Original Article

# Estimation Of Cxcl10 With Some Biochemical Parameters In Covid-19 Patients

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## Abstract

Coronavirus disease 2019 (COVID-19) is the present global public health problem that has already caused pandemic since 2020. This respiratory corona viral infection can cause severe respiratory illness and death might be the outcome in severe cases. COVID-19 can manifest several atypical clinical presentations including neurological presentation. An important neurological problem is neurovascular thrombotic disorder A thrombotic event might be due to arterial or venous system affection. The study was conducted in the public laboratories on the outskirts of Baghdad after collecting 100 samples, (60) of people infected with Covid - 19 and (40) of healthy people and the ages of the people ranged from 18-80 years and the ages of the healthy ones from 18-70 years old. The study was conducted to investigate some biochemical indicators which includes Chemokine CXCL10, Fibrinogen, D-dimer, ferritin, C-reactive protein, iron and fibrinogen. The results showed a significant increase in the level of the chemokine CXCL10 in patients infected with Covid-19 virus compared to the control group, and a significant increase in the levels of D-dimer, ferritin, C-reactive protein, iron and fibrinogen which are important biochemical indicators in Covid – 19 patients.

**Keywords:** Covid-19, Chemokine CXCl10, d-dimer, Ferritin, C-reactive Protein, Fibrinogen, Iron.

## INTRODUCTION

Chemokine CXCL10 also referred to as interferon-inducible protein-10 (IP-10), is an antiviral inflammatory chemo protein, possessing a molecular weight of 10 kDa and 1173 base pairs (nitrogen base), and containing 4 exons. The exons are encoded by a protein of 98 amino acids. CXCL10 is secreted by IFN-γ (Interferon gamma)-dependent posterior cells (1-2). The chemokine CXCL10 is a biomarker associated with obesity, insulin resistance, atherosclerosis, neurodegenerative disorders associated with tumors and infection (3). The CXCL10 chemokine binds to its cellular receptor CXCR3 found in T lymphocytes and natural killer cells by the CXCL10 gene located on chromosome 4, and is secreted by monocytes, endothelial cells, adipose tissue, and fibroblasts (4). The CXCL10 chemokine plays a role in inhibiting angiogenesis, cell chemo taxis, regulating cell growth and proliferation, and cell death (5). A study indicated an increase in CXCL10 levels with acute respiratory infections, as CXCL10 has a direct antiviral effect by stimulating a group of phenomena that lead cells to determine an anti-viral state. These phenomena include activation of apoptosis or direct killing for cells infected by activated immune cells (6). Interferon's (IFNs) can stimulate surrounding cells to express potent antiviral proteins including enzymes, transcription factors, cell surface glycoproteins, cytokines, and chemokine's. Furthermore, they can inhibit cell proliferation, regulate apoptosis and modulate the immune response (7). The chemokine CXCL10 has a key role in the organism's antiviral response, particularly in respiratory infections (8). Several studies have shown that CXCL10 levels estimated in serum, bronchoalveolar lavage fluid, or nasal secretions are consistently associated with the severity and duration of acute respiratory infection due to viral infections (9,10). In previous studies with SARS-CoV and MERS-CoV patients, enhanced expression of CXCL10 was also observed in patient samples and was associated with characteristics of increased disease severity, lung inflammation and lung damage (11,12) and interactions between chemokine and chemoreceptors have recently been suggested to be of interest. in the initiation and progression of cancer. CXCL10 has dual actions on tumor genesis depending on the spliced variant of the corresponding CXCR3 receptor. CXCR3-B has growth inhibitory properties, while CXCR3-A promotes cell proliferation (13).

## MATERIALS AND METHODS

### Sample and Blood Collection

The study included 100 samples, (60) from people infected with COVID-19 and (40) from healthy people (control group) from public laboratories on the outskirts of Baghdad city for the period from 25/8/2021 to 10/1/2021. The ages of the infected people ranged from 18-80 years old, and healthy subjects ranged in age from 18-70 years, 3-5 ml of blood were collected from healthy and patients people by drawing blood from a vein in the arm or elbow using a medical syringe,

### Estimation the CXCL 10

The chemokine was estimated using Elisa technique to measure the Elisa group technique according to the body Elisa sandwich provided by the company (Melsin, china).

