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ORIGINAL ARTICLE

Effects of Sarilumab on IL-6, IL-10 and IP-10 Levels in Critically ill COVID-19 Patients

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ABSTRACT

Background: *Pandemic COVID-19 caused by SARS-CoV-2. The infection is associated with an inflammatory cytokine storm, which is characterized by elevated levels of pro-inflammatory cytokines as IL-6 and IP-10. Some non-inflammatory cytokines have been investigated in COVID-19 critical cases as IL-10. Early blockade of IL6-pathway might be beneficial in decreasing disease severity. The prospect of employing tocilizumab and sarilumab to treat or prevent the cytokine storm has generated a lot of interest recently.* ***Objective:*** *A trial to evaluate effects of sarilumab on IL-6, IL-10, IP-10 in critically ill COVID-19 patients was done in this study.* ***Methodology:*** *Thirty critically ill COVID-19 patients were enrolled in this study and received sarilumab. Serum baseline, 24hrs and 72hrs after treatment levels of IL-6, IL-10 and IP-10 were evaluated by ELISA kits.* ***Results:*** *Serum levels of IL-6, PaO2 and P/F ratio increased significantly 24hrs after treatment, while levels of IL-10, IP-10 decreased significantly after treatment. There was positive correlation between some markers at baseline level, 24hrs after treatment and 72hrs after treatment, suggesting that these markers are affected by treatment with sarilumab. Accuracy of IL-6, IL-10 and IP-10 measurements 72 hrs after treatment with sarilumab shows significance, indicating that they can help in pathophysiology.* ***Conclusion:*** *COVID-19 infection is significantly associated with high CRP, D-dimer and accompanied with low levels of PaO2 and P/F ratio in critically ill cases. More than half of the ICU patients showed clinical amelioration after sarilumab administration. Dosing and timing of receiving sarilumab play a crucial role in the outcome.*

INTRODUCTION

In Wuhan, China, an epidemic of a mutated virus that is a member of the coronavirus family was discovered around the middle of December 2019. WHO designated the virus as coronavirus disease-19 (COVID-19) and the illness as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1].

Until 31 January 2021, there have been 103,286,991 coronavirus cases reported globally, with 2,232,776 fatalities. On May 2023, Egypt would have seen 516,023 coronavirus cases with 24,613 fatalities [2].

Coronaviruses are a member of positive-stranded enveloped RNA virus family that can infect the vertebrates. RNA viruses have higher mutation rates than DNA viruses, which may indicate that their adaptation mechanism for survival is more effective. Four major structural proteins; nucleocapsid, spike, envelope and membrane proteins as well as several additional proteins that support replication and make cell entry easier are encoded by the genome [3].

A cytokine storm, primarily typified by increased interleukin 6 (IL-6) plasma levels, is also linked to SARS-CoV-2 infection [4]. Interleukin 6 levels were shown to be greater in the severe group compared to the mild group in a number of COVID-19 clinical trials [5], indicating the potential utility of IL-6 as a biomarker for severity assessment [6].

Patients of severe COVID-19 have been shown in various studies to have higher levels of interferon-gamma induced protein-10 (IP-10), granulocyte colony stimulating factor (G-CSF), tumor necrosis factor alpha (TNF-α), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1 alpha (MIP-1α), IL-2, IL-6, IL-7 and IL-10[7,8].

As of right now, there is no particular COVID-19 treatment available[9]. The prospect of employing tocilizumab (TCZ) to treat or prevent the cytokine storm has generated a lot of interest recently [5].

Treatment with sarilumab and TCZ, IL-6 receptor antagonists, improved survival outcomes. Consequently, the National Health Service (NHS) advised physicians to think about giving sarilumab or TCZ for the treatment of ICU patients with COVID-19 pneumonia [10].TCZ; a humanized antibody; inhibits IL-6R in both its soluble and membrane-bound forms [11].

The food and drug administration (FDA) has approved sarilumab; a fully human antibody against the IL-6 receptor; for the treatment of rheumatoid arthritis (RA). Sarilumab binds to both soluble and membrane-

bound IL-6 receptors. Furthermore, using this medication off-label to treat COVID-19 has been explored [12].TCZ-treated COVID-19 patients with highly elevated IL-6 shown an early improvement in their respiratory condition [13]. So, a trial to evaluate the effects of sarilumab on IL-6, IL-10, IP-10 in critically ill COVID-19 patients was done in this study.

