

# Role of Interleukin-6 Receptor in the Clinical Status of Covid-19 Patients who Admitted to Al-Shifaa Epidemiological Hospital in Kirkuk City

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## Abstract

**Background:** The clinical presentation of COVID-19 patients is varied from mild symptoms to severe respiratory failure with multiple organ failure. **Aim of the study:** This study was conducted to estimate the level of IL-6 receptor and some biochemical parameters: **Patients and Methods:** A case-control study done in Kirkuk city 1st of December 2021 to 28th of February 2022. The study included 60 people already infected with Covid-19 virus who admitted to Al-Shifaa Epidemiological Hospital in Kirkuk city with different age groups ( $\geq 50$  years) of both sexes. Covid-19 patients derived in to 3 groups (20 patients with mild Covid-19 infection, 20 with moderate infection and 20 with severe infection) depending on specialized physicians in internal medicine in the hospital and CT-Scan outcomes. The study also included 30 healthy control individual who apparently haven't any chronic disease with the same age range and box sexes. The clinical spectrum of COVID-19 in this study was classified according to standards in the China Center for Disease Control and Prevention, covid-19 infection ranges from being asymptomatic to being in severe acute respiratory distress. Blood sample collected from each subject enrolled in this study for determination of IL-6R by ELISA **Results:** The study showed that majority of patients were above 60 years, as the risk of covid-19 infection increased with age as elderly was most affected and the severity increase with the increasing in age. The study also found that males were more affected by the virus from females. The study showed that, the prevalence of smoking among Covid-19 infection was 25% (15 of 60), as compared with 13.33% in the healthy control group. The study demonstrated that obesity revealed at s risk factor of covid-19 severity. The study showed that the highest mean of IL-6R was observed in Covid-19 patients ( $39.68 \pm 27.92$  ng/ml) and the lowest mean was in the control group ( $13.65 \pm 4.56$  ng/ml) and the difference was highly significant at P. value: 0.0001. The study showed negative correlation between IL-6R and PO<sub>2</sub> among Covid-19 patients. It was concluded that the highest mean of IL-6R, among Covid-19 patients and these elevations seem to reflect that the multiple organ injury. Recommended to uses IL-6R in parallel with other parameters (Ferritin, D-Dimer, CRP and LDH) as biomarkers for Covid-19 severity.

**Keywords:** IL6R; Covid-19; SARS Cov2; Severity; Smoking

## 1. Introduction

Coronavirus disease-19 (COVID-19) is the result of 2019-nCoV/SARS-CoV-2 infection. SARS-CoV-2 is characterized by its high transmissibility and its unusual lethality. Human-to-human transference occurs via respiratory droplets, especially when people cough or sneeze, or through contact with a contaminated surface, as the virus can survive for several days on immobile surfaces (1,2,3). The incubation period is between 2 and 14 days, with a mean of 5 days. Patients with no symptoms are contaminating, and transmission of the virus is mainly important in the few days before the appearance of symptoms and during the first days of illness (4,5). Infection with (SARS-CoV-2) exist with upper respiratory symptoms like cough, fever, myalgia, and watery diarrhea, etc. (6). COVID-19 is associated with remarkably heterogeneous presentations and outcomes in humans. The

majority of those infected are asymptomatic or have mild ambulatory disease, but approximately 2%–10% develop severe disease leading to hospitalization and 25%–30% of hospitalized patients will require intensive care (810). Interleukin-6 (IL-6) is a cytokine that has diverse and pivotal roles in the inflammatory and immune responses to infection, and as an important downstream regulator of the coagulation cascade (7,8). Dysregulation of IL-6 signalling pathways has been linked to inflammatory-mediated conditions such as rheumatoid arthritis, juvenile idiopathic arthritis, and the cytokine release syndrome that can sometimes follow chimeric antigen receptor T-cell therapy. The characterisation of IL-6 as a pleiotropic cytokine implicated in different diseases has led to the search for therapeutic interventions that target the blockade of IL-6 and its downstream signaling pathways (9,10). This study is conducted to estimate the level of IL-6 receptor in sera on hospitalized

Covid-19 patients and its relation clinical status of patients and some biochemical parameters

## 2. Patients and Methods

A case-control study done in Kirkuk city 1st of December 2021 to 28th of February 2022.

The study included 60 people already infected with Covid-19 virus who admitted to Al-Shifaa Epidemiological Hospital in Kirkuk city with different age groups ( $\geq 50$  years) of both sexes. Covid-19 patients derived in to 3 groups (20 patients with mild Covid-19 infection, 20 with moderate infection and 20 with severe infection) depending of specialized physicians in internal medicine in the hospital and CT-Scan outcomes. The study also included 30 healthy control individual who apparently haven't any chronic disease with the same age range and box sexes

- Approval of the council of College of Medicine/ Tikrit University was obtain for the proposal of the study.

