ORIGINAL ARTICLE

ROLE OF IL-6 IN THE ADJUSTMENT OF THE MEDICAL TREATMENT OF PATIENTS WITH COVID-19 ASSOCIATED ACUTE RESPIRATORY DISTRESS SYNDROME

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Background: Many cytokines propose to play a role in the pathogenesis of Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV-2) associated COVID-19 disease. High interleukin-6 (IL-6) levels are associated with mortality and other poor clinical outcomes in COVID-19. **Methods:** In this retrospective study, the correlation of IL-6 level with clinical and other inflammatory parameters, its role in treatment change and its relationship with mortality in COVID-19 patients developing acute respiratory distress syndrome (ARDS) were investigated. **Results:** Totally 76 patients were included in the study; Thirty-four (44.7%) patients were female and 42 (55.3%) patients were male. All patients had IL-6 levels above the upper reference value (>5.9 pg/mL). Overall, 48 patients (63.1%) had a severe clinical presentation (tachypnoea, tachycardia, fever) that was clinically compatible with IL-6 values, and medical treatment was changed for COVID-19 in this group. A positive correlation was detected between IL-6 and CRP on the day of the change in treatment (p=0.035, r=0.76). There was no decrement observed in IL-6 level on the 3rd day in patients that was clinically thought to have cytokine storm and whose treatment was changed. Mortality was higher in the group whose treatment was changed. **Conclusion:** We believe that IL-6 level alone is insufficient to decide on a change in treatment, and correlation of IL-6 with the patient's clinical status is more significant in such decision.

Keywords: Interleukin-6; COVID-19; ARDS; Cytokine storm; Medical treatment

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INTRODUCTION

Severe acute respiratory coronavirus type 2 (SARS-CoV-2) is the largest pandemic of the last century. More than 180 million confirmed cases of COVID-19 with nearly 4 million deaths reported worldwide.[1] Although a lot of information has been obtained about the pathogenesis and immunology of SARS-CoV-2-related disease (COVID-19) since its first appearance, there is still no medical treatment that has proven its efficacy and safety against SARS-CoV-2 at a high level of evidence. Acute respiratory distress syndrome (ARDS) is a well-known complication of COVID-19 that causes mortality and morbidity in critically ill COVID-19 patients.[2,3] Coronaviruses are reported to activate excessive and dysregulated host immune response, which may contribute to the development of ARDS.[2,3] Autopsy studies of patients who developed COVID-19 associated ARDS revealed hyperactivation of cytotoxic T cells with cytotoxic granules at high concentrations.[4] Hyperactivation of the humoral immune pathway plays a critical role in respiratory failure, shock and multi-organ dysfunction. Inflammatory cytokines and chemokines, including interleukin-6 (IL-6), interleukin-1β (IL-1β), induced protein 10 (IP10), and monocyte chemoattractant protein-1 (MCP-1), are significantly increased in COVID-19 associated ARDS patient group.[5]

Many biomarkers have been searched and investigated in order to follow the course of the disease and to make medical treatment adjustments in COVID-19 disease characterized by an increased immune response.[6–8] Higher interleukin-6 (IL-6) levels were detected in critical and severe COVID-19 cases, while lower levels were associated with mild illness.[9,10] It has been stated that high IL-6 levels are determinative in the need for mechanical ventilation (MV).[11] In this retrospective study, we aimed to reveal the correlation between IL-6 levels and clinical and inflammatory parameters, its role in the treatment adjustment in patients who developed COVID-19 associated ARDS, and its relationship with mortality in critically ill COVID-19 patients.

MATERIAL AND METHODS

This study included patients who were older than 18 years old, had positive COVID-19 real-time polymerase chain reaction (RT-PCR) or rapid antibody test, and were examined and treated at corresponding COVID-19 intensive care unit (ICU) due to pneumonia (fever, cough, sputum and infiltration on chest X-ray) or acute respiratory failure (ARF) between July 1 to October 5 2020. All COVID-19 patients that were treated in our ICU within this period were enrolled in the study. Patients that do not have IL-6 levels within the study period were excluded from the study. Three patients died just before we measured 3th day of IL-6 level, therefore those patients were excluded.