METHODOLOGY

Study design and population

This prospective observational study was performed at the Department of Medical Microbiology and Immunology, Faculty of Medicine. **(NCT05367882, www.clinicaltrials.gov)**

Patients admitted to ICU in the Quarantine Department at the Chest Hospital and Fever Hospital and patients admitted in ICU in the Chest Department at Assiut University Hospital from the 1st of November 2021 to 1st of November 2022 with confirmed COVID-19 infection were included in this study, to be treated with a single dose of 200 mg subcutaneously or 200 to 800 mg intravenously of sarilumab. Each treatment involved the infusion of 200 mg of sarilumab in 1.14 mL (175 mg per mL) into 100 mL of 0.9% sodium chloride for 60 minutes.

Thirty patients were selected according to inclusion criteria described by *López et al.* [14]. Each patient had a complete clinical examination and a detailed medical history [15] and laboratory investigations [16].

Ethical aspect

Patients were given permission to take part in the trial after giving their informed consent. Patients' refusal to take part in the study had no bearing on the quality of care they received in the hospital. The study's procedure was authorized by Assiut University, Faculty of Medicine, Ethical Review Board **(IRB: 17101714).**

Interventions

Each patient had a complete clinical examination and a detailed medical history [15]. Laboratory investigations; complete blood counts, D-dimer, C-reactive protein (CRP), and ferritin were also performed to all patients. Additionally, patients were monitored daily for arterial blood gases (ABG) and partial pressure of arterial oxygen (PaO2)/fraction of inspired oxygen (FiO2) (P/F ratio) [16].

Materials and methods

1- Sample collection and preparation [17]

- Five milliliters of blood were collected at baseline, after 24 hrs and72hrs of receiving treatment with sarilumab.
- Blood sample was centrifuged for 10 minutes, then a clear serum solution in the tube was separated using a micropipette.
- Serum samples after isolation were preserved at -80°C until use.

2- Quantitative estimation of IL-6, IL-10 and IP-10

The serum levels of IL-6, IL-10 and IP-10 were measured before treatment, 24 hrs and 72 hrs after treatment for all research groups using enzyme linked immunosorbent assay kits (ELISA) [18] according to manufacturer's instructions.

Statistical analysis:

Statistical analysis was done with SPSS, version 23.0. Data are presented as median (min-max) or as the number and percentage, as appropriate. The paired t-test and Wilcoxon test were used for comparing between each two periods of time according to the normality of distribution whenever appropriate. Mann-Whitney U test and Chi-squared test were used to compare between the improved and died groups. Pearson and Spear man test was used for correlation coefficients. A P-value of less than 0.05 was considered statistically significant.

RESULTS

Laboratory data

Table (1) shows the different laboratory parameters of patients before initiation of sarilumab therapy (at baseline) and after 24, 72 hours after treatment. IL-6 was significantly higher 24 hrs after treatment compared with the baseline level, while IP-10 and CRP were significantly lower 24 hrs after treatment compared with the baseline level, significantly lower 72 hrs after treatment compared with the baseline level and were also significantly lower 72 hrs after treatment compared with measurement after 24 hrs. There was no statistically significant difference between measurements of ALC and D-dimer.

