-9) and figure.14. In details, whereas the difference between the percent of anemia in males and females was very low during the first week of infection -as we have mentioned above- simply, we can observe that the difference in anemia prevalence between both genders was high. Significantly, whereas the prevalence of anemia between males was 37.84% we found that the prevalence between females has reached 54.55% and out of 70 covid-19 patients the general prevalence of anemia between both genders was 45.71%.

Table 7: Distribution of anemia among COVID-19 patients after one week of infection according to gender

Groups / Distribution of anemia	Males COVID-19 patients (n=37)		Females COVID-19 patients (n=33)		Both genders COVID-19 patients (n=70)	
	Frequency	Percent (%)	Frequency	Percent (%)	Frequency	Percent (%)
Anemic Patients	**13**	35.14	**12**	36.36	**25**	35.71
None anemic Patients	**24**	64.86	**21**	63.64	**45**	64.29

Table 8 : Distribution of anemia among COVID-19 patients after two weeks of infection according to gender.

Groups	Males COVID-19 patients (n=37)		Females COVID-19 patients (n=33)		Both genders COVID-19 patients (n=70)	
Distribution of anemia	Frequency	Percent (%)	Frequency	Percent (%)	Frequency	Percent (%)
Anemic Patients	**14**	37.84	**18**	54.55	**32**	45.71
None anemic Patients	**23**	62.16	**15**	45.45	**38**	54.29

Table 9: Distribution of anemia among COVID-19 patients.

Period of infection	One week		Two weeks	
Distribution of anemia	Frequency	Percent (%)	Frequency	Percent (%)
Anemic Patients	**25**	35.71	**32**	45.71
None anemic Patients	**45**	64.29	**38**	54.29

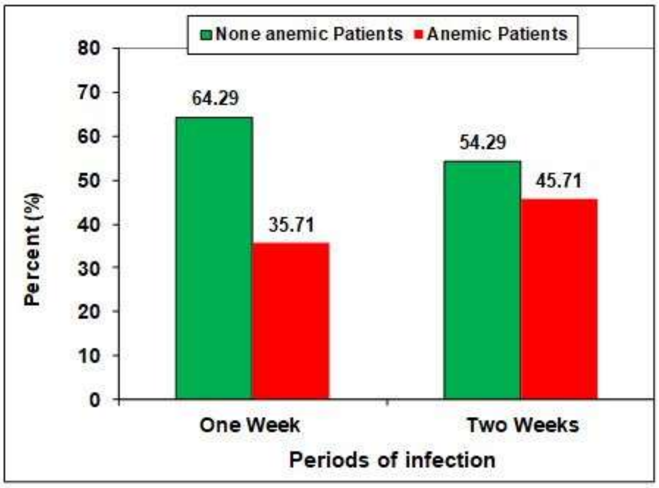

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Figure 14: Distribution of anemia among COVID-19 patients.

Similarly, whereas the degree of anemia (Mild) among males covid-19 infected patients during the first week was higher than those of females infected patients (76.92% and 58.33%) respectively, the degree of male anemic patients with (Moderate) was 23.08% whereas in females was 41.67%.

On the other hand, during the second week, that degree (Mild) was slightly changed into 78.57% between males and into 50.00% between females (Table. (10-11). Consequently, out of 32 anemic patients of both genders, the percent of mild degree of anemia has reached 62.50% and for moderate degree of anemia has reached 37.50% (Table 12 and Figure 15).

Table 10: The degrees of anemia among COVID-19 patients after one week of infection.

Groups	Males COVID-19 patients (n=13)		Females COVID-19 patients (n=12)		Both genders COVID-19 patients (n=25)	
Degrees of anemia	Frequency	Percent (%)	Frequency	Percent (%)	Frequency	Percent (%)
Mild	**10**	76.92	**7**	58.33	**17**	68.00
Moderate	**3**	23.08	**5**	41.67	**8**	32.00

Table 11: The degrees of anemia among COVID-19 patients after two weeks of infection.

