RESEARCH ARTICLE

Retrospective evaluation of efficacy in cytokine storm management among critically ill COVID-19 patients

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ABSTRACT

Objective: The objective of the present study was to assess the impact of tocilizumab, intravenous immunoglobulin and methylprednisolone on the clinical and laboratory parameters of critically ill COVID-19 patients hospitalized in the intensive care unit. Additionally, the study also aimed to determine whether there were any differences among these drugs concerning these parameters, as well as the number of non-survivors following anticytokine therapy.

Material and methods: A total of 227 critically ill COVID-19 patients, who were hospitalized in the intensive care unit and clinically presented with a cytokine storm, were retrospectively divided into three groups. Group 1 (n=87) received tocilizumab, group 2 (n=70) received intravenous immunoglobulin and group 3 (n=70) received methylprednisolone as ant cytokine therapy. Clinical and laboratory parameters of the patients were compared before and after receiving ant cytokine therapy. Clinical and laboratory parameters, as well as the number of non-survivors, were compared between the three groups after receiving ant cytokine therapy.

Results: When comparing the groups, a statistically significant difference was observed in the number of non-survivors, with group 2 having a significantly higher number of non-survivors compared to the other groups 63 (50.9%) ($p<0.001$). There was no statistically significant difference between group 1 and group 3 in terms of the number of non-survivors. In group 1, there was a decrease in the need for both noninvasive and invasive mechanical ventilation following ant cytokine therapy. However, it was observed that the need for oxygen supplementation *via* a face mask or a reservoir mask increased in this group. In group 3, after receiving ant cytokine therapy, there was an increase in the number of patients who were breathing with nasal cannula and those who were on room air. In group 2, there was an increase in the number of patients who required noninvasive and invasive mechanical ventilation. In all three groups, the levels of C-reactive protein decreased after the therapy. However, it should be noted that ant cytokine therapies do not prevent lung injury and result in patients surviving with severe Acute Respiratory Distress Syndrome (ARDS) for at least up to day 7 following anticytokine therapies. In group 1, there was no statistically significant difference between the Sequential Organ Failure Assessment (SOFA) scores before and after receiving anticytokine therapy. However, in groups 2 and 3, there was a significant increase in SOFA scores after therapy.

Conclusion: Due to the significant increase in SOFA scores after anticytokine therapy in groups 2 and 3, it was considered that organ failure further worsened and sepsis deepened in these two groups. However, the number of non-survivors was similar between group 1 and group 3. The number of non-survivors was significantly higher in group 2 than in groups 1 and 3. The authors of this manuscript believe that the anticytokine efficacy of intravenous immunoglobulin for treating cytokine storm in critically ill COVID-19 patients aged 65-95 years is inadequate. Furthermore, they suggest that the use of intravenous immunoglobulin may contribute to an increased number of non-survivors. Likewise, no improvement was observed in ARDS up to day 7 following anticytokine therapy when utilizing these three agents.

Keywords: SARS-Cov-2; Cytokine release syndrome; Tocilizumab; Intravenous immunoglobulin; Methylprednisolone; Critically ill COVID-19 patient.

INTRODUCTION

Interleukin-6 (IL-6) is recognized as one of the key cytokines implicated in the development of the cytokine storm observed in Coronavirus Disease 2019 (COVID-19) patients. Tocilizumab (TCZ) is an IL-6 receptor blocker. There are publications that provide both recommendations and cautions regarding the use of corticosteroids in the treatment of cytokine storm. Methylprednisolone (MP) has also been recommended in a low dose and for a short duration in patients with severe COVID-19 pneumonia. Intravenous Immunoglobulin (IV-IG) therapy is also recommended for the treatment of COVID-19-related cytokine storm due to its ability to block Fc-gamma receptors [1].

The authors of the present study hypothesized that tocilizumab, IV-IG and MP, administered to critically ill COVID-19 patients hospitalized in the Intensive Care Unit (ICU) for the treatment of cytokine storm caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), could potentially improve clinical and laboratory parameters, increase the number of surviving patients, and demonstrate comparable efficacy in terms of these parameters.

The objective of the present study was to assess the effects of TCZ, IV-IG and MP on the clinical and laboratory parameters of critically ill COVID-19 patients hospitalized in the ICU, including the number of non-survivors. Additionally, the study aimed to investigate potential differences among these three therapies in terms of clinical and laboratory parameters, as well as the number of non-survivors [2].

MATERIALS AND METHODS

This study was conducted at Gazi Yasargil education and research hospital of the ministry of health of Turkey between March 22, 2020, and October 30, 2020. A retrospective assessment was performed on 227 out of 495 patients who received anticytokine therapy among a total of 725 patients hospitalized in the ICU. A total of 268 patients were excluded from the study as they did not meet the inclusion criteria. After obtaining preliminary approval from the scientific information platform of the Ministry of Health, the study also received approval from the hospital management (Date: August 27, 2020; Number: 58146266-000-17663). The study was conducted in compliance with the ethical principles outlined in the Helsinki Declaration of 2008. Patient data was obtained through the utilization of hospital file records and the hospital information system [3].