Table 1: Laboratory data of the studied group

Laboratory data	Normal range	Baseline level	After 24hrs	After 72hrs	P1	P2	P3
ALC (10^3 /µL) Mean±SD	1.5 - 3.5	0.85 ± 0.55	0.88 ± 0.44	1.06 ± 0.67	0.757	0.210	0.146
IL-6 (pg/mL) Median (IQ range)	< 5	61.9 (57 – 83)	76.2 (63.3 – 97.7)	70.6 (57.7 – 97.3)	**0.012***	0.411	0.123
IL-10 (pg/ml) Median (IQ range)	4.8 – 9.8	353.3 (303.2 – 580.4)	351 (299.7 – 569.4)	210.6 (189.3– 605.2)	0.510	**0.001****	**0.002***
IP-10 (pg/ml) Mean ± SD	150 - 200	915.5 ± 232	840.7 ± 273.8	681.8 ± 226	**0.036***	**<0.001****	**<0.001****
CRP (mg/L) Median (IQ range)	0 - 5	138 (72.1 – 217.3)	88 (51.4 - 133.3)	56 (20.3 – 129.2)	**0.001****	**<0.001****	**0.019***
Ferritin (ng/ml) Median (IQ range)	10 - 291	262.5 (118.8 – 315.8)	246 (129.7 – 310.6)	201.7 (110.5– 299.6)	0.478	**0.047***	**0.046***
D-dimer (mg/L) Median (IQ range)	0 - 0.55	0.9 (0.65 - 2.55)	1.4 (0.78 - 2.0)	1.1 (0.58 - 2.14)	0.073	0.181	0.237

Used paired t-test and Wilcoxon test for comparing between each two periods of time according to the normality of distribution.
P1: statistically difference between baseline level, after 24hrs.
P2: statistically difference between baseline level, after 72hrs.
P3: statistically difference between levels after 24hrs, after 72hrs.
* There is a statistically significant difference ($p \leq 0.05$)
**There is a highly statistically significant difference ($p \leq 0.001$)
ALC: absolute lymphocyte count; CRP: C-reactive protein

Arterial blood gases (ABG) parameters' measurements

Table (2) shows that PaO_2 and P/F ratio were significantly higher 24 hrs after treatment compared with the baseline level. P/F ratio was significantly higher 72 hrs after treatment compared with the baseline level. PaO_2 was also significantly lower 72 hrs after treatment compared with measurement at 24 hrs.

Table 2: Arterial blood gases (ABG) parameters' measurements among the studied group

ABG parameters	Baseline level	After 24hrs	After 72hrs	P1	P2	P3
PaO_2(mmHg) Mean±SD	60.34 ± 15.77	68.30 ± 12.36	63.70 ± 9.99	**0.002***	0.301	**0.045***
FiO_2(%) Median (IQ range)	40 (38.8 - 56.3)	40 (29.5 - 60)	37.5 (28 - 60)	0.305	0.183	0.167
P/F (mmHg) Mean±SD	148.4±62.34	175.11±63.92	174.56±62.18	**<0.001****	**0.020***	0.942

Used paired t-test and Wilcoxon test for comparing between each two periods of time according to the normality of distribution.
P1: statistically difference between baseline level & after 24hrs.
P2: statistically difference between baseline level & after 72hrs.
P3: statistically difference between levels after 24hrs & after 72hrs.
* There is a statistically significant difference ($p \leq 0.05$)
**There is a highly statistically significant difference ($p \leq 0.001$)
PaO_2: partial pressure of oxygen (millimeter of mercury); FiO_2: the fraction of inspired oxygen;
P/F: ratio between arterial PaO_2 divided by the FiO_2

The outcome of the studied group

Thirteen patients (43.3%) died, while the others improved including 3 patients (10%) improved with O_2 concentrator, one patient (3.3%) improved with quarantine and 13 patients (43.3%) improved without need for O_2 supply or quarantine.

Correlation matrix between various laboratory measurements before treatment, 24 hrs and 72 hrs after treatment

Table (3) shows that there was a significant positive correlation between D-dimer / CRP, P/F ratio / PaO_2, and IP-10 / IL-6 at baseline before treatment. There was no significant correlation between other variables at baseline.

There was a significant positive correlation between P/F ratio / PaO_2, P/F ratio / ALC, IL-10 / IL-6, IP-10 / IL-6, and IP-10 /IL-10 at 24 hrs after treatment. There was no significant correlation between other variables at 24 hrs after treatment.

There was a significant positive correlation between P/F ratio / PaO_2, IL-10 /IL-6, IP-10 / IL-6, and IP-10 / IL-10 at 72hrs after treatment. There was a significant negative correlation between IL-10 / P/F ratio. There was no statistically significant correlation between other variables at 72hrs after treatment.