Demographic data of patients (age, gender), Acute Physiology and Chronic Health Evaluation II (APACHE-II) score, ICU hospitalization Sequential Organ Failure Assessment (SOFA) score, medical treatments (favipiravir, methylprednisolone, dexamethasone, tocilizumab), level of IL-6 and other inflammatory parameters [C-reactive protein (CRP), procalcitonin, ferritin], admission symptoms (fever, cough, sputum, weakness, myalgia, shortness of breath, chest pain), contact histories for COVID-19, radiological findings and other laboratory values were recorded. The type of respiratory support treatments they received during ICU follow-up [conventional low flow oxygen systems, high-flow nasal oxygen (HFNO), non-invasive mechanical ventilation (NIMV), invasive mechanical ventilation (IMV)], anti-bacterial, anti-viral, and COVID-19 specific treatments and ICU outcomes [length of stay in ICU, length of stay in IMV or NIMV, total length of hospital stay, and hospital outcome (transfer to ward, transfer to another ICU, exitus)] were retrieved from patients' medical records.

Anti-microbial, anti-viral and COVID-19 specific treatments of the patients were determined by the joint decision of the ICU specialists and the infectious diseases specialists who followed the patient based on the Scientific Committee Study of the Ministry of Health General Directorate of Public Health of the Republic of Turkey COVID-19 (SARS-CoV-2 Infection) Guidelines.[12] All patients in study received favipiravir for at least 5 days from the time of hospitalization, taking into account the previous treatment period.

Clinically, patients with tachypnoea (respiratory rate >24 breaths/minute, tachycardic pulse >100 beats/min) and worsening hypoxia (a decrease of more than 20 mmHg PaO_2/FIO_2 ratio and radiological progression demonstrated by increased areas of consolidation on chest X-ray) who had more than two-fold increase in CRP, ferritin, IL-6 and D-dimer levels, with was considered in cytokine storm. Levels of IL-6 and other inflammatory parameters (Ferritin, CRP, procalcitonin), clinical (body temperature, arterial systolic blood pressure, respiratory rate, IL-6 on the first and 3rd day of cytokine storm) and other laboratory findings [Arterial blood gas (pH, $PaCO_2$, PaO_2, HCO_3, base excess, lactate, SpO_2), complete blood count (White blood cell count, haemoglobin, haematocrit, lymphocyte count, neutrophil count, platelet), kidney function (blood urea nitrogen, creatinine), electrolytes (Na, K, Cl), bleeding and coagulation parameters [Activated prothrombin time (Aptt), International Normalized Ratio (INR), D-dimer, prothrombin time (PT) at ICU admission and on the 3rd day tests] were recorded. In patients who were considered to have cytokine storm, treatment changes (starting steroids, giving tocilizumab, giving steroids and tocilizumab together) were made by taking into account the IL-6 levels. All general characteristics, clinical and ICU results of the group with and without treatment changes were compared.

The IL-6 level was measured by taking 100 µl serum or plasma with EDTA or without heparin that was preserved at 2–8 °C and processed within the same day with IMMULITE 2000 test. IMMULITE 2000 (Siemens, USA) is an enzyme-labelled, sequential immunometric chemiluminescence test. Incubation cycles are 2x20 min. Physiological IL-6 concentration of serum was accepted as 1–5 pg/ml.

Statistical analysis was performed using SPSS Statistics (Version 17.0, SPSS Inc). The normal distribution of the data was measured using the Shapiro-Wilk test. Continuous variables were shown as mean±standard deviation or median (25^{th} and 75^{th} percentiles) depending on data distribution and were evaluated using Student's t-test or Mann-Whitney U test. Categorical variables were expressed as numbers (%) and compared by using Chi-square test or Fisher exact test. Bivariate Pearson correlation test was used to determine whether there was a correlation between IL-6 and CRP on the first day, on the day of treatment change, and on the third day.

