Correlation Study of Interleukin-6 Biomarker with Coronavirus 19 Severity

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Abstract
Background: Coronavirus disease 2019 (COVID-19) is an infectious illness brought on by coronaviruses that cause severe acute respiratory syndrome the global coronavirus pandemic, which started in the Chinese city of Wuhan, in December 2019, has quickly spread to more than 58 countries and in January 3rd, 2020 witnessed the emergence of coronavirus disease-19(COVID-19) in Iraq, and since then the infection incidence has appeared at increasing rates with high morbidity and mortality. Method: The study is a case controls study that included 104 patients. The participants were made up of 30 controls (COVID19 –ve), patients with COVID-19 are, 37 severe patients, and 37 moderate patients (47 males and 57 females) with age range from (30 to 85) years, who were attending in Healing Specialist Center for Crisis in Medical City and Hospital Ibn Al Khatib, during the period from November 2021 to April 2022. in the study patients were divided into three groups based on the severity of their lung involvement as determined by their pulmonary computed tomography scores: severe, moderate. Blood sample was collected two times from patients in primary of entrance to the hospital and after one week of entrance to the hospital for measurement of CRP and IL6 level. Results: Serum levels of CRP: in severe group in both readings (P=<0.001) and Moderate group R1 and R2 (P=<0.001) This Study shows that the level of CRP for both groups is highly significant, sever group and moderate comparison with control group showed highly significant difference with (P=<0.001) sever group was the higher concentration in CRP than moderate group, and also than control group, moderate group was higher than control. IL6 results showed no significant difference between R1 and R2 (P =0.45) in sever group and no significant different between R1 and R2 (P =0.89) in moderate group while there was high significance difference between these two group in comparison with control group at (P=<0.001), additionally there was significant difference between sever group and moderate group at (P= 0.04). Conclusion: there was significant difference in the levels of biomarkers CRP, IL6, between patients and control and between reading one and two so this biomarker was a good indicator for COVID19 severity.
Keyword: COVID-19, Severity of COVID-19, Interleukin-6, CRP.

1. Introduction

One of the major infections that target the human respiratory system is the coronavirus (1). The severe acute respiratory syndrome and the Middle Eastern respiratory disease are two coronavirus epidemics that have previously been identified as being serious threats to community health. A group of people were hospitalized to hospitals in late December 2019 with an initial diagnosis of pneumonia with an unclear cause Epidemiological evidence connected these individuals to a wholesale market for seafood and wet animals in Wuhan, Hubei Province, China (2). The global coronavirus pandemic (COVID-19), which started in the Chinese city of Wuhan, in December 2019(3), has quickly spread to more than 58 countries (4). There have been 211,373,303 confirmed cases of COVID-19, including 4,424,341 deaths, reported to WHO The extremely contagious coronavirus disease 2019 (COVID-19) is caused by coronavirus 2 which results in severe acute respiratory syndrome has had a devastating impact on global demography, causing more than 3.8 million fatalities globally, and is perhaps the most significant global health emergency since the influenza pandemic of 1918 (5).

According to the severity and prognosis, this infection has been categorized into three clinical phases (6, 7) Stage I is characterized by mild, nonspecific symptoms such as myalgia, dry cough, headache, and subfrigerant temperature, but not by any laboratory or radiographic abnormalities. Stage II is distinguished by a cough, a high fever, dyspnea, abnormal chest imaging, lymphopenia, and elevated inflammatory marker values. Stage III culminates in acute respiratory failure with a poor prognosis and clinical signs of a severe systemic inflammatory disease. Values of a number of inflammatory markers are exceedingly high at this stage of the illness, and macrophage activation syndrome may ensue (8). Interferon-gamma (IFN-) and tumor necrosis factor (TNF-) IL-1, IL-1RA, IL-2, IL-6, IL-7, IL-8 (CXCL8), IL-9, IL-10, IL-17, IL-18, IL-2RA,and a wide number of other cytokines have all been shown to be highly elevated in severe COVID-19 individuals (9, 10). The fact that several of them, including IL-6, IL-8, and TNF-, are recognized as independent indicators of the severe condition is crucial (11) We refer to IL6 them her, controlling numerous viral infections depends on the inflammatory. Interleukin IL-6, which

doi.org/10.31838/hiv22.02.481 Received: 01.05.22, Revised: 14.06.22, Accepted: 09.08.22

is primarily generated by macrophages and T cells in response to pathogens (12, 13). While IL-6 at homeostatic levels aids in the healing of infections and tissue injuries, its over production significantly aids in cytokine storms (22–24). IL-6 exhibits a favorable correlation with the stages of the illness and radiologic alterations in COVID-19 (14-16) Numerous studies characterised the blood IL-6 levels during the whole SARS-CoV-2 infection phase. According to the illness stage, IL-6 levels rise and are associated with respiratory failure. Moreover, early distinction between survivors and non-survivors was possible because to the kinetic measurement of IL-6 levels. Overall, we argue that kinetic IL-6 measurement is essential to predicting the prognosis of SARS-CoV-2 patients and may be extremely helpful in determining the best course of therapy (17).

