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Some immunological parameters levels in COVID-19 patients in Al-Muthanna governorate, Iraq

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Abstract: Coronavirus disease (COVID-19), caused by SARS-CoV-2, has led to a global pandemic and devastating health crisis. Coronavirus (COVID-19) is associated with severe acute respiratory syndrome (SARS-CoV-2), and the exaggerated immune response resulting from infection with this disease leads to high rates of morbidity and mortality. Activation may have a contribution to disease severity.A case study was carried out in order to find the association between COVID-19, TNF-α, IL-8 and IL-2. The effect of age, sex, smoking, diabetic and hypertention on the level of the studied cytokines were evaluated. Inaddition, the influnce of COVID-19 severity on TNF-α, IL-8 and IL-2 levels were studied. Blood samples were collected from 50 Coronavirus disease (COVID-19) patients who visited of Al-Hussein Teaching hospital and 50 control people, during the period from (May -November 2021). The ages of the patients ranged from (Twenty two years to seventy six years). The serum samples were used in detection of TNF-α , IL-8 and IL-2 by using ELISA test. Then the collected data was analysed using Statistical Package for Social Science (SPSS) program version 11. The results showed that that the most affected age group was (40-60) years old followed by less than 40 years old and more than 60 years old. The numbers of patients were 29, 11 and 10 respectively. Most of COVID-19 patients were male (56 %:28), while the rest cases were females (44%:22). The mean values of the studied cytokines in COVID-19 patients in both sex and all age groups were more than their counter parters in H.C group. The effect of main risk factors for severe and long COVID-19 include age, sex, smoking, presence of comorbidities (diabetes, hypertension) on variations in the level of studied cytokines of the host were found significantly. Moreover, the effect of COVID-19 severity on the studied cytokines was highly significants. The maximum values of cytokines were obtaind in critical degree followed by severe and moderate severity. It is concluded from the study's results that patients infected with severe SARS-CoV-2 experience increasing proinflammatory tumor necrosis factor-α, interleukin-2 and interleukin-8 that produce signaling the initial phase of cytokine storm. Thus, further studies should be conducted to use the studied cytokines inhibitors as a treatment for COVID-19 patients.

Keywords: *COVID-19, COVID-19 Severity, TNF-α , IL_2,IL-8.*

1. Introduction

Coronaviruses are viruses that contain single-stranded positive-sense RNA that infect mammals and birdsand belong to the family of coronaviruses of the order Arthroviridae [1]. These viruses were named "Corona" because of their appearance under an electron microscope, which looks like a crown because it contains proteins [2]. The length of the coronavirus genome ranges between 26 thousand and 32 thousand nucleotides, and it is the longest genome among RNA viruses [3]. The coronavirus subfamily is divided into four genera: alpha coronavirus, beta coronavirus, gamma coronavirus, and delta coronavirus. The alpha and beta genera infect only mammals and their common ancestor could be

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a bat virus, while the gamma and delta genera mainly infect birds, with a few species infecting mammals [4] and their common ancestor is presumed to be a bird virus. SARS-CoV and SARS-CoV-2 belong to the type of viruses associated with SARS, which belongs to the subgenus Sarbeviridae, which belongs to the genus Betaviruses [5].