Table 3: Correlation matrix between various laboratory measurements before treatment, 24 hrs and 72 hrs after treatment

Correlation matrix between various laboratory measurements before treatment										
		IL-6	**CRP**	**D-dimer**	**Ferritin**	**PaO_2**	**ALC**	**P/F ratio**	**IL-10**	**IP-10**
IL-6	r	1								
	p									
CRP	r	0.178	1							
	p	0.346								
D-dimer	r	0.300	0.744	1						
	p	0.107	**0.000****							
Ferritin	r	-0.047	-0.084	-0.010	1					
	p	0.806	0.659	0.959						
PaO_2	r	-0.258	-0.019	0.000	-0.190	1				
	p	0.169	0.919	0.998	0.315					
ALC	r	0.074	-0.260	-0.137	-0.173	0.189	1			
	p	0.696	0.165	0.470	0.361	0.317				
P/F ratio	r	-0.163	-0.165	-0.002	-0.083	0.801	0.215	1		
	p	0.388	0.384	0.990	0.663	**<0.001****	0.254			
IL-10	r	0.318	-0.037	-0.018	0.095	0.188	-0.180	0.066	1	
	p	0.086	0.845	0.925	0.617	0.320	0.342	0.729		
IP-10	r	0.418	0.049	0.100	-0.014	0.163	-0.148	0.054	0.284	1
	P	**0.022***	0.799	0.599	0.924	0.390	0.437	0.776	0.186	
Correlation matrix between various laboratory measurements 24 hrs after treatment										
		IL-6	**CRP**	**D-dimer**	**Ferritin**	**PaO_2**	**ALC**	**P/F ratio**	**IL-10**	**IP-10**
IL-6	r	1								
	p									
CRP	r	-0.024	1							
	p	0.898								
D-dimer	r	0.070	0.117	1						
	p	0.711	0.539							
Ferritin	r	0.033	-0.104	0.015	1					
	p	0.864	0.583	0.936						
PaO_2	r	-0.319	0.024	-0.248	-0.090	1				
	p	0.086	0.901	0.186	0.635					
ALC	r	-0.028	-0.072	0.080	-0.228	0.230	1			
	p	0.885	0.707	0.873	0.225	0.222				
P/F ratio	r	-0.132	-0.205	-0.118	-0.056	0.569	0.435	1		
	p	0.486	0.276	0.534	0.768	**0.001****	**0.016***			
IL-10	r	0.469	0.018	0.039	0.028	-0.287	-0.179	-0.334	1	
	p	**0.009***	0.925	0.839	0.884	0.123	0.344	0.071		
IP-10	r	0.542	0.018	0.069	-0.239	-0.147	-0.239	-0.326	0.718	1
	P	**0.002***	0.925	0.716	0.215	0.439	0.204	0.076	**<0.001****	

Correlation matrix between various laboratory measurements 72 hrs after treatment										
		IL-6	**CRP**	**D-dimer**	**Ferritin**	**PaO_2**	**ALC**	**P/F ratio**	**IL-10**	**IP-10**
IL-6	r	1								
	p									
CRP	r	-0.130	1							
	p	0.495								
D-dimer	r	0.322	0.361	1						
	p	0.083	0.050							
Ferritin	r	0.131	0.285	0.208	1					
	p	0.489	0.127	0.269						
PaO_2	r	-0.308	0.219	-0.089	-0.097	1				
	p	0.098	0.245	0.639	0.610					
ALC	r	-0.118	0.249	0.071	-0.261	0.132	1			
	p	0.534	0.184	0.710	0.164	0.487				
P/F ratio	r	-0.347	-0.042	-0.258	-0.131	0.591	0.267	1		
	p	0.061	0.825	0.169	0.490	**0.001****	0.154			
IL-10	r	0.589	0.214	0.058	-0.069	-0.098	-0.125	-0.403	1	
	p	**0.001****	0.157	0.761	0.717	0.605	0.509	**0.027***		
IP-10	r	0.541	0.354	0.205	0.038	-0.096	0.085	-0.326	0.661	1
	P	**0.002***	0.339	0.278	0.843	0.615	0.656	0.079	**<0.001****	