RESULTS

Among 76 patients, 34 (44.7%) were female and 42 (55.3%) were male with a mean age of 65.4±12.8 years. The median APACHE II value of the patients was 16.0 [12.2–20.0], and the median SOFA value at ICU admission was 4.0 [3.0–5.0]. At least one SARS-CoV-2 oro-nasopharyngeal swab of 61 (80.3%) patients was positive by RT-PCR. Fifteen (19.7%) patients had a history of contact with a COVID-19 patient, had findings of specific involvement for COVID-19 on thorax CT, and positive IgM/G value measured with the rapid antibody test. The most

common comorbidities were hypertension (55.3%) and diabetes mellitus (40.8%). Eighteen (23.7%) patients had underlying lung disease (chronic obstructive pulmonary disease, asthma, bronchiectasis). The mean PaO_2/FIO_2 ratio at ICU admission was 127.0±74.7 mmHg. Seven (9%) patients had mild ARDS, while 69 (90.8%) patients had moderate-severe ARDS. Mean values of body temperature (BT) of the patients were 36.7±0.6 °C, respiratory rate was 27.9±8.8 breaths/min, systolic blood pressure was 124.0±18.6 mmHg, pulse was 95.0±22.3 beats/min, and SpO2 was 85.5±8.5% at the time of admission to ICU.

Among the laboratory and inflammatory markers of the patients, median CRP was measured as 132 [60–232] mg/L, mean lymphocyte $0.91\pm0.6x10^3/\mu L$, lactate dehydrogenase (LDH) 407±344 U/L, median D-Dimer 1.55 [0.46–2.78] µg/ml, fibrinogen 558 [444–695] mg/dl, ferritin 598 [271.5–3875] µg/L, and procalcitonin was measured as 0.37 [0.12–1.68] µg/L. Details of other laboratory parameters were presented in Table-1.

All patients had IL-6 levels above the upper limit (>5.9 pg/mL), and the median IL-6 level of the patient population was 69.4 pg/ml (20->1000). Four patients had IL-6 levels above 1000 pg/mL. Among patients with higher than 1000 pg/ml IL-6 levels, 3 patients died and 1 patient was transferred to the service. The median IL-6 level was 180 [42.5–360] pg/ml in the group with treatment change and 21.1 [9–83.6] pg/ml in the group with no treatment change. The IL-6 level was higher in the group whose treatment was changed (p=0.011). The clinical presentation of twenty-eight (39.6%) patients was not compatible with their IL-6 levels. Medical treatment was not changed in these patients, their current treatment was continued and standard ICU care was provided. Total of 48 (63.1%) patients showed clinical, radiological worsening and increase in other inflammatory parameters consistent with IL-6 levels, and medical treatment was changed in this group. Tocilizumab was started in 40 (52.6%) patients, tocilizumab and methylprednisolone in 4 (5.3%) patients, dexamethasone in 1 (1.3%) patient, and methylprednisolone in 3 (3.9%) patients for whom treatment changes were made.

Demographic characteristics, comorbidities, APACHE II and SOFA scores of the group with and without treatment modification groups were similar (p>0.05)**.** At the time of ICU admission, the body temperature of the group with treatment change was higher than the group without treatment (36.8±0.7 vs 36.5±0.4, p=0.029); this group was also more hypoxic and tachypnoeic [SpO_2 81.6±12.3% vs 90.1±5.2%, respectively, p<0.05; respiratory rate 30.1±6.2 vs 26.2±7.2 breaths/min, p=0.024]. The group with treatment change had lower rates of PaO_2, SpO_2/FiO_2, and PaO_2/FIO_2 at ICU admission (62.7±17.6 vs 81.4±27.7 mmHg, respectively, p=0.001; 146.1±64.7 vs 203.5±101.1 p=0.001; 103±38.5 mmHg vs 169±99.7 mmHg, p=0.003). The majority of the treatment change group had severe ARDS (n=28, 58.3%), while 20 (41.7%) patients had moderate ARDS. Higher number of patients died in the group whose treatment was changed due to IL-6 elevation, and fewer patients were admitted to the service in this group. Overall, thirty-one (40.8%) of all patients died (Table-2).

Initial IL-6 levels were higher in the treatment change group, [79.4 pg/ml (20-204.5) vs 21.1 pg/ml (9–83), p=0.01]. Fibrinogen was lower in the first group, while aPTT was higher in the group that underwent treatment change [524 (482–664) mg/dl vs 670 (564-699) mg/dl, p= 0.04; 40.8±12.7 sn vs 35.6±6.6 sn, p=0.05]. There was no significant difference between the two groups in terms of other inflammatory parameters (CRP, procalcitonin, ferritin) and prognostic markers (D-Dimer, LDH) (p>0.05) (Table-3).