Groups / Degrees of anemia	Males COVID-19 patients (n=14)		Females COVID-19 patients (n=18)		Both genders COVID-19 patients (n=32)	
	Frequency	Percent (%)	Frequency	Percent (%)	Frequency	Percent (%)
Mild	11	78.57	9	50.00	20	62.50
Moderate	3	21.43	9	50.00	12	37.50

Table 12: General degrees of anemia among COVID-19 patients

Period of infection	One week		Two weeks	
Degrees of anemia	Frequency	Percent (%)	Frequency	Percent (%)
Mild	**17**	68	20	62.50
Moderate	**8**	32	12	37.50

On the other hand, with regard to the types of anemia that possibly present in patients infected with covid-19 and depending on the classification criteria of the types on anemia (Microcytic hypochromic (MCV<80, MCH<27, and Normocytic hypochromic (MCV(80-98)) we found that males anemic patients suffering from microcytic hypochromic anemia during the first week of covid-19 infection have reached 53.85% whereas the same type of anemia between females has reached 83.33% with a general percent of 68% for both genders. (Table 13-15).

Conversely, with regard to the other type of anemia (Normocytic hypochromic) we found that the males patients suffering from this type representing 46.15% whereas females were representing 16.67% with a general percent of 32% for both genders.

Additionally, during the second week of covid-19 infection, the prevalence of both types of anemia was slightly different. As shown in table 19 the prevalence of (Microcytic hypochromic) anemia among males was 64.29% and among females was 83.33% with a general percent of 75.00% among both genders. On the other hand, the percent of the other type of anemia (Normocytic hypochromic) was less prevalent among males (35.71%) with same percent among females (16.67%) and with a general percent of prevalence of 25.00% for both genders (Table 13-15, figure 16).

Table 13: Types of anemia among COVID-19 patients after one week of infection

Gender	Males COVID-19 patients (n=13)		Females COVID-19 patients (n= 12)		Both genders COVID-19 patients (n=25)	
Types of anemia	Frequency	Percent (%)	Frequency	Percent (%)	Frequency	Percent (%)
Microcytic hypochromic (MCV<80)	7	53.85	10	83.33	17	68.00
Normocytic hypochromic [MCV(80-98)]	6	46.15	2	16.67	8	32.00

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Table 14: Types of anemia among COVID-19 patients after two weeks of infection

Gender / Types of anemia	Males COVID-19 patients (n=14)		Females COVID-19 patients (n= 18)		Both genders COVID-19 patients (n=32)	
	Frequency	Percent (%)	Frequency	Percent (%)	Frequency	Percent (%)
Microcytic hypochromic (MCV<80)	9	64.29	15	83.33	24	75.00
Normocytic hypochromic [MCV(80-98)]	5	35.71	3	16.67	8	25.00

Table 15: General types of anemia among COVID-19 patients

Period of infection / Types of anemia	One week		Two weeks	
	Frequency	Percent (%)	Frequency	Percent (%)
Microcytic hypochromic (MCV<80)	17	68	24	75
Normocytic hypochromic [MCV(80-98)]	8	32	8	25

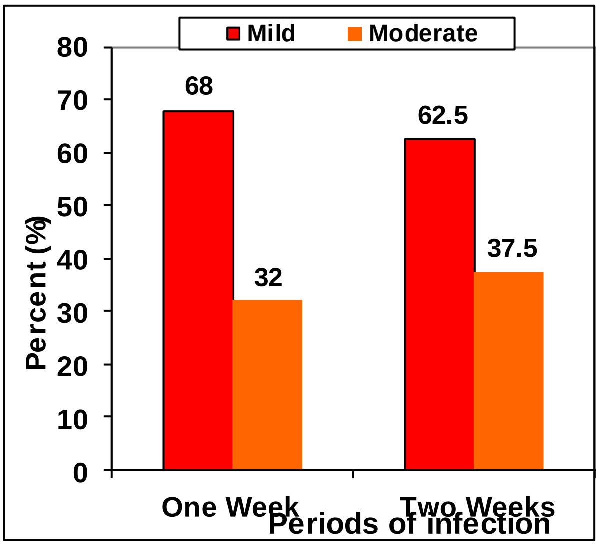

Figure 15: General degrees of anemia among COVID-19 patients.