### Estimation the fibrinogen

Fibrinogen was estimated using KC1Delta semi-automated analyzer technique for clot detection for coagulation assays (kc1 delta stago German).

### Estimation the Iron

Iron was determined by absorption process and wavelength was calculated by bio system.

### Estimation the D-dimer

D-dimer was estimated using an icroma II instrument which is a Europium automated portable nanoparticle scanner for the determination of synthesized concentrations (boditech, Korea).

### Estimation the ferritin

Ferritin was estimated using an icroma II instrument which is a Europium automated portable nanoparticle scanner for the determination of synthesized concentrations (boditech, Korea).

### Estimation the CRP

C-Reactive Protein was estimated using an icroma II instrument which is a Europium automated portable nanoparticle scanner for the determination of synthesized concentrations (boditech, Korea).

### Statistical analysis

The statistical program SPSS Statistical Package for the Social Sciences version 20 was used to analyze the results obtained, and the arithmetic mean and standard deviation (SD) for all measurements were used, and the T-test was used to compare the biochemical variables between the two groups of patients and healthy people at the probability level of $P< 0.05$.

## Results and Discussion

The results showed a significant increase in the concentration of chemokine CXCl10 in Covid-19 patients compared to healthy people, also the data revealed an increase in the levels of D.dimer, ferritin, CRP, Iron and fibrinogen and in people with Covid-19 compared to healthy people. As shown in Table (1)

| Parameters | Control | Patients |
|---|---|---|
| CXCL10 (Pg/ml) | 0.078±0.014 | 0.104±0.058 * |
| D.dimer (ng/ml) | 173.678±72.434 | 376.666±128.273 * |
| Ferritin (ng/ml) | 89.228±59.107 | 274.215±176.624 * |
| CRP (mg/L) | 2.815±0.915 | 17.007±7.440 * |
| Iron ( µmol/l) | 16.899±6.857 | 21.316±5.101 * |
| Fibrinogen( g/l) | 1.864±0.777 | 2.935±1.334 * |

* This sing means different significant at $P\leq0.05$.

The concentration of CXCl10 was found in the serum of COVID-19 patients much higher than in the control group. As in Figure (1).