Used Pearson and Spearman correlation coefficients test.
r: correlation coefficient (0.8:1 is very strong positive, 0.6:0.79 is strong positive, 0.4:0.59 is moderate positive, 0.2:0.39 is weak positive, -1: -0.8 very strong negative, -0.79: -0.6 is strong negative, -0.59: -0.4: moderate negative, -0.39: -0.2 is weak negative); p: p- value.
* There is a statistically significant difference ($p \leq 0.05$)
**There is a highly statistically significant difference ($p \leq 0.001$)

Accuracy of IL-6, IL-10 and IP-10 measurements to predict the outcome in COVID-19 patients

There was a significant difference in IL-6 levels after 72 hrs, in IL-10 levels at baseline, after 24 hrs and 72 hrs and in IP-10 levels after 24 hrs and 72 hrs indicating that the measurements of IL-6 levels after 72 hrs, IL-10 levels at baseline, after 24 hrs and 72 hrs and IP-10 levels after 24 hrs and 72 hrs were useful in diagnosis of COVID-19 patients as shown in table (4).

Table 4: Accuracy of IL-6, IL-10 and IP-10 measurements to predict the outcome in COVID-19 patients

	IL-6			**IL-10**			**IP-10**		
	Baseline	**After 24 hrs**	**After 72 hrs**	**Baseline**	**After 24 hrs**	**After 72 hrs**	**Baseline**	**After 24 hrs**	**After 72 hrs**
AUC	0.629	0.575	0.756	0.796	0.860	0.986	0.500	0.805	0.824
SE	0.106	0.110	0.089	0.095	0.075	0.015	0.117	0.079	0.078
P value	0.233	0.490	**0.018***	**0.006***	**0.001****	**<0.001****	1.000	**0.005***	**0.003***
95% CI	0.421 – 0.837	0.359 – 0.790	0.581 – 0.930	0.610 – 0.983	0.713 – 1.000	0.759 – 1.000	0.270 – 0.730	0.650 – 0.961	0.671 – 0.976
Cutoff point	85.7	110.5	82.5	375.7	359.6	251.5	1195	706	626.8
Sensitivity	38.5%	30.8%	61.5%	76.9%	69.2%	92.3%	30.8%	92.3%	84.6%
Specificity	94.1%	94.1%	82.4%	88.2%	94.1%	94.1%	94.1%	58.8%	76.5%

AUC: area under the curve; SE: standard error. CI: confidence interval.
* There is a statistically significant difference ($p \leq 0.05$)
**There is a highly statistically significant difference ($p \leq 0.001$)

DISCUSSION

In this trial, 30 critical COVID-19 patients in ICU were observed after receiving sarilumab. IL-6 levels increased significantly 24 hrs after treatment with sarilumab while decreased after 72 hrs but without significance.

In agreement with the present study, according to *Ogata et al.*[19], when TCZ is first administered, IL-6 levels rise over time, and stopping TCZ can occasionally cause a flare-up of the illness. Since TCZ doesn't directly stop the production of IL-6, it interferes with IL-6's ability to bind to its receptor, causing accumulation of unbound IL-6 in the blood. Following termination of immunological activation, IL-6 levels progressively decline[20].

The current study reported that the levels of IL-10 and IP-10 in all patients were statistically significant lower 72 hrs compared with the baseline level, also there was statistically significant difference between the levels of both IL-10 and IP-10 24hrs and 72hrs after treatment. Moreover, IP-10 levels were statistically significant lower 24hrs after treatment compared with the baseline level, nevertheless there was no statistically significant difference between the baseline level and 24hrs after treatment in IL-10 levels.

The critical patients' IL-10 levels did not decrease 24 hrs after sarilumab, which could be explained by many ways. First, the time of sarilumab dosing has a role [21]. TCZ was less effective in critical patients, and it was more advantageous to administer it earlier in the course of the disease [22]. Elevations in cytokines from other immune pathways suggest that sarilumab alone may be insufficient in reducing the inflammation brought on by the illness in these critically ill patients [23]. In disagreement with our results, *Guo et al.* [24] reported elevated IL-10 levels in all patients following treatment and this elevation might be a feedback response to elevated levels of IL-6.

Elevated IP-10 levels were described by *Petruccioli et al.* [25] as an early and specific biomarker in COVID-19 cases [26] and it is related to critical condition of the infection [24].