On day of IL-6 level control there was a decrease in tachycardia and tachypnoea in the group that underwent treatment modification (mean heart rate 90±11 beats/minute, mean respiratory rate 28±6 breath/minute). Although there was a decrease in CRP levels in both groups on the third day of ICU admission, no difference was found between the groups (p>0.05). In both groups, the IL-6 level was found high on the 3rd day, while the group whose treatment was changed showed higher IL-6 values [304.5 pg/ml (34–690) vs 95 pg/ml (10.6–62.0), p=0.025]. There was a moderate increase in lymphocyte level in both groups, with no difference between the groups (p>0.05) (Table-4).

A positive correlation was found between IL-6 and CRP on the day of treatment change (p=0.035, r=0.76) (Figure-1).

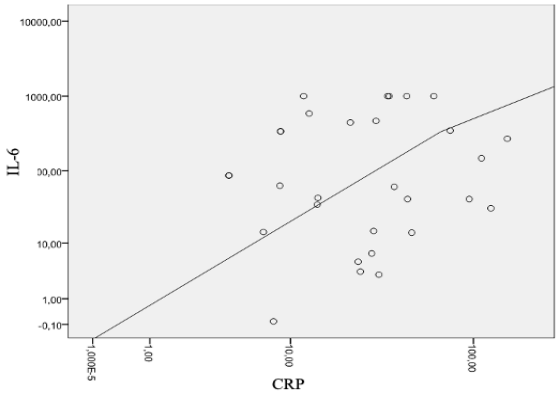

Figure-1: Correlation between IL-6 and CRP levels on the third day of ICU

Table-1: Laboratory parameters of patients at the time of intensive care unit admission

Labaratory Values	n=76 (mean±SD)
WBC (103/µL)	10.383± 7.168
Hg (g/dl)	12.2± 2.3
Hct (%)	37.7± 6.6
Platelet (103/µL)	238.8± 106.1
Neutrophil count (103/µL)	9.1± 6.2
Lymphocyte count (103/µL)	0.91± 0.6
Urea (mg/dl)	68.3± 44.6
Creatinine (mg/dl)	1.3± 1.15
AST (U/L)*	36 [23-57]
ALT (U/L)*	24 [15-46)]
CK (U/L)*	123 [15-7934]
CK-MB (U/L)*	24 [9-1155]
Na (mEq/L)	138.5± 6.1
K (mEq/L)	4.3± 0.8
Cl (mEq/L)	100.6± 9.2
D-Dimer (µg/ml)*	1.55 [0.46-2.78]
Fibrinogen (mg/dl)*	558 [444-695]
Ferritin (µg/L)*	598 [271.5-3875]
CRP (mg/dl)*	132 [60-232]
Interleukin-6 (pg/ml)*	69.4 (20- >1000)
Procalcitonin (µg/L)*	0.37 [0.12-1.68]
International normolized ratio (INR)	1.3± 0.8
aPTT (sec)*	38.5± 11.9
Prothrombin time (sec)	12.7± 9.3
Total protein (g/L)	11.9± 6.12
Albumin (g/L)	3.1± 1.9

WBC:White blood cell count, Hg:Hemoglobin, Hct: Hematocrite, AST:Aspartat transaminase ALT:Alanin transaminase, CK:Creatinin kinase, CK-MB: Creatinin kinase myoglobulin, Na:Natrium, Cl:Chlorine, K:Potasium, CRP:C-reactive protein, Aptt:Activeted protrombin time
**Median [interquartile range 25-75]*

Table-2: Comparison of the characteristics of the groups with and without treatment changes according to IL-6 level