SARS-CoV-2 is an infectious respiratory disease that is zoonotic in nature and is caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). This virus is nearly identical to the SARS virus. The virus was initially detected in Wuhan, China in 2019 and has since circulated globally, leading to the worldwide outbreak of the coronavirus. Typical signs of the illness consist of fever, cough, and difficulty breathing, whereas muscle pain, sputum production, and sore throat are not usually seen. Although many cases are mild and show minimal symptoms, some develop into severe pneumonia and multiple organ failure. Although most infected individuals experience mild symptoms similar to the common cold, individuals with acute respiratory distress syndrome (ARDS) may face conditions such as multi-organ failure, septic shock, and blood clots [6]. Symptoms usually appear within two to 14 days after being exposed to the virus, with an average of five days. Organ damage, especially to the lungs and heart, has been noted in the long run [7] with worries regarding many patients who have overcome the initial stage but still experience various symptoms [8] like extreme tiredness, memory issues, slight fever, muscle weakness, difficulty breathing, and more - lasting for months post-recovery [9]. Tumor necrosis factor-a (TNF) was firstly distinguished by its construction of hemorrhagic necrosis of tumors in vivo and its cytotoxicity. This cytokine is produced mainly by macrophages and lymphocytes during the inflammatory response. TNF-α plays a significant role by inducing hepatocyte apoptosis, which mediates hepatotoxicity in lipopolysaccharide (LPS)- or concanavalin A-induced liver injury [10]. The overall impact of TNF on the host can range from beneficial to harmful, depending on its concentration at different levels within the body. At low levels, TNF aids in the inflammatory process by changing capillary permeability and causing adhesion molecule expression in endothelial cells for immune cell recruitment [11]. At elevated TNF levels, like those seen in septic shock, this cytokine is involved in starting the cytokine cascade that triggers the inflammatory response, leading to various symptoms linked to sickness [12]. In some patients with severe COVID-19 pneumonia, may be the reason for increasing proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, signaling the initial phase of cytokine storm [13]. The intense release of cytokines resulting from the activation of immune system cells in response to viral invasion is referred to as a "cytokine storm." The cytokine storm may have a potential role in the poor outcomes in Covid-19 patients, and immune responses have been associated with the emergence and development of the virus, and it was found that there is a crucial role for interleukins (ILs) in the development of Covid-19, as this appears clear in many researches in this subject. Interleukin levels in the blood of Covid-19 patients with serious illnesses were significantly higher compared to those with milder illnesses [14]. In addition, there were differences in cytokine levels between COVID-19 individuals who survived and those who did not. Moreover, it is possible that the cytokine IL-2 and IL_8 change upon severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections [15]. Several studies have indicated that the cytokines IL-2 and IL-8 rise during infection and cause a severe inflammatory response and cytokine storm [14]. The pathologic process begins with the recognition of viral antigens, followed by the increase in macrophage cells in target organs and the activation of the immune system, resulting in cytokine storm, and then death [16].

2. Materials and Methods

Blood samples were collected from 50 Coronavirus disease (COVID-19) patients who visited of Al-Hussein Teaching Hospital, Al Muthanna Province, Iraq and 50 control people, during the period from (May -November 2021). The ages of the patients ranged from (twenty two years to seventy six years). A total 10 ml blood sample was drawn from each patient and control; 2ml was used for COVID-19 rapid test and 8ml of blood was put in centerfuge and run at 1500 rpm for five mintuts in order to saperate the serum. The serum samples were used in the detection of TNF-alpha, IL-8 and IL-2 by using ELISA

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test. The assay was performed according to the steps layed dawn by the kit manufacturer company (Bioassay Technology Laboratory).

Statistics Analysis: The Chi-square test was used to determine the statistical significance of the data by using SPSS program (Statistical Package for Social Science) version 11, and significance was assumed at $p \leq 0.05$.

3. Results and Discussion

3.1. Sex And Age Distribution of Study Samples

Fifty COVID-19 patients who visited of Al-Hussein Teaching Hospital, Al Muthanna Province, Iraq and 50 healthy control subjects had been randomly selected for this study. The age of COVID-19 patients and healthy control groups was ranged from 22 years to 76 years. The patients and control groups were subdivided into 3 age groups; less than 40; 40-60 and more than 60 years for both sexes. The numbers of male and female COVID-19 patients in each of the above age groups were 10, 19, 7 and 2, 5, 7 respectively. Whereas, the numbers of male and female H.C group in each of the above age groups were 8, 12, 6 and 7, 11, 6 respectively. However, there was no significant difference among the age groups of COVID-19 patients and H.C. in both sexes (Fig.1).