- Approval permission was presented to the director of Kirkuk Health Directorate / Al-Shifaa Epidemiological Hospital.

- An interview was carried out with these patients using questionnaire form designed by the investigator including their demographic characteristics, age, weight, length.

Covid-19 diagnosis was made based on WHO criteria and/or confirmed by RT-PCR of nasopharyngeal specimens and based upon the instructions for the companies that manufacture laboratory materials for diagnosing the Covid-19 virus by means of the PCR device by the laboratory staff working in the Public Health Laboratory in the city of Kirkuk, where the infection was confirmed by them through the protocols followed by the Ministry of Health.

The clinical spectrum of COVID-19 in this study was classified according to standards in the China Center for Disease Control and Prevention, covid-19 infection ranges from being asymptomatic to being in severe acute respiratory distress. Chest CT imaging was conducted to determine the extent of lung involvement and to detect Covid-19 pneumonia with different imaging features including GGO, patchy consolidation, and crazy paving signs. Chest CT was performed within 3-7 days from infection. Five ml of blood sample was taken by vein puncture without using tourniquet from each subject enrolled in this study. Blood samples were divided in to two tubes, 2 ml of blood added to tubes containing sodium citrate as anticoagulant for determination of d-dimer by ELISA. The second part, 3 ml added to jell tubes, after blood clotting, centrifuged at 3000 rpm for 15 minutes then clot removed and remain re-centrifuged at 3000 for 10 minute and the obtained serum were aspirated using mechanical micropipette and transferred into clean test tubes which labelled and stored in deep freeze at  $-20^{\circ}\text{C}$  for determination of IL-6R by ELISA

## 3. Results

In this study, 60 Covid-19 patients and 30 healthy controls. Covid-19 patients derived in to 3 groups (20 patients with mild Covid-19 infection, 20 with moderate infection and 20 with severe infection).

The study showed that majority of patients were above 60 years, as the risk of covid-19 infection increased with age as elderly was most affected. The study also found that males were more affected by the virus from females, [Table 1](#).

Age groups (year)	No.	%
50-59	27	36.67
60-69	19	30
>69	14	33.33
Total	60	100
Sex		
Females	25	41.67
Males	35	58.33

The study showed that 45% of patients were with normal BMI, 20% were overweight and 35% obese, [Table 2](#).

BMI	No.	%
Normal (BMI: 18.5 - 24.9 kg/m <sup>2</sup> )	27	45
Overweight (BMI: 25-29.9 kg/m <sup>2</sup> )	12	20
Obese (BMI: $\geq 30$ kg/m <sup>2</sup> )	21	35
Total	60	100

The study showed that, the prevalence of smoking among Covid-19 infection was 25% (15 of 60), as compared with 13.33% in the healthy control group (P. value 0.038), [Table 3](#).

Smoking	Covid-19 patients		Control group	
	No.	%	No.	%
Smokers	15	25	4	13.33
Non-smokers	45	75	26	86.67
Total	60	100	30	100
P. value: 0.038				

The study showed that, most of mild infection was observed in patients within the age group 50-59 years, while majority of moderate and severe infection of Covid-19 were above 60 years as the severity increase with the increasing in age, (P. value 0.0001), [Table 4](#).

Age groups (year)	Mild		Moderate		Severe	
	No.	%	No.	%	No.	%
50-59	17	85	5	25	0	0
60-69	2	10	12	60	4	20
>69	1	5	3	15	16	80
Total	20	100	20	100	20	100
P. value: 0.0001						

The study showed that, most of overweight and obese patients were suffered from moderate and severe infection of Covid-19 and obesity revealed at s risk factor of covid-19 severity, (P. value 0.007), Table 5.

Severity	Normal		overweight		Obese	
	No.	%	No.	%	No.	%
Mild	15	56	3	14	2	17
Moderate	4	15	9	43	7	58
Severe	8	30	9	43	3	25
Total	27	100	21	100	12	100

P. value: 0.007

The study showed that the highest mean±SD was observed in Covid-19 patients (39.68±27.92 ng/ml) and the lowest mean±SD was in the control group (13.65±4.56 ng/ml) and the difference was highly significant at P. value: 0.0001, Table 6.

IL6R (ng/ml)	Mean	SD	Minimum	Maximum
Covid-19 patients	39.68	27.92	4.6	88.2
Control group	13.65	4.56	2.66	17.98

P. value: 0.0001

The study showed that the highest mean of IL-6R level was found in patients with severe Covid-19 infection (69.28±16.29 ng/ml) and reduced significantly in patients with moderate infection (40.66±15.07 ng/ml) and the lowest mean was in patients with mild infection (9.09±4.39 ng/ml), the difference was highly significant at P. value: 0.0001, Table 7.

Covid-19 patients	No.	IL-6R (Mean±SD)	P. value
Mild infection	20	9.09±4.39	0.0001
Moderate infection	20	40.66±15.07	
Severe infection	20	69.28±16.29	

The study showed a significant negative correlation between IL-6R and PO2 among Covid-19 patients, Figure 1.