Concerning serum levels of CRP in the current study, it was observed that they decreased significantly after 24hrs and after 72 hrs compared with their levels before treatment. Serum ferritin levels decreased significantly 24hrs and also continued to decrease significantly 72hrs after treatment. This is in harmony with previous studies [27,28,29].

In the current study; D-dimer increased in all patients 24hrs after treatment but without significance, then decreased 72hrs after treatment. Previous studies [30,31] reported that there was no significant association between COVID-19 severity and D-dimer levels, this agreed with our results. Whereas, in a previous study [32], D-dimer showed no change.

There was high mortality rate in the present study reached 43.3% of patients and this in accordance to *Macedo et al.*[33] and *Xu et al.*[22].

By revising the correlation matrix between various laboratory measurements before treatment in the current work, it was noted that there was a significant positive correlation between D-dimer / CRP, P/F ratio / PaO_2, and IL-6 / IP-10 at baseline before treatment. There was no significant correlation between other variables at baseline. However, there was negative correlation between; ferritin / IL-6, CRP / D-dimer, PaO_2 / IL-6, CRP / ferritin, ALC / CRP, D-dimer /ferritin, P/F / IL-6, CRP, D-dimer /ferritin, IL-10/ CRP, D-dimer / ALC, and IP-10 /ferritin, ALC.

Also, there was significant positive correlation between P/F ratio / ALC at 24 hrs after treatment. There was a significant positive correlation between P/F ratio / PaO_2, IL-10 / IL-6, IP-10 / IL-6, and IP-10 / IL-10 at 24hrs and 72hrs after treatment. However, there was a significant negative correlation between IL-10/ P/F ratio at 72hrs after treatment. There was no statistically significant correlation between other variables at 24hrs and 72hrs after treatment.

On the contrary, *Onuk et al.*[34] reported that IL-6 concentrations showed a positive correlation with ferritin and CRP levels. *Galván-Román et al.* [13] reported that there was no significant correlation between PaO_2 and IL-6 serum levels at baseline. IL-6 levels showed a significant negative correlation with PaO_2/FiO_2.

Kesmez Can et al.[35] reported a significant positive correlation between serum IL-6 /IP-10 and IL-6 /CRP. No significant correlation was found between IL-6 /Ferritin and IL-6, IP-10/ D-dimer.

According to the accuracy in this study, AUC of IL-6, IL-10 and IP-10 were above 0.75; thus, they had very good accuracy. They are effective and may have a predictive value for predicting efficacy of sarilumab in COVID-19 patients. In addition, there was a significant difference in IL-6 levels after 72 hrs, in IL-10 levels at baseline, after 24 hrs and 72 hrs and in IP-10 levels after 24 hrs and 72 hrs after treatment, indicating that the measurement of IL-6, IL-10 and IP-10 levels is useful in diagnosis of COVID-19 patients after 24hrs and 72hrs after treatment.

Cabaro et al.[36] showed that in the initial waves of the pandemic, the severity of COVID-19 was associated with increased levels of pro-inflammatory cytokines, with high AUC values for IL-6 and IL-10.

Xu et al. [22] showed that TCZ is a promising treatment for critically ill COVID-19 patients.

In this study, it was noticed that timely administration of immunomodulatory drugs in COVID-19 is a concern that should be taken into attention; for

example, *Wang et al.*[37] demonstrated that early IFN-α therapy decreased hospital mortality, while late IFN administration was linked to higher mortality and slower recovery. *López et al.*[14] suggested that patients with increased inflammatory markers might get less severe inflammation if sarilumab is used early in moderate situations.

Lastly, it is hypothesized that early sarilumab administration in severe COVID-19 cases may slow disease development and lower mortality rates. To confirm or refute this finding, more multicentric, larger-scale research is still advised.

CONCLUSION

COVID-19 infection is significantly associated with high CRP, D-dimer and mostly accompanied with low levels of PaO_2 and P/F ratio in critically ill cases. There was positive correlation between some markers at baseline level, 24hrs after treatment and 72hrs after treatment, suggesting that these markers are affected by treatment with sarilumab. Accuracy of IL-6, IL-10 and IP-10 measurements 72 hrs after treatment with sarilumab shows significance, indicating that they can help in pathophysiology. More than half of the ICU patients showed clinical amelioration after sarilumab administration. Dosing and timing of receiving sarilumab play a crucial role in the outcome.