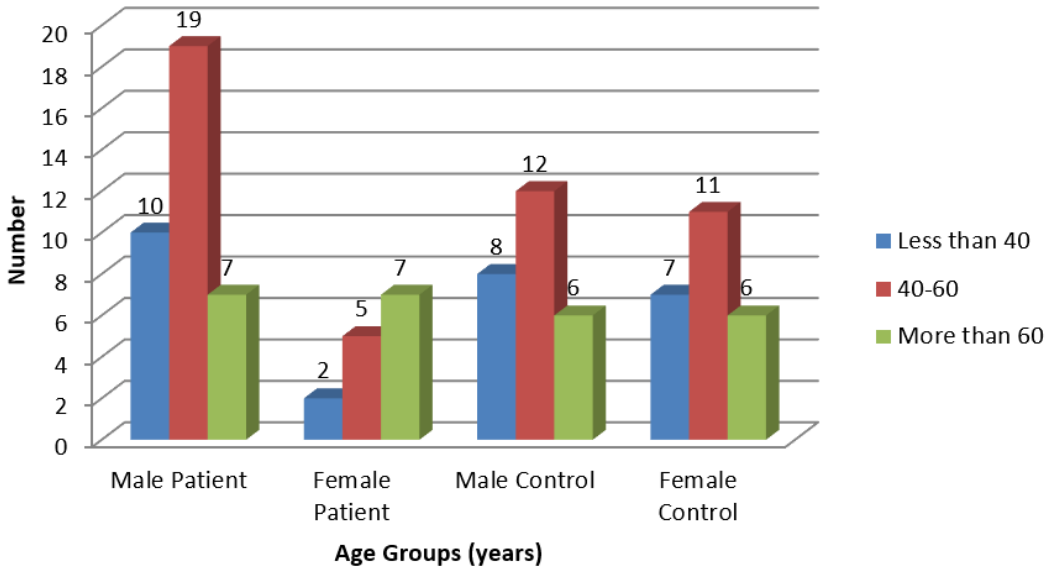

Figure 1.
Sex and age distribution of study samples.

3.2. Tumor Necrosis Factor alpha (TNF-α) Levels in Covid-19 and H.C groups

Table.1 showed that the mean values of TNF-α in Covid-19 patient in both sex were more than their values in H.Control group.The mean value of TNF-α for female was 155.02 and 1.82 pg/ml for Covid-19 patient and H. Control group respectively where as, for male Covid-19 and H.C group, the TNF-α mean value was 165.01 and 1.89 pg/ml respectively. This finding is agreed with results obtained by Jia, et al. [17]. The difference between the mean value of TNF-α in Covid-19 patients and H.C groups was higly significant. The mean value of TNF-α in female Covid-19 patient was lower than male Covid-19 patients. The difference between them was not significant at 5 per cent level and this finding is similar to finding of Queiroz, et al. [18]. In addition, Table.1 revealed that TNF-α mean value in Covid-19 patients increased with aging. The minimum value was obtaind in less than 40 year age group followed by 40-60 and more than 60 years age groups. The TNF-α mean value was 138.331,

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155.916 and 161.128 pg/ml respectively. The difference between them was significant at 1 % level of sginficants except between 40-60 and more than 60 years age groups was not significant at 5% level. These findings are almost agreed with the findings of Pirabe, et al. [19].

The TNF-α mean value in Covid-19 patients was higher than H.C group and the difference between them was highly significant. Although, the smoking habit has increased the TNF-α mean value but the difference between smoker and non-smoker patients was nonsignificant at 5 % level. The effect of diabetes mellitus on TNF-α was expressed in Table (1).The TNF-α mean value for diabetic and non-diabetic was 138.304 and 129.49 pg/ml and the differnce between them was significant at 5 % level. Similarly, the Covid-19 patients with hypertension were having TNF-α mean value higher than non-hypertension Covid-19 patients. The TNF-α mean value was 139.4341 and 129.49 pg/ml respectively and the differnce between them was significant at 5 % level. These oucomes are typically agreed with the findings of Asgharzadeh, et al. [20] who found that hypertension led to increase TNF-α in Covid-19 patients. This may be due to that patients with hypertension have a special immune state characterized by endothelial dysfunction and oxidative stress They are often affected by low-grade chronic inflammation, which may affect how people with high blood pressure respond to SARS-CoV-2. This state may promote cytokine storms, with severe consequences for those infected with COVID-19, potentially leading to death [21].

Table 1.
TNF-α Level according to selected parameters.

Parameters		Control			Positive patients			P (Positive v control)
		No	Mean	SD	No	Mean	SD	
Sex	Male	28	1.89	0.37	36	165.01	64.63	0.000
	Female	22	1.82	0.42	14	155.02	45.1	
Age group (Year)	Less than 40	21	1.881	0.347	13	138.331	32.830	0.000
	40-60	18	1.754	0.463	27	155.916	65.550	
	More than 60	11	1.836	0.495	10	161.128	64.281	
Smoking habit	Smoker	26	1.81	0.497	30	136.897	19.09	0.000
	Non-Smoker	24	1.86	0.385	20	135.28	13.98	
Diabetic	Diabetic	8	1.67	0.54	24	138.304	18.19	0.000
	Non- diabetic	42	1.85	0.395	26	129.49	16.223	
Hypertension	Hypertension	35	1.371	0.4902	23	139.4341	20.59	0.000
	No- hypertension	15	1.333	0.4879	27	133.541	13.24	