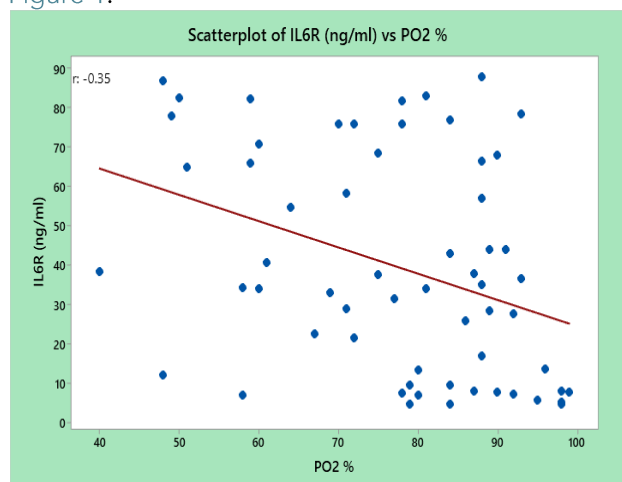


Figure 1: Correlation between IL-6R and PO<sub>2</sub> of Covid-19 patients

## 4. Discussion

The study showed that majority of patients were above 60 years, as the risk of covid-19 infection increased with age as elderly was most affected. The study also found that males were more affected by the virus from females, Table 4.1. In agreement with our finding, Najim (2) in Kirkuk city showed that, majority of patients were elderly, and males were mostly affected. A study from Baghdad also found that, majority of COVID-19 patients were above 50 years of old and most of them were males (1). Another study on 99 patients confirmed to had COVID-19 disease found that the age group were ranged from 21-82 years and higher percentage (30%) were patients between 50-59 years old and as with other studies most of them were men (68%) (3). According to previous studies, the most important risk factors were age, gender, and co-existing diseases. A review study found that older people were more liable to get the infection than younger age groups. The mortality among males was significantly higher compared to females with no approval of susceptibility to infection among two genders. The presence of pre-existing and any condition that weakens the immune system can be a risk factor for infection with COVID-19 (4,5). A descriptive study between a small sample of 24 critically ill patients diagnosed with COVID-19 in the Seattle region was one of the first studies to report BMI data with 20 of the patients being either overweight or obese (6). Although the numbers were too small for statistical analyses, 20 of the patients needed mechanical ventilation and 15 died. The obesity-related effects on the immune system play a key role in the pathogenesis and outcome of most viral infections such as COVID-19 disease, and obesity is also linked to an increased inflammation response in adipose tissue. In turn, the inflammatory response in adipose tissue can lead to metabolic dysfunction, potentially resulting in dyslipidemia, insulin resistance, diabetes mellitus, hypertension, and CVD (7,8,9). In general population, the prevalence of active smokers ranged from of 12% to 18% indifferent countries of the world (10,11). The prevalence of active smokers among hospitalized patients with COVID-19 has been a consistent finding across most published studies (12,13). A recent meta-analysis of 13 studies (n=5960 patients) demonstrated that the pooled prevalence of smokers among hospitalized patients with COVID-19 in China was 14.5%(14). Evidence from three published studies from the USA, all reporting data on hospitalized patients with COVID-19 in New York City, have reported different prevalence of active smokers. A recent meta-analysis of three studies reported an increased need of invasive mechanical ventilation in COVID-19 patients with a BMI >35 kg/m<sup>2</sup> (15). A study in China which investigated the association between obesity and COVID-19 illness severity among patients with confirmed SARS-CoV-2 infection

found that each unit increase in BMI was associated with a 12% increase in the risk of severe COVID-19 (16). IL-6 is thought to be a key mediator of cytokine storm, causing tissue injury and the progression of COVID-19. Levels of serum IL-6 and IL-6 receptors (IL-6R) were significantly elevated in patients with COVID-19 (112), and were closely associated with respiratory failure, acute respiratory distress syndrome, secondary infections, and death (17). A meta-analysis of 21 studies involving 3,377 patients with COVID-19 supported the notion that IL-6 and IL-6R was a significant indicator for the severity of COVID-19 (18). In patients infected with SARS-CoV-2, it has been described that disease severity and outcomes are related to the characteristics of the immune response. Interleukin (IL)-6 and other components of the inflammatory cascade contribute to host defense against infections (19). However, exaggerated synthesis of IL-6 can lead to an acute severe systemic inflammatory response known as cytokine release syndrome (CRS) (20).

## 5. Conclusions and Recommendations

It was concluded that the highest mean of IL-6R, among Covid-19 patients and these elevations seem to reflect that the multiple organ injury. Recommended to uses IL-6R in parallel with other parameters (Ferritin, D-Dimer, CRP and LDH) as biomarkers for Covid1-9 severity.

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