REFERNECES

1. Li A, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. New England journal of medicine, 2020a; 85(9): 47-52.
2. WHO, 2023. world health organization, 2023.
3. Schoeman D & Fielding BC. Coronavirus envelope protein: current knowledge. Virology journal, 2019;16(1): 1-22.
4. Zumla A, Hui DS, Azhar EI, Memish ZA & Maeurer M. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. The Lancet, 2020; 395(10224): e35-e36.
5. Chen G, Zhu H, Yuan C, Yao C, Luo W, Shen X, et al. Clinical and immune features of hospitalized pediatric patients with coronavirus disease 2019 (COVID-19) in Wuhan, China. JAMA network open, 2020; 3(6): e2010895-e2010895.
6. Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). MedRxiv, 2020; 02.10.20021832.
7. Iba T, Levy JH, Thachil J, Wada H & Levi M. The progression from coagulopathy to disseminated intravascular coagulation in representative underlying diseases. Thrombosis research, 2019;179: 11-14.
8. Liu F, Li L, Xu M, Wu J, Luo D, Zhu Y, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. Journal of clinical virology, 2020; 127: 104370.
9. Sun P, Lu X, Xu C, Sun W & Pan B. Understanding of COVID-19 based on current evidence. Journal of medical virology, 2020; 92(6): 548-551.
10. Torrente-López A, Hermosilla J, Navas N, Cuadros-Rodríguez L, Cabeza J & Salmerón-García A. The relevance of monoclonal antibodies in the treatment of COVID-19. Vaccines, 2021;9(6): 557.
11. Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N & Kakehi T. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. Blood, 2008;112(8): 3959-3964.
12. Kim GW, Lee NR, Pi RH, Lim YS, Lee YM, Lee JM, et al. IL-6 inhibitors for treatment of rheumatoid arthritis: past, present, and future. Archives of pharmacal research, 2015;38: 575-584.
13. Galván-Román JM, Rodríguez-García SC, Roy-Vallejo E, Marcos-Jiménez A, Sánchez-Alonso S, Fernández-Díaz C, et al. IL-6 serum levels predict severity and response to tocilizumab in COVID-19: An observational study. Journal of Allergy and Clinical Immunology, 2021;147(1): 72-80. e8.
14. López RL, Fernández SC, Pérez LL, Palacios AR, Fernández-Roldán MC, Alonso EA, et al. Efficacy and safety of early treatment with sarilumab in hospitalised adults with COVID-19 presenting cytokine release syndrome (SARICOR STUDY): protocol of a phase II, open-label, randomised, multicentre, controlled clinical trial. BMJ open, 2020; 10(11): e039951.
15. Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. Emerging Microbes Infections, 2020; 9(1):687-690.
16. Ahsan MN, Asghar MS, Iqbal S, Alvi H, Akram M, Fayyaz B, Irshad SG, Ullah I, Alvi S, Yousaf Z. Outcomes of COVID-19 patients with acute kidney injury and longitudinal analysis of laboratory markers during the hospital stay: A multi-center retrospective cohort experience from Pakistan. Medicine (Baltimore) ,2023;102(6): e32919.