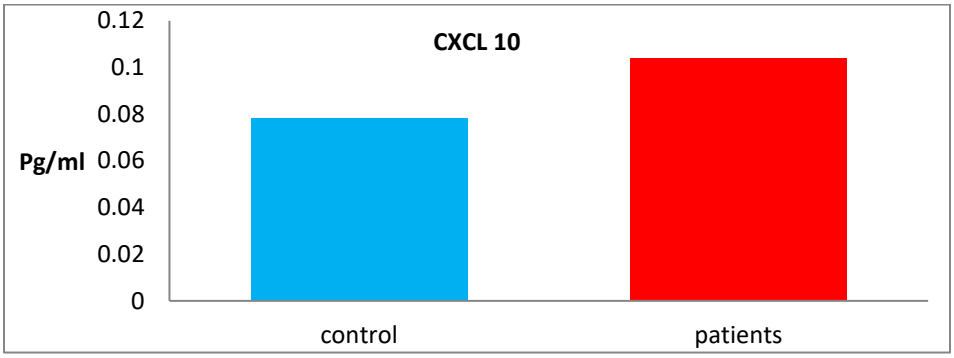

Figure (1): CXCL10 chemokine concentration in the two groups

The results shown in Figure (1) showed that the average chemokine was 0.104 ± 0.058 in patients compared to the healthy group, which was 0.078 ± 0. 014.The above results indicated a significant increase in the concentration of chemokine CXCL 10 in the group of patients compared to the healthy group. Current research with the study by Chen showed. (14) reported that the level of CXCL10 was significantly increased in patients with severe COVID-19 disease compared to patients with non-severe disease (P<0.002). As a study conducted by Zhao showed. (15), which revealed that CXCL10 was significantly elevated in sick COVID-19 patients in both mild and severe cases at the onset of infection when compared to healthy controls. Whereas in the moderate patient group, CXCL10 levels decreased from Week 2 and returned to normal at Week 4. Suggesting that CXCL10 can serve as an excellent biomarker to differentiate between healthy and COVID-19 patients and predict disease progression (16,17) Acute respiratory distress syndrome associated with COVID-19 can be considered a direct cause of death in many patients. It has been observed that acute respiratory distress syndrome caused by SARS-CoV-2 has different and distinct a etiologies compared to acute respiratory distress syndrome which is caused by SARS-CoV-2. Caused by bacterial infection eg cytokine response comparison between acute respiratory distress syndrome associated with COVID-19 and ARDS not associated with COVID-19. Using the Luminex assay, researchers measured concentrations of 45 biomarkers in plasma and bronchoalveolar lavage fluid, and revealed increased CXCL10 concentrations in plasma and epithelial endothelial fluid in a group of patients with COVID-19-induced acute respiratory distress syndrome compared to groups of patients without COVID-19. 19. Furthermore, the concentrations of CCL5, CXCL2, and CXCL10 were higher in SARS-CoV-2-infected patients. It should be noted that CXCL10 concentration correlates with the number of ventilator-free days (18) Henceforth, it is well known that lymphocytes are a very important component of the immune system and through activation of other immune components and elimination of infected cells (19). This is considering that CXCL10 is the major binding of the CXCR3 receptor presented on effector lymphocytes. It appears that chemokines are likely one of the main mediators causing imbalances in immune responses in COVID-19. It has been suggested that it may be an indicator of the necessity of mechanical ventilation in patients infected with SARS-CoV-2. Furthermore, if a significant association is observed between the immune response to CXCL10 and COVID-19, a potential therapy targeting the CXCL10-CXCR3 axis should be considered (20). Of the inflammatory factors in plasma samples taken from SARS-COV2 patients, the results showed that the levels of cytokines and chemokines such as (CCL5, IL-2Ra, and CXCL10 were significantly elevated in patients, while their level decreased after the patients' condition improved, and it was also shown that the concentration of CXCL10 was higher Seven times in severe cases and four times higher in moderate cases of COVID-19 patients compared to healthy controls The level of CXCL10 also varies according to the severity of the disease, being 100% higher in severe cases. Compared to milder cases of COVID-19. Lower levels of chemokines after improved health and mild illness indicate a reduced inflammatory response (21).

The results shown in Table (2) showed the dimer concentration in the two groups of patients and healthy subjects, as it reached 376.666 ± 128.273 ng/ml for patients, compared with 173.678 ± 72.434 ng/ml in healthy subjects, as shown in Figure (2).