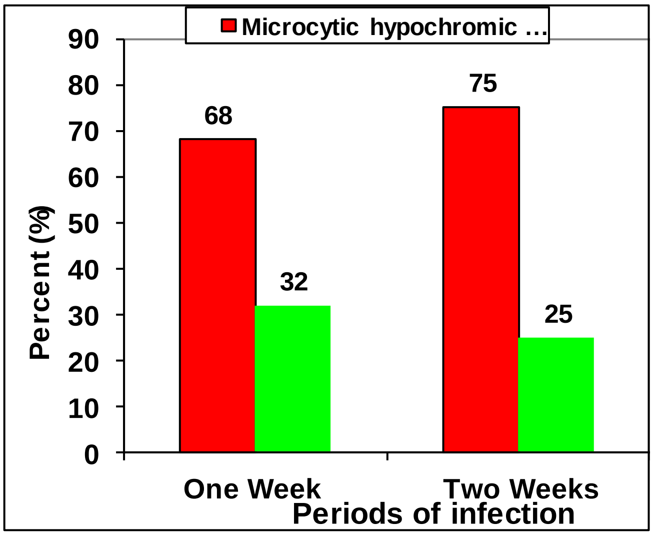

Figure 16: General types of anemia among COVID-19 patients.

4. Discussion

As it has been mentioned above that coronavirus disease-2019 (COVID-19) is an illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has become a pandemic with a high number of deaths. Therefore, biological markers and predictors have become important for infectious conditions to be evaluated and to have the proper interventions. Some of the most important markers related to this infectious condition are ferritin level, serum iron, and hemoglobin concentration.

This study has conducted to evaluate the effect of covid-19 infection on the variation of those markers. One of these markers is ferritin-iron storage protein, an acute phase protein of the immune response that can be a predictor of the patient's condition since it is independently associated with poor prognosis in COVID-19 [13, 14].

It is worth to mention in this context that while ferritin synthesis increases with increased cellular iron levels [15], serum levels of ferritin increase in response to systemic inflammation, in addition to the response to elevated iron levels. Accordingly, serum ferritin has been extensively used as a marker to assess iron status, infection or inflammation, malignancy [16], and autoimmune conditions [17].

Experimentally, depending on the results that has been confirmed by the current study that the mean value of ferritin level (ng/mL) has increased significantly into high levels during both periods (first and second period) with a value of (336.6±33.1 and 459.8±38) and high significant difference (P value = 0.000) respectively.

In COVID-19 patients, depending on many results that had been confirmed by a lot of published studies as well as the results that has been observed by the current study, serum

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ferritin was greatly increased (hyperferritinemia) compared to COVID-19 negative controls [18]. Elevated serum ferritin in concomitance with hypoferremia indicates that the elevation in ferritin is a response to COVID-19-induced hyper-inflammation and not iron loading.

Also, previous studies have confirmed that serum ferritin levels were higher in critical patients (compared to those with mild/moderate severity), severe patients (compared to non-severe patients), non-survivors (compared to survivors), in patients and critically ill patients (compared to outpatients), and in those patients requiring ICU and mechanical ventilation compared to those who didn't require these [18-20].

Therefore, ferritin level as an important marker used to assess the severity of covid-19 infection has been obviously demonstrated by the current study. Additionally, this result also compatible with the previous results confirming that ferritin is not only a marker of disease severity [18] but also one of the independent predictors of disease severity [21].

With regard to serum iron, this study have revealed the fact that covid-19 infection has big effect on the serum iron (mcg/dL). Whereas the mean value of serum iron of the control group was 93.69±3.9, it is value has decreased into 71.84±3.0 at the first week of covid-19 infection then it has slightly increased to the mean value of 72.23±2.9 at the second week of infection.

Similarly, depending on many of the previous studies which shown that serum iron levels were below the normal range in about 90% of hospitalized COVID-19 patients [22, 23]. These results demonstrates that low serum iron levels in the presence of infection reflect a physiological attempt to scavenge iron within the reticuloendothelial system to restrict iron availability to the growing pathogens, and thereby control the spread of infection. Therefore, in the aforementioned scenario, low serum iron is more likely to be a consequence of advanced inflammation than being a cause of hospitalization [24]. Accordingly, low serum iron levels tend to show an association with increasing COVID-19 severity, but apparently only up to a certain stage of severity and not beyond.

Depending on the aforementioned results, the logic explanation reflects the fact that the reduction in serum iron levels was associated with progression to the severe stage [24] and this reduction could predict disease transition from mild to severe status. However, there was no significant difference between serum iron levels of the severe and critical groups implying that there was no further reduction in serum iron levels from the severe to the critical stage [22].

However, higher iron levels in those with severe respiratory failure compared to those with mild respiratory failure indicates that the increment in iron may play a role in the pathological progression of the disease [24]. Of course, generally, the levels of serum iron vary remarkably between individuals and can vary every hour.