17. Nasonov E, Samsonov M. The role of Interleukin 6 inhibitors in therapy of severe COVID-19. Biomed Pharmacotherapy, 2020;131:110698.
18. Bioassay Technology Laboratory, China. www.bt.laboratory.com#2025/f 2Bldg.501changsheng 5 Rd, Nanhu Dist, Jiaxing, Zhejiang, China.2022; Tel:86 2131007137/ Fax: 86 2165109711 816/ E-mail: save@bt-laboratory.com.
19. Ogata A, Hirano T, Hishitani Y & Tanaka T. Safety and efficacy of tocilizumab for the treatment of rheumatoid arthritis. Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders, 2012;5: CMAMD. S7371.
20. Ogata A, Kato Y, Higa S & Yoshizaki K. IL-6 inhibitor for the treatment of rheumatoid arthritis: a comprehensive review. Modern rheumatology, 2019; 29(2): 258-267.
21. Merchante N, Cárcel S, Garrido-Gracia JC, Trigo-Rodríguez M, Moreno MÁE, León-López R, et al.Early use of Sarilumab in patients hospitalized with COVID-19 pneumonia and features of systemic inflammation: the SARICOR randomized clinical trial. Antimicrobial Agents and Chemotherapy, 2022;66(2): e0210721.
22. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proceedings of the National Academy of Sciences, 2020;117(20): 10970-10975.
23. Rizk JG, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y & Forthal DN. Pharmaco-immunomodulatory therapy in COVID-19. Drugs, 2020;80: 1267-1292.
24. Guo J, Wang S, Xia H, Shi D, Chen Y, Zheng S, et al. Cytokine signature associated with disease severity in COVID-19. Frontiers in immunology, 2021;12: 681516.
25. Petruccioli E, Najafi Fard S, Navarra A, Petrone L, Vanini V, Cuzzi G, et al. Exploratory analysis to identify the best antigen and the best immune biomarkers to study SARS-CoV-2 infection. Journal of translational medicine, 2021;19(1): 272.
26. Lu Q, Zhu Z, Tan C, Zhou H, Hu Y, Shen G, et al. Changes of serum IL-10, IL-1β, IL-6, MCP-1, TNF-α, IP-10 and IL-4 in COVID-19 patients. International journal of clinical practice, 2021;75(9): e14462.
27. Khiali S, Rezagholizadeh A & Entezari-Maleki T. A comprehensive review on sarilumab in COVID-19. Expert Opinion on Biological Therapy, 2021;21(5): 615-626.
28. Montesarchio V, Parrella R, Iommelli C, Bianco A, Manzillo E, Fraganza F, et al. Outcomes and biomarker analyses among patients with COVID-19 treated with interleukin 6 (IL-6) receptor antagonist sarilumab at a single institution in Italy. Journal for immunotherapy of cancer, 2020;8(2): e001089.
29. Mushtaq MZ, Mahmood SB, Almas A, Wasti SA & Ali SA.Tocilizumab in critically ill COVID-19 patients: An observational study. International Immunopharmacology, 2022;102: 108384.
30. Omran, D, Al Soda M, Bahbah, E, Esmat G, Shousha H, Elgebaly A & Heiba A. Predictors of severity and development of critical illness of Egyptian COVID-19 patients: A multicenter study. Plos one, 2021;16(9), e0256203.
31. Ramadan HK-A, Mahmoud MA, Aburahma MZ, Elkhawaga AA, El-Mokhtar MA, Sayed IM, et al. Predictors of severity and co-infection resistance profile in COVID-19 patients: First report from upper Egypt. Infection and drug resistance, 2020;13: 3409-3422.
32. Iqtadar S, Khan A, Mumtaz S, Pascual-Figal D, Livingstone S & Abaidullah S. Tocilizumab therapy for severely-ill COVID-19 pneumonia patients: a single-centre retrospective study. Journal of Physiology & Pharmacology, 2022; 73(4): 10.26402.
33. Macedo A, Goncalves N & Febra C.COVID-19 fatality rates in hospitalized patients: systematic review and meta-analysis. Annals of epidemiology, 2021; 57: 14-21.
34. Onuk S, Sipahioğlu H, Karahan S, Yeşiltepe A, Kuzugüden S, Karabulut A, et al. Cytokine levels and severity of illness scoring systems to predict mortality in COVID-19 infection. Healthcare, (Basel, Switzerland), 2023;11(3): 387.
35. Kesmez Can F, Özkurt Z, Öztürk N & Sezen S. Effect of IL-6, IL-8/CXCL8, IP-10/CXCL 10 levels on the severity in COVID 19 infection. International Journal of Clinical Practice, 2021;75(12): e14970.
36. Cabaro S, D'esposito V, Di Matola T, Sale S, Cennamo M, Terracciano D, et al. Cytokine signature and COVID-19 prediction models in the two waves of pandemics. Scientific Reports, 2021;11(1): 20793.
37. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. (2020): Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. jama, 323(11): 1061-1069.