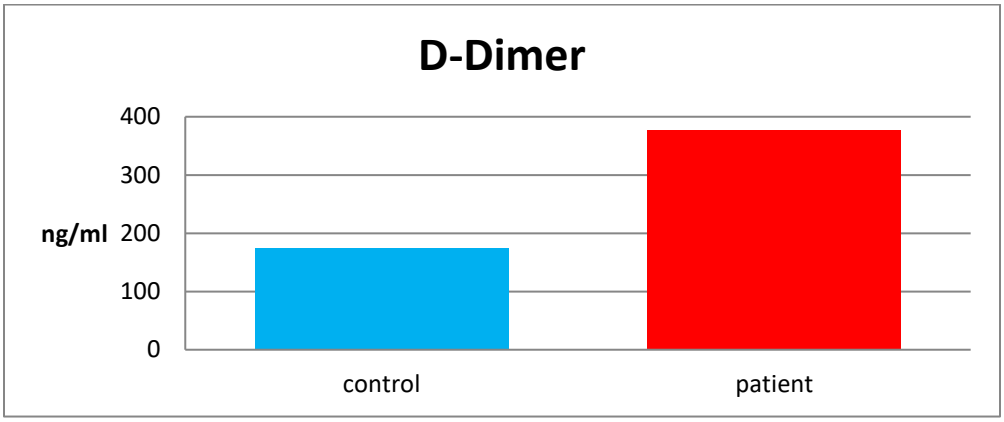


Figure (2): concentration of dimers in two groups

The current study agrees with findings made by Wang et al. (22) that showed that D-dimer levels are significantly higher in COVID-19 patients, especially those who were either ill or severely ill or deceased (23). Some have hypothesized that regular levels of D-dimer in severely infected individuals novel coronavirus infection may be associated with highly pathogenic infection, higher rates of thrombotic activity, and higher mortality rates in these patients (24, 25). In 2020, Guan et al. presented the results of a large retrospective study that indicated the relationship between abnormal levels of D-dimer and disease severity of first-time COVID-19 patients (26). Lippi noted that the D-dimer levels of COVID-19 patients with mild or moderate level of disease, that is, those who did not require ICU admission, were significantly lower than the D-dimer levels of patients with severe level of disease, is those whose admission is required ICU (27). In another study, Yao and co. showed that COVID-19 patients who were classified as having severe level of illness on the basis of oxic index, CT lung scans, and corresponding clinical guidelines showed a significant association between disease severity and (28) D-dimer levels.

The results of Table (3-4) indicated that the mean ± standard deviation of ferritin in Covid-19 patients was 274.215 ± 176,624 ng/cm3, compared to 89.228 ± 59.107 ng/cm3 as well in the healthy group.

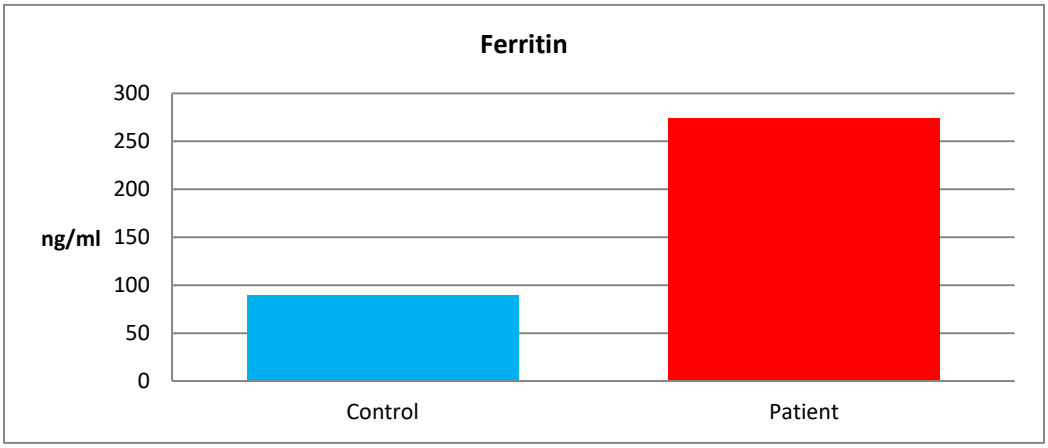


Figure (3): Ferritin concentration in the two groups

The present study agrees with the study by Abbaspour et al that ferritin was considered a major mediator of immune dysregulation, especially under severe hyperferritinemia, through direct immunosuppressive and pro-inflammatory effects, contributing to cytokine storm (29). The lethal outcome of COVID-19 has been reported to be associated with cytokine storm syndrome (30), and thus it has been suggested that disease severity depends on the cytokine storm syndrome. Many people with diabetes show elevated levels of ferritin in their blood (31, 32). They are known to face a higher likelihood of developing serious complications from COVID-19 (33). On this basis, we briefly review the evidence supporting the hypothesis that ferritin levels may be a critical factor influencing the severity of COVID-19.

In one study conducted by Zhou et al on 20 patients with COVID-19, it was found that individuals with severe and very severe COVID-19 showed an increase in serum ferritin level, with serum ferritin in the very severe COVID-19 group being significantly higher than Severe COVID-19 group. (34) In agreement with this, another study revealed that in patients who died of COVID-19, ferritin levels were elevated upon hospital admission and throughout the hospital stay. Mean values of serum ferritin levels after day 16 of hospitalization exceeded the upper limit of detection in these patients, indicating that ferritin levels increased without stopping (35). Table (3-4) shows that the mean ± standard deviation of C-reactive protein in patients with Covid-19 was

(17.007 ± 7,440 mg/l), while in the healthy group, its value was 2.815 ± 0.915 mg/l), as shown in Figure 3. -4).