C-reactive protein CRP is a sensitive indicator of systemic inflammation. As a part of the innate immune system CRP can identify some foreign infections as well as the membrane components of injured cells. Because it has greater temporal stability and there are trustworthy tests available, In clinical contexts, CRP is a particularly useful inflammatory measure for prognostic (18). The hyper inflammatory C-reactive protein levels rise after COVID-19 infection in this post-infection condition (19). According to one research, COVID-19 patients' chance of experiencing major events rises by 5% for every increment in C-reactive protein levels (20). C-reactive protein may serve as a guide for the prognosis and development of COVID-19 patients, much as the other laboratory parameters stated above. It has been shown that the more severe the symptoms, the greater the levels of C-reactive protein (21).

Pneumonia was a mild patient's presenting symptom: Frequent fever, dry cough that progresses to active cough, wheezing in some, but no obvious symptoms of hypoxia or breathlessness, and possible rhonchi on lung auscultation (22).

Early respiratory symptoms in a severe patient, gastrointestinal signs, such as diarrhea, may also accompany symptoms like fever and cough. Approximately one week into the disease's progression, dyspnea and central cyanosis commonly appear. Less than 92 percent of the body is oxygenated, and additional signs of hypoxia are present. Increase the risk of developing multiple organ dysfunction, acute renal damage, myocardial infarction, acute respiratory distress syndrome, or respiratory failure (22).

Each of the five lung lobes was visually assessed on a scale of 1 to 5, with the sum of the individual lobar values representing the overall lung involvement, score 1 represents engagement below 5%, Score 2 represents involvement between 5% and 25%, Score 3 represents involvement between 25% and 50%, Score 4 represents involvement between 50% and 75%, and Score 5 represents involvement over 75%. According to the score range from 8 mild, 9 - 15 moderate, and >15 severe based on the research model by Chung, the total lung score out of was categorized as mild, moderate, and severe.

2. Material and Methods

Study includes 104 people who have been diagnosed into (37severe, 37 moderate and 30 control) who were attending Healing Specialist Center for Crisis in Medical City and Hospital Ibn al Khatib. during the period from November 2021 to April 2022. The patients were diagnosed as COVID-19 positive and negative by RT PCR test, severity of patients depended on (pulmonary computed tomography used to make the diagnosis of lung involvement, Clinical sign and symptoms) The information included gender, age, and presence and absence of chronic diseases, smoker or not.

Sample collection

Sample Processing

104 patients had their blood drawn using venipuncture, 7-10 millimeters of venous were drawn using a disposable syringe and placed in a tube using a sterilizing process then, allowed to clot; following that, let the serum to coagulate for 10 to 20 minutes at room temperature in a gel tube. Centrifuge for 20 minutes at 2000–3000 RPM. the serum was collected, and some biomarker was tested at the time of collection and then stored at -20 °C for use in an ELISA test to evaluate the levels of IL-6 (YLbiont- ELISA Kit). When sampling taken, safety and health precautions were used (sporting a face shield, gloves, goggles, and a mask).

3. Results

Distribution of study groups according to age

The age of the sample was demonstrated to be associated with the severity of the illness in the present investigation, despite the severity of the disease assumed to be largely impacted by the patient's age. age groups' averages in general were for sever group 85.77±9.32, Moderate 62.46±10.29 and Control 47.58±8.85 range from (30 -85) years, as in the table (1)

Table (1) Distribution of age according to severity of disease.

Group NO. p. infection%	M±SD
Sever 37 > 75%	85.77±9.32
Moderate 37 25-75	62.46±10.29
Control 30 < 5 %	47.58±8.85

Correlation of COVID 19 and Gender with studies groups.

The current study included 104 individuals distributed as (sever, moderate and control) with both sex male and female, the results show that Significant gender disparity existed across among the groups study. severe group (37) There was a large disparity between male and female patients. male (23) and female (14), (the higher

percentage was in male) at p 0.05 in comparison with the moderate group (37) there was significant difference between male (13) and female (24), (the higher percentage was in female), while in control group (30) there was There is no discernible difference between males (14) and females (16). As show in table(2)

Table(2)show the distribution of gender according to the severity of disease			
Studied group	Male	Female	Total
Sever	23	14	37
Moderate	13	24	37
Control	14	16	30

Correlation of IL6 with studies group

The results showed no significant Difference between R1M±SD 57.86±20.54, and R2 54.93±18.07 with (P =0.45) in sever group and no significant difference between R1 M±SD 49.24±13.57and R2 49.8±17.98 (P =0.89) in moderate group while there was high significance Difference between these two group in comparison with control group at (P=<0.001) additional showed significant difference between sever group and moderate group at (P= 0.04) As shown in Table (3)