Characteristics	Patient group with treatment change (n=48,%)	Patient group without treatment change (n=28,%)	*p*
Age (year) (ortalama±SD)	66.3±12.7	63.7±13.0	0.402
Gender			
Female	19 (39.6)	15 (53.6)	0.237
Male	29 (60.4)	13 (46.4)	
APACHE II (median) (25-75)	16 (13-21)	14 (11.2-16.3)	0.332
SOFA (median) (25-75)	4 (3.0-5.75)	3 (2-4.75)	0.423
Comorbidities			
Hypertension	28 (58.3)	14 (50.0)	0.381
Diabetes Mellitus	18 (37.5)	13 (46.4)	0.256
Atherosclerotic heart disease	10 (20.8)	6 (21.4)	0.554
Heart disease	3 (6.25)	3 (10.7)	0.370
Preexisting lung disease	14 (29.2)	4 (14.3)	0.150
Vital signs at ICU admission (mean±SD)			
Body temperature (°C)	36.8±0.7	36.5±0.4	**0.029**
Pulse (beats/min)	94.3±24.2	95.3±19.5	0.858
Arterial blood pressure (sistolik)(mmHg)	126.4±19.0	120.6±17.8	0.210
SpO_2 (%)	81.6±12.3	90.1±5.2	**0.001**
Respiratory rate (breaths/min)	30.1±6.2	26.2±7.2	**0.024**
Blood gas results at ICU admission (mean± SD)			
pH	7.42±0.06	7.42±0.09	0.794
$PaCO_2$ (mmHg)	34.1±8.4	36.7±13.3	0.299
PaO_2 (mmHg)	62.7±17.6	81.4±27.7	**0.001**
HCO_3 (mEq/L)	28.7±3.13	23.6±4.8	0.408
Lactate (mmol/L)	1.7±0.8	1.5±0.8	0.210
SpO_2/FiO_2 (%)	146.1±64.7	203.5±101.1	**0.001**
PaO_2/FiO_2 (mmHg)	103±38.5	169±99.7	**0.003**
ARDS Classification			**0.001**
Mild ARDS	0	7 (25.0)	
Moderate ARDS	20 (41.7)	12 (42.9)	
Severe ARDS	28 (58.3)	9 (32.1)	
Status at the exit of ICU			
Exitus	24 (50.0)	7 (25.0)	**0.053**
Transfer to service	14 (29.2)	16 (57.1)	**0.050**
Transfer to another ICU	10 (20.8)	5 (17.9)	0.690

APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA:Sequentail Organ Failure Assesment score, ARDS:Acute respiratory distress syndrome, ICU: Intensive Care Unit

Table-3: Comparison of laboratory and inflammatory parameters in intensive care admission of two groups

Labaratory values (median± SD)	Patient group with treatment change (n=48)	Patient group without treatment change (n=28)	*p*
WBC (10^3/µL)	9.63±4.7	9.14±3.7	0.635
Hg (g/dl)	12.7±2.1	12.0±2.2	0.184
Htc (%)	38.6±6.1	37.4±6.6	0.414
Platelet (10^3/µL)	223±91.8	258.6±95.6	0.112
Neutrophil count (10^3/µL)	7.8±4.5	7.7±3.3	0.855
Lymphocyte count (10^3/µL)	0.71±0.37	0.82±0.41	0.199
Urea (mg/dl)	61.9±32.9	67.1±49.1	0.582
Creatinine (mg/dl)	1.2±0.6	1.5±1.4	0.237
AST (U/L) (median) (25-75)	97.1±23.0	62.8±14.7	0.786
ALT (U/L) (median) (25-75)	57.8±11.6	55.4±12.0	0.892
CK (U/L) (median) (25-75)	456±100.1	169±166	0.145
CK-MB (U/L) (median) (25-75)	34.2±22.5	27.0±17.1	0.158
Na (mEq/L)	137.2±4.9	139±7.1	0.250
K (mEq/L)	43±0.5	4.5±0.8	0.079
Cl (mEq/L)	99.7±4.3	102,0±6.7	0.058
LDH (U/L)	542±203	461±203	0.116
D-Dimer (µg/ml)*	0.91 [0.17-2.17]	1.14 [0.40-3.10]	0.495
Fibrinogen (mg/dl) *	524 [482-664]	670 [564-699]	0.040
Ferritin (µg/L)	1177±128.6	1091±118.5	0.785
CRP (mg/dl) *	109 [44.9-189]	114 [64-171.5]	0.467
Procalcitonin (µg/L) *	0.27 [0.16-1.0]	0.45 [0.12-1.7]	0.180
Interleukin-6 (pg/ml) *	79.4 (20-204.5)	21.1 (9-83)	**0.01**
INR	1.3±0.8	1.2±0.4	0.667
aPTT (sec)	40.8±12.7	35.6±6.6	**0.050**

WBC:White blood cell, Hg:hemogram, Hct: Hematocrite, AST: Aspartat aminotransferaz, ALT:Alanin aminotransferaz, CK:Creatinin kinaz, CK-MB:Creatinin kinaz miyoglobulin, CRP:C-reaktive protein, INR:International normalized ratio,*Median [Interquartiel range 25-75], aPTT:Activated protrombin time.