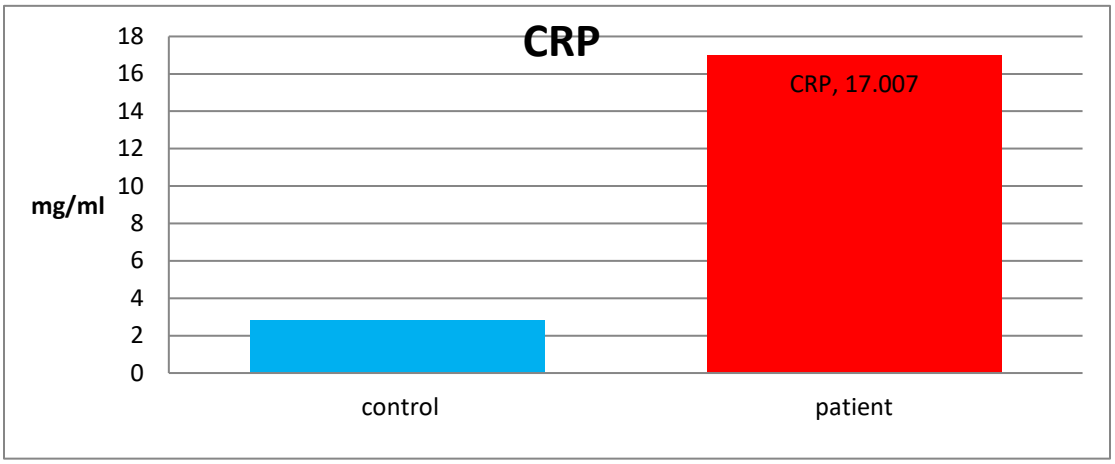


Figure (4): The average concentration of C-reactive protein in the two groups

The current study agrees with the study by Azar et al. that excessive inflammation was considered the main cause of serious illness and death in patients with COVID-19, CRP is a sensitive indicator for assessing tissue injury. It is clear that levels of C-reactive protein in the blood increase when there is acute inflammation, major insults and coronary heart disease. After the inflammation subsides, it may return to the normal range. It is stable in vivo and is unaffected by shocks and hormones. CRP can enhance phagocytosis through a specific CRP receptor, and it eliminates many pathogenic microorganisms. During the process of COVID-19 pneumonia, a cellular response storm (CRS) can be triggered, which is associated with higher mortality in COVID-19 (36). Cytokines such as IL-6 and TNF-α stimulate hepatocytes to produce CRP. Table (3-5) shows that the mean ± standard deviation of iron was 21.316 ± 5.101 µmol/L for patients with COVID-19 compared to 16.899 ± 6.857 µmol/L in healthy subjects.