By comparison, the current study has revealed that the mean value of hemoglobin concentration of the control group was 14.14±0.3 whereas it's concentration has decreased at the first week of covid-19 infection to the concentration of 13.27±0.2 and then again decreased into 12.78±0.2 at the second week of infection with highly significant difference (P value=0.000) and (F=22.533).

Patients with severe disease showed a clear decrease in hemoglobin levels [25]. Also, Zhang *et al.* [26] reported that severe cases showed significantly lower hemoglobin levels than mild and moderate cases. One of the most important recent studies (compatible with the results of the current study) had shown that patients with COVID-19 had a significant (P=0.0088) decrease in hemoglobin concentration [(median (IQR) g/ dl], 13.35 (11.73-14.00), 13.05 (12.10-14.05), and 12.60 (11.45-13.60) at 0 day, 14 days, and 21 days, respectively compared with the healthy individuals (13.95 (12.70-15.53) [27].

This result led to the fact that hemoglobin concentration might be decreased depending on the severity of covid-19 infection. Thus, it was possible to distinguish between moderate and severe cases based on hemoglobin levels and other blood parameters.

Clinically, a link between COVID-19 infection symptoms and the consequences of excess heme does not have to be relevant for every patient; but, in certain circumstances, it may correlate or even create a more severe illness development due to pre-existing hemolytic diseases or hemolysis-provoking events [28]. Therefore, WHO has recently taken into consideration the possible contribution of blood changes within the COVID-19 course [29].

Moreover, it is worth to mention here that various hypotheses about the relation between the COVID-19 and the 1-beta Hemoglobin chain were assault. Theoretical research relies on the ability of COVID-19 proteins with porphyrin to form a conserved domain and release free iron leading to a drop in the affinity of hemoglobin binding to oxygen and interfere with the hemoglobin anabolism [30].

Additionally, previous studies have revealed that Hemoglobin concentration is not related to overall survival., Hemoglobin is affected by factors like red blood cell population, age, lactate dehydrogenase. Also adding the ratio of arterial partial oxygen pressure to inspired oxygen percentage. Anemia is a condition that affects the old and feeble, and it can have a detrimental impact on their health [31].

As we have confirmed above that disturbed iron metabolism may led to a complicated process. Indeed, recent data show that COVID-19 patients tend to present decreased hemoglobin levels indicating the presence of anemia.

According to the results of the current study, the percent of anemia among males was slightly low in comparison with females during the first week of infection (35.14% and 36.36%) respectively. Dependently, the percent of non anemic patients during the first week of covid-19 infection represents 64.29%. Conversely, the prevalence of anemia during the

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second week of infection has changed. Also, the current results showed that that males anemic patients suffering from microcytic hypochromic anemia during the first week of covid-19 infection have reached 53.85% whereas the same type of anemia between females has reached 83.33% with a general percent of 68% for both genders. Conversely, with regard to the other type of anemia (Normocytic hypochromic) we found that the males patients suffering from this type representing 46.15% whereas females were representing 16.67% with a general percent of 32% for both genders.

Predominantly, anemia could be the result of iron-restricted erythropoiesis arising from alterations in iron metabolism. Increased ferritin levels could be indicative of a strong inflammatory reaction in COVID-19 or related to viral entry into the human body and its impact on iron metabolism [32, 33]. In addition, the innate immune response could restrict iron availability during infections to deprive the pathogen of it, a mechanism that would also lead to anemia [34].

Giacomelli *et al*. [35] reported that anemia (defined as hemoglobin levels below 125 g/L) was more prevalent in Covid-19 non-survivors (66.7%) compared to survivors (42.7%).

More excitingly, depending on results that had been conducted by Theural et al. [36] that most patients with multifactorial anemia after one week were normocytic and normochromic (83.9%) with elevated median ferritin levels of 795 µg/L. This result matches the results of the current study which demonstrating that most cases of anemia were due to inflammation as we have observed above.

Finally, in this context, we can conclude that anemia is a common and persistent finding in COVID-19 infection especially during the second week of infection. Given the impact that anemia has on quality of life [37-39], the problem cannot be overlooked and the pathogenesis of anemia should be investigated and treatment instituted whenever possible.

5. Conclusion

Results of the current study confirmed the observations and other results revealed by the previous studies regarding the variations in hematological parameters and some other inflammatory factors in patients infected by covid-19. Therefore, further hematological studies are needed to confirm these results to help the clinicians for better understanding of COVID-19 infection and to provide more clinical treatment options.

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