3.3. Interleukin -8 (IL-8) Levels in COVID-19 and H.C Groups

Table (2) showed that the mean values of IL-8 in Covid-19 patient in both sex were more than their values in H. Control group.The mean value of IL-8 for female was 81.151 and 26.87 pg/ml for Covid-19 patient and H. Control group respectively whereas, for male Covid-19 and H.C group, the IL-8 mean value was 82.268 and 27.77 pg/ml respectively. This finding is agreed with results obtained by Jia, et al. [17]. The difference between the mean value of IL-8 in Covid-19 patients and H.C groups was highly significant. The mean value of IL-8 in female Covid-19 patients was lower than male Covid-19 patients but the difference between them was not significant at 5 per cent level. In addition, Table (2) revealed that IL-8 mean value in Covid-19 patients increased with aging. The minimum value was obtaind in less than 40 year age group followed by 40-60 and more than 60 years age groups. The IL-8 mean value was 68.44, 79.35 and 99.98 pg/ml respectively. The difference among them was significant at 5 % level. These findings are mostly agreed with the findings of Pirabe, et al. [19]. The IL-8 mean value in Covid-19 patients was higher than H.C group and the difference between them was highly significant. The smoking habit led to an increase in the average value of IL-8(75.71 and 85.29 for non-smoker and smoker Covid-19 patients respectively), the difference between smoking and non-smoking patients was significant at the 5% level. The effect of diabetes mellitus on IL-8 was expressed in Table (2). The IL-8

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mean value for diabetic and non-diabetic Covid-19 patient was 87.38 and 76.42 pg/ml and the differnce between them was significant at 5 % level.

This may be due to that most patients with high blood glucose levels are at greater risk of contracting Covid-19 than others due to increased glucose concentrations in the surface fluid of the airways and inside cells, which create suitable conditions for the virus to evade the innate defense of the lungs and thus facilitate Viral infection and reproduction. High blood glucose also facilitates hyperinflammation that leads to a cytokine storm [22]. Likewise, the Covid-19 patients with hypertension were having IL-8 mean value higher than non- hypertension Covid-19 patients. The IL-8 mean value was 92.11 and 72.39 pg/ml respectively and the differnce between them was significant at 5 % level. The results of this study are mostly agreed with the outcomes of Moll-Bernardes, et al. [23] who found that hypertension and diabetes are associated with COVID-19 development and increased IL-8.

Table 2.
IL-8 Level according to selected parameters.

Parameter (Total)		Control			Positive patients			P
		No	Mean	SD	No	Mean	SD	
Sex	Male	28	27.77	12.416	36	82.268	25.1516	0.000
	Female	22	26.87	12.33	14	81.151	22.711	
Sex group (Year)	Less than 40	21	25.92	10.70	13	68.44	9.27	0.000
	40-60	18	29.76	8.58	27	79.35	22.49	
	More than 60	11	29.74	14.01	10	99.98	28.99	
Smoking habit	Smoker	26	27.54	11.41	30	85.29	26.33	0.05
	Non-Smoker	24	28.34	11.263	20	75.71	20.06	
Diabetic	Diabetic	8	27.86	7.37	24	87.38	25.25	0.049
	Non- diabetic	42	27.95	12.078	26	76.42	22.65	
Hypertension	Hypertension	35	27.92	11.29	23	92.11	30.90	0.030
	No- hypertension	15	28.56	11.21	27	72.39	10.77	

3.4. Interleukin-2 (IL-2) Levels in Covid-19 and H.C Groups

The results of this study which illustrated in Table (3) showed that the mean values of IL-2 in Covid-19 patients in both sex were more than their values in H. Control group.The mean value of IL-2 for female was 27.63 and 3.68 pg/ml for Covid-19 patient and H. Control group respectively where as, for male Covid-19 and H.C group, the IL-2 mean value was 35.05 and 3.77 pg/ml respectively. This finding is agreed with results obtained by Jia, et al. [17]. The difference between the mean value of IL-2 in Covid-19 patients and H.C groups was higly significant. Although the mean value of IL-2 in female Covid-19 patients was lower than male Covid-19 patients, the difference between them was not significant at 5 per cent level and this finding is similar to finding of Queiroz, et al. [18]. In addition, Table.3 exposed that IL-2 mean value in Covid-19 patients. The minimum value was obtaind in 40-60 year age group followed by less than 40 and more than 60 years age groups. The IL-2 mean value was 20.36, 26.90 and 33.28 pg/ml respectively. The difference among them was significant at 5 % level. The IL-2 mean value in Covid-19 patients was higher than H.C group and the difference between them was highly significant in all age groups. In addition the smoking habit led to an increase in the average value of interleukin 2, the difference between smoking and non-smoking patients was significant at the 5% level. The mean IL-2 value for smoker and no-smoker patients was 37.19 and 26.24 pg/ml.