Table-4: Comparison of IL-6 and other inflammatory parameters measured on the third day

Labaratory values (median± SD)	Patient group with treatment change (n=48)	Patient group without treatment change (n=28)	*p*
PaO_2/FiO_2 (mmHg)*	103.0±38.5	169.0±99.7	**0.003**
CRP (mg/L) **	24 [9.4-44.0]	26.7 [10.0-69.4]	0.790
IL-6 (pg/ml)**	304.5 [34-690]	95 [10.6-62.0]	0.025
Lymphocyte (10^3/µL) *	0.82±0.72	0.94±0.68	0.484

IL-6:Interleukin-6, CRP:C-reaktive protein, *mean±standart deviation, **Median [Interquartiel range 25-75]

DISCUSSION

Our study highlights that high IL-6 levels are not always correlated with clinical and other inflammatory parameters in all patients with COVID-19 associated ARDS, and spot IL-6 level may not always a determinant for medical treatment modification in this patient group with immune dysregulation. We found that the marker CRP was correlated with IL-6 level and mortality was higher in the group with high IL-6 level.

While a positive correlation was detected between IL-6 and CRP on the day of treatment change, there was a decrease in CRP level on the 3rd day in the group that was thought to be in a cytokine storm with high IL-6 level and accompanying clinical findings and underwent treatment modification. However, no decrease in IL-6 was detected in the treatment change group. The fact that IL-6 levels did not decrease in the group whose treatment was changed on the 3rd day was attributed to a high rate of tocilizumab use. It was observed that elevated IL-6 level alone was insufficient to decide on treatment change, and after the use of IL-6 monoclonal antibody (tocilizumab), there was no decrease in IL-6 level, on the contrary, an increase was observed in this group.

Interleukin-6 (IL-6) which has a wide effect on the immune system, also has hormone-like effects that regulate the homeostatic process. Stimulation of toll-like receptors, generation of prostaglandins and adipokines, stress responses and other cytokines can increase the IL-6 synthesis. Normal physiological IL-6 concentration is 1–5 pg/ml in serum. The cut-off value of IL-6 in systemic inflammatory response syndrome (SIRS) and macrophage activation syndrome (MARS) is unknown, however, it has been reported that IL-6 levels in the blood are high and present decreasingly for 16 days five-fold elevation of the IL-6 level, NLR (Neutrophil/lymphocyte ratio) >3.13, lymphocyte count <500/µL, IL-2R, IL-8, INF-γ ve IP-10 may predict SIRS.[13]

A meta-analysis of nine studies evaluated 1426 patients and reported that the IL-6 cut-off value above 55 pg/ml is associated with the severity of the

disease in COVID-19.[9] In our study, the IL-6 level of most of the patients was above this cut-off value. Few studies have investigated the relationship between IL-6 and mortality in critical and mortal COVID-19 patients. In the study of Herold *et al*.[11], IL-6 level above 80 pg/ml was reported as being predictive for the need for invasive mechanical ventilation (MV). IL-6 levels in our study were quite high (69.4 pg/ml in the total group and 79.4 pg/ml in the group that underwent treatment change). This was attributed to the fact that all patients in our study were in critical conditions with ARDS according to the World Health Organization (WHO) disease severity classification, and the overall disease severity was high. In our study, all patients needed invasive or non-invasive MV.