Table (3) Correlation of IL6 with studied groups					
IL-6		P value (sig≤0.05)			
Group	M±SD	Sever R2	Moderate R1	Moderate R2	Control
Sever R1	57.86±20.54	0.45	0.03	0.04	<0.001
Sever R2	54.93±18.07		0.14	0.19	<0.001
Moderate R1	49.24±13.57			0.89	0.02
Moderate R2	49.8±17.98				0.02
Control	39.84±9.66				

Correlation of CRP with studies groups

There was a substantial difference between the analyzed groups with CRP, and the severe group had high levels of CRP, according to the findings. M±SD r1 122.34±50.71, r2 113.25±46.50 in both readings with (P=<0.001) while Moderate group M±SDR1 61.16±31.56, R2 49.5±24.7 with (P=<0.001) This Study show that the level of CRP for both groups is highly significant, sever group and moderate comparison with control group showed Different significant M±SD 8.47±2.97 sever group was the higher concentration in CRP than moderate group and also than control group and moderate group was higher than control. As show in the table (4)

Table (4) Correlation of CRP with studies groups					
CRP		P value (sig≤0.05)			
Group	M±SD	Sever R2	Moderate R1	Moderate R2	Control
Sever R1	122.34±50.71	0.28	<0.001	<0.001	<0.001
Sever R2	113.25±46.50		<0.001	<0.001	<0.001
Moderate R1	61.16±31.56			0.17	<0.001
Moderate R2	49.5±24.7				<0.001
Control	8.47±2.97				

4. Discussion

Distribucion of study groups according to age

This study agrees with (23) whom that reported Age is a risk factor for many diseases and has a significant impact on the severity and mortality of infectious diseases anther study by (24) shows that Previous studies identified that age ≥65 years is one of the risk variables predicting COVID-19 patients' death addition to study(25) who approve that the cases severety rate and COVID-19 mortality rate increase with the proportion of older people (those over 65). The explanation of old age severity evidenced The particular changes in the pulmonary pathology and function that occur throughout the infection period are those that occur as people age, Age is a significant determinant of COVID-19 morbidity and death(26) .Another study mentions Identification of preventative and therapeutic approaches requires knowledge of patients' age-associated immunological markers. When the immunological profiles of COVID-19 hospitalized patients were examined, a specific age-dependent immune signature connected to the severity of the illness was found (26).

Correlation of COVID 19 and Gender with studies groups.

This study agree with (27) whom approve There is strong evidence that gender factors influence the severity of COVID-19, men seem to have more severe COVID-19 instances, Male COVID-19 patients had a greater death rate than female COVID-19 patients, in addition to increased severity, according to multiple studies, another study by (28) In Europe, COVID-19 is deadlier among men than women, another study by (29) whom approve men and women have the same prevalence, However, COVID-19 puts males at higher risk of inferior results and mortality regardless of age. Additional study by (30) that various viral infections cause distinct reactions in men and women, gender also affects viral infection prevalence and prognosis, this difference has a complex underlying process that is influenced by a number of factors, including behavioral, genetic, hormonal, and immunological factors.

Correlation of IL6 with studies group

This study agree with (31), infected with COVID-19 has led to significant elevation in the level of IL-6,spicifecly in severe cases. another study by (32) approved that The median age of severe and moderate cases was 61.0 and 52.0 years, that have the higher levels of IL-6. Another study by (33) IL-6 levels in those with severe to critical COVID-19 and those with mild to moderate COVID-19 were disclosed (non-severe) Serum levels of IL-6 were considerably greater in the severe group compared to the non-severe group, according to an overall

random effects meta-analysis. Additional study by (34) approved that analysis of clinical characteristics of COVID-19 showed that in severe group the level of the inflammatory cytokine IL-6 increased significantly, almost 10 times than in other patients groups.

Correlation of CRP with studies group

This results agree study (35), Examination of C-reactive protein (CRP) trends reveals that a rapid rise in CRP levels precedes in severe cases , another study by (36) that showed A mixed model analysis revealed substantial variations in the levels of CRP in the critically sick and severe/moderate classes of hospitalized patients. (37),whom observed that CRP might be utilized to distinguish between severe/moderate COVID-19 patients and the critically unwell, having a superior outcome in differentiating between moderately sick and critically ill patients (38)another study by critical and severe clinical types had elevated levels of CRP compared with moderate group ($P < 0.05$). while, there was a statistical increased trend of CRP among the three groups, with the lowest in the moderate group , then in the severe group , and the highest in the critically severe group ($P < 0.05$) another study by (39) reported that Patients with severe COVID-19 had CRP levels that were significantly higher than those in the non-severe group. Additionally, their multivariate regression studies identified CRP as a separate risk factor for the severity of COVID-19 (37), another study by (40) In terms of systemic organ indices, the findings showed that patients in the severe COVID-19 group demonstrated substantially raised percentages and high CRP levels, high more than those in the moderate group, pointing to the possibility that these variables might be risk factors for COVID-19 severity in the general population, Additional results are in line with earlier research' findings of abnormalities in the parameters in each of (CRP, LDH and ferritin) (40).

5. Conclusion

IL-6 and CRP was good parameter for indication of severity of COVID19.

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