The effect of diabetes mellitus on IL-2 was showed in Table.3. The IL-2 mean value for diabetic and non-diabetic was 33.75 and 32.31 pg/ml and the differnce between them was not significant at 5 % level. Similarly, the Covid-19 patients with hypertension were having IL-2 mean value higher than non-hypertension Covid-19 patients. The IL-2 mean value was 30.90 and 28.69 pg/ml respectively and the differnce between them was non significant at 5 % level. These oucomes are typically agreed with the findings of Asgharzadeh, et al. [20].

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Table 3.
IL-2 Level according to selected parameters.

Parameter (Total)		Control			Positive patients			P
		No	Mean	SD	No	Mean	SD	
Sex	Male	28	3.77	1.22	36	35.05	17.03	
	Female	22	3.68	1.09	14	27.63	9.917	0.000
Sex group (Year)	Less than 40	21	3.86	1.32	13	26.90	8.69	
	40-60	18	3.91	0.61	27	20.36	16.12	0.000
	More than 60	11	3.58	1.04	10	33.28	22.78	
Smoking habit	Smoker	26	3.78	1.13	30	37.19	17.72	
	Non-Smoker	24	3.71	1.07	20	26.64	9.027	0.000
Diabetic	Diabetic	8	4.28	1.27	24	33.75	15.37	
	Non- diabetic	42	3.62	1.035	26	32.31	16.14	0.065
Hypertension	Hypertension	35	3.75	1.22	23	30.90	20.44	
	No- hypertension	15	3.81	1.17	27	28.69	8.128	0.053

3.5. Distribution of Cytokines levels According to Infection Severity

Table 4 showed that majority of patients were suffering moderate follwed by severe and critical covid-19 infection severity. The number of patients was 27, 18 and 5 for moderate, severe and critcal covid-19 infection severity respectively.the effect of covid-19 infection severity on TNF-α, IL-8 and IL-2 cytokines. The results showed that the effect was highly significant. The least values of cytokines were obtaind in moderate followed by severe and the maximum values were obtaind in critical stage and these outcomes pointed out that the levels of these proinflammatory cytokines were associated with disease severity. The TNF-α values were 70.23, 100.51 and 130.35 pg/ml for moderate, severe and critical infection severity respectively. While the IL-8 values were 66.350, 85.94 and 146.95 pg/ml for moderate, severe and critical infection severity respectively.whereas the IL-2 values were 23.46, 39.30and 61.55pg/ml for moderate, severe and critical infection severity respectively. The outcomes of the study mostly agreed with the out come of Jia, et al. [17] who stated that the amount of infiltrated monocytes and macrophages in damaged lung are linked with the injury of alveolar. "TNF-α was a risk factor for the mortality of COVID-19 infection based on logistic regression analyses, indicating that TNF-α could be a potential treatment target for severe or critical COVID-19 pneumonia cases" [24].

Consequently, monocyte or macrophage related cytokines (e.g., TNF-α, IL-2, and IL-8) intention organ injury or lead cytokine storm. It is very important for the intending of future therapies to recognize the mechanism of the immune response in sequence to decrease cytokine storm. Targeted immune cell-based therapies have proven benefits among patients because they target a specific cytokine without causing a widespread effect on the immune system.

Table 4.
Distribution of cytokines levels according to infection severity.

Cytokines	Covid-19 infection severity						P
	Moderate		Severe		Critical		
	No	Mean	No.	Mean	No.	Mean	
TNF-α	27	70.23	18	100.51	5	130.35	0.000
IL-8	27	66.350	18	85.94	5	146.95	0.000
IL-2	27	23.46	18	39.30	5	61.55	0.000

4. Conclusion

The effect of main risk factors for severe and long COVID-19 include age, sex, smoking, presence of comorbidities (diabetes, hypertension) on variations in the level of studied cytokines of the host were found significantly. Moreover, the effect of COVID-19 severity on the studied cytokines was highly significants. The maximum values of cytokines were obtaind in critical degree followed by severe and moderate severity. It is concluded from the study's results that patients infected with severe SARS-

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CoV-2 experience increasing proinflammatory tumor necrosis factor-α, interleukin-2 and interleukin-8 that produce signaling the initial phase of cytokine storm. The pathological process begins with the recognition of viral antigens, followed by an increase in macrophages in target organs and activation of the immune system. These effectors contribute to lung inflammation and injury, endothelial damage and dysfunction, and the subsequent spread of the inflammatory response to the circulation and other organs.Thus, further studies should be conducted to use the studied cytokines inhibitors as a treatment for COVID-19 patients.

Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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