In the review by Calabrese *et al*.[14], after drug administration's targeting the IL-6 receptor, an increase in IL-6 level was observed immediately after drug administration, and this increase was attributed to the fact that tocilizumab affected receptor-bound IL-6 and relatively increased the free IL-6 level. IL-6 monitoring was not recommended after tocilizumab use.[14] A single-center study with 15 patients which the effectiveness of tocilizumab treatment was investigated in COVID-19 by Luo *et al*.[15] included patients with severe (respiratory rate ≥30/min, SpO_2 ≤%93, PaO_2/FiO_2 ≤300 mmHg) and critical (respiratory failure requiring MV, shock or organ failure requiring ICU) conditions. In this study, a decrease in CRP level was observed except for 1 patient, and an increase in IL-6 level was observed in 12 patients on the contrary. This was thought to be due to the increase in soluble IL-6 level since tocilizumab was started competitively with the receptor, and it was stated that IL-6 after tocilizumab may be effective in evaluating the severity of infection, predicting prognosis and evaluating the response to treatment, however dynamic follow-up may be required.[15]

In the study conducted by Liu *et al*.[16] in which the role of IL-6 monitoring in severe COVID-19 patients was investigated, there was a significant decrease in IL-6 level and a significant improvement in CT findings. Therefore, it has been suggested that dynamic changes in IL-6 can be utilized as a biomarker in severe COVID-19 patients. In our study, 7 patients had mild ARDS, while 69 patients had moderate-severe ARDS. The IL-6 level of 30 patients was evaluated before and after the treatment, the IL-6 level of 4 patients increased due to progression of the disease, the IL-6 level increased compared to baseline in 3 patients despite the clinical improvement, and the IL-6 level of the remaining 23 patients decreased after tocilizumab treatment.

In a recent study, IL-6 level higher than 30 pg/ml was reported as the best predictor for predicting the need for invasive MV and was associated with other poor outcomes. All patients in that study had mild-to-moderate ARDS with basal IL-6 level 21.36 (7.53-54.21) pg/ml. The group with the highest mortality was determined as the group with high IL-6 level and not given tocilizumab treatment.[17] The baseline median IL-6 level of the patients included in our study was 69.4 pg/ml (20- >1000 pg/mL), and all patients had IL-6 levels above the upper limit (>5.9 pg/mL). In addition, the mean PaO_2/FIO_2 ratio in the ICU admission group in our study was 103±38.5 mmHg, and the group that did not undergo treatment modification was 169±99.7 mmHg, indicating that our patients were more critical and severe. Therefore, IL-6 levels in our study were higher compared to literature.

Sayah *et al*.'s study[18] patients were grouped as severe and non-severe according to plasma IL-6, CRP, soluble-IL-2 receptor (IL2rα), procalcitonin and ferritin values. An IL-6 value above 42 pg/ml accurately determined the severity in more than 90% of the patients (Area under ROC curve 0.972), and a threshold value of 83 pg/ml of IL-6 (area under ROC curve 0.94 OR= 184) was found to have a high predictive value for mortality. IL-6 also showed positive correlation with other inflammatory parameters. The median IL-6 level of the entire study group was 35 (13–85) pg/ml. However, in their study, when patients were grouped according to the COVID-19 disease severity score of the WHO, only 34% of the patients were classified as critically ill.[18]

In conclusion; we believe that correlation of IL-6 level with the clinical presentation has more significant effect in deciding the treatment change. We concluded that IL-6 elevation may be effective in changing treatment and predicting mortality in severe COVID-19-associated ARDS patients, however, it is insufficient in making the decision to change the treatment in critical COVID-19 patients in ICU. We do not recommend IL-6 monitoring in the follow-up of treatment success. There is a need for larger series of studies investigating the role of IL-6 in diagnosis, monitoring and treatment success in critically ill COVID-19 patients in the ICU.

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Ethics Statemen: All the patients read the patient information form about the study procedure and

written informed consent was obtained from each of the patient. This study was performed in accordance with the ethical principles in the Good Clinical Practice (GCP) guidelines and Declaration of Helsinki, applicable local regulatory requirements and the protocol were approved by Ethics Committee of tertiary hospital.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Data availability: The research article data used to support the findings of this study are available from the corresponding author upon request.

AUTHORS' CONTRIBUTIONS

All authors have contributed sufficiently in the conception and design of the study, data collection, and interpretation as well as the preparation of the manuscript. All authors read and approved the final version of the manuscript.

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