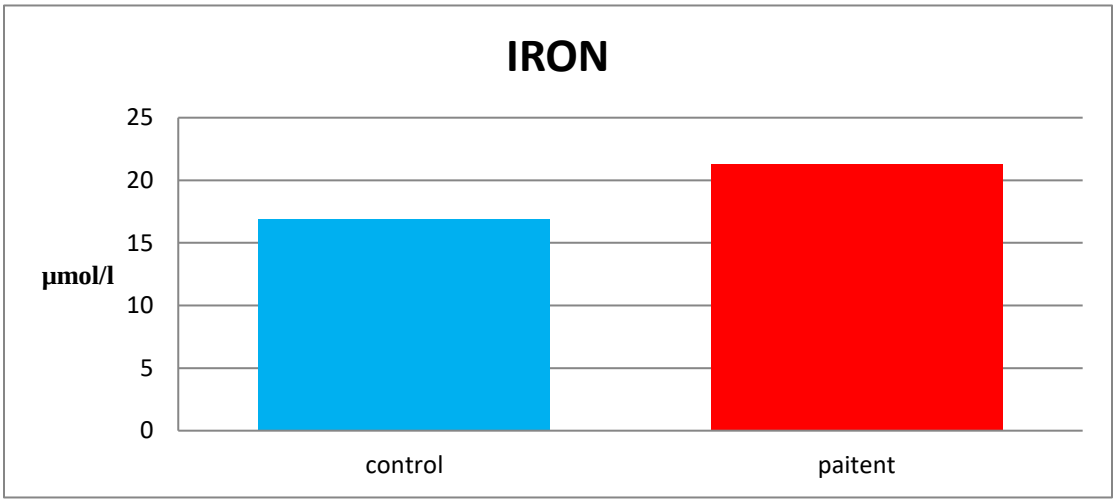


Figure (3-6) iron concentration in the two groups

The study agrees with the study by Lukas, (37) that first, pre-existing anemia is associated with an increased risk of death in hospitalized patients with COVID-19. Second, entry anemia is also associated with an increased risk of death (38). Third, hemoglobin levels decreased during hospitalization, which was associated with a higher incidence of anemia, specifically inflammatory anemia, and its prevalence reached 87.8% in people who were hospitalized for at least two weeks. Most importantly, patients were of anemia more likely to be admitted to the intensive care unit. Fourth, hemoglobin levels returned to normal in most patients during a median observation period of four months.

Decreased hemoglobin and the development of anemia during treatment are associated with immune activation and cytokine-mediated changes to iron homeostasis, which are hallmarks of inflammatory anemia (39). Table (3-5) indicates that the standard deviation of fibrinogen was 2.935 ± 1.334 in the group of patients compared with 1.864 ± 0.777 in the healthy group. (3-5).

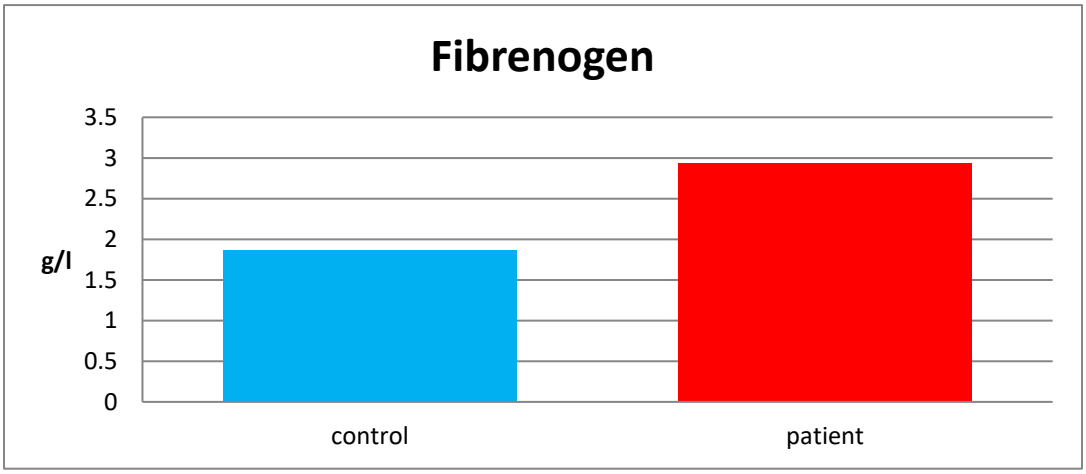

Figure 3-5 Estimation of the fibrinogen concentration in the two groups

Fibrinogen is a glycoprotein that is produced in the liver as an anti-infective organ. The liver reacts during the acute inflammatory phase in hospitalized COVID-19 patients and secretes many reactants such as fibrinogen, C-reactive protein (CRP), ferritin and many cytokines (40) Guan et al (41) showed that the fibrinogen chains of FGA, FGG and FGB These are the higher central proteins associated with COVID-19 deaths. The release of these reactants is the body's defense mechanism against invading pathogens. In this regard, the dual function of fibrinogen is important, as it regulates the antimicrobial activity of immune cells and the formation of thrombi of Ko et al. Summarized several host defense mechanisms of fibrinogen, in short two main mechanisms are fibrin matrix barrier formation and host immune protective functions (42).

Clotting formation can limit the spread of pathogens as a defense mechanism and researchers believe that local formation of lung clots can limit the spread of SARS-CoV-2 (43).

The D dimer is the product of fibrin degradation in the blood after fibrin clot hydrolysis. Increase in D-dimer is associated with decreased release of fibrinogen from platelets (43)

## CONCLUSIONS

From the results of the current study, we can conclude that the level of chemokine CXCl10 in those infected with Covid-19 compared to the healthy ones has a higher level of ferritin, iron and C-reactive protein in the infected compared with the healthy ones, and it can be adopted as an indicator of the severity of the disease. Elevated fibrinogen and dimer in patients compared to healthy controls and is an indicator of liver damage

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