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Inclusion criteria

- Patients with a laboratory-confirmed infection by the SARS-Cov-2.
- Patients with a procalcitonin value of less than 1.
- Patients aged 65-95 years.
- Patients who have not received prior anticytokine therapy.
- Patients with a grade 2-4 Cytokine Release Syndrome (CRS) (Grade 2: Moderate; grade 3: Severe and grade 4: Life-threatening.
- Patients diagnosed with early (first 1-3 days of illness) and late (8-11 days of illness) cytokine storm.
- Patients with a Glasgow Coma Scale (GCS) score above 10 who were not intubated.
- Patients who have not been vaccinated against SARS-CoV-2.
- Patients receiving standard therapy in line with the interim guidelines of the World Health Organization (WHO) and the ministry of health of Turkey.

Exclusion criteria

- Patients with Kidney Disease Improving Global Outcomes (KDIGO) stages 1-2-3 (n=34).
- Patients who underwent organ transplantation and receiving therapy (n=5).
- Patients with an Acute Physiology and Chronic Health Evaluation II (APACHE II) score above 25% (n=75).
- Patients who were intubated and died before completing the full course of anticytokine treatment doses (n=48).
- Patients with hepatic failure (n=24).
- Patients with low IgA levels (n=2).
- Patients with missing data (n=17).
- Patients with a GCS score below 10 (n=25).
- Patients with a Procalcitonin (PCT) value >1 (n=38).

In our study, the anticytokine treatment administered to critically ill COVID-19 patients hospitalized in ICUs, following the diagnosis of cytokine storm, was as follows: Group 1 (TCZ-treated patients) received 2 doses of 400 mg TCZ intravenously over 2 hours (Actemra 400 mg/20 mL infusional solution, Roche mustahzarları sanayi anonim Sirketi, Istanbul, Ayazaga, Turkey) and group 2 (IV-IG-treated patients) received Intravenous Immunoglobulin (IV-IG) at a dose of 0.4 g/kg/day for 5 days. Each vial of GENIVIG human immunoglobulin (pH 4) 5 g/100 mL, containing a solution for IV infusion by GEN drug and health products san. *ve* tic. A.S., Cankaya, Ankara, Turkey, was administered in 15 minutes. Group 3 (MP-treated patients) received Methylprednisolone (MP) that was administered intravenously over 2 hours using ampoules of 53 mg methylprednisolone sodium succinate (Mustafa Nevzat Ilac Sanayi AS., Gayrettepe, Istanbul) equivalent to 40 mg methylprednisolone (Four doses of 80 mg were given for 3 days, followed by three doses of 80 mg for 1 day, two doses of 80 mg for 1 day, one dose of 80 mg for 1 day and one final dose of 80 mg on the 7th day). The study recorded thoracic CT images of the included patients upon their initial presentation to the emergency department, as well as Anteroposterior (AP) chest x-rays taken just before the administration of anticytokine agents and on the 7th day after the completion of the anticytokine therapy.

The AP chest x-rays taken just before the initiation of anticytokine therapy were compared with the AP chest x-rays obtained on the 7th day after the completion of anticytokine treatment. Any worsening of infiltration observed on the AP chest x-rays taken on day 7 after receiving anticytokine therapy was categorized as negative. Conversely, any improvement in infiltration was coded as positive, and if there was no change in the infiltration, it was coded as neutral (Tables 1-2). Clinical and laboratory parameters of the patients in the groups were compared between two time points: immediately before anticytokine administration and 7 days after the administration of anticytokine therapy. The groups were further compared with each other to assess any differences in terms of clinical and laboratory parameters, as well as the number of non-survivors. Tracheal aspirate cultures were collected from the patients who underwent intubation after receiving anticytokine therapy on the 7th day and onwards. The obtained cultures were analyzed and any microbial growths were recorded [4].

Statistical analysis

The statistical analysis of the study data was performed using SPSS version 11.0 for Windows (SPSS Inc., Chigago, IL, USA). The normality of the data was assessed using the Kolmogorov-Smirnov test. The data that met the assumptions of normality distribution were analyzed using paired-samples t-test and one-way Analysis of Variance (ANOVA), and the Tukey test was used to identify the group that caused a significant difference. The data is presented as mean ± SD. Data that did not meet the assumptions of normality distribution were analyzed using the Wilcoxon t-test and Kruskal-Wallis test, and the Mann-Whitney U test was used to identify the group that caused a significant difference. The data is presented as median (Minimum-Maximum). The *chi-square* test was employed to compare categorical data in the study. When the conditions for the *chi-squared* test were not met, Fisher's exact test was utilized. The data is presented as number and percentage (n, %). In all statistical analyzes, a p-value of less than 0.05 was considered statistically significant.

RESULTS

During the study period, a total of 725 patients were followed up in the intensive care unit. Out of the 495 critically ill COVID-19 patients who were admitted to the ICU and diagnosed with cytokine storm, a total of 268 patients were excluded from the study as they did not meet the specified inclusion criteria. A total of 227 patients were included in the study. When the patients in the groups were compared in terms of mortality after receiving anticytokine therapy, it was observed that the number of non-survivors was significantly higher (n=63, 50.9%) and the number of survivors was significantly lower (n=7, 6.8%) in group 2 ($p<0.001$) (Table 1). When comparing the oxygen intake patterns of patients in the different treatment groups after receiving anticytokine therapy, a statistically significant difference was observed (Table 1). The number of patients who were using a nasal cannula for oxygen supplementation and those who were on room air was found to be significantly higher in group 3 compared to groups 1 and 2 ($p<0.001$) (Table 1). The number of patients receiving oxygen supplementation *via* a face mask or a reservoir mask was significantly higher in group 1 compared to groups 2 and 3 ($p<0.001$) (Table 1). The number of patients receiving high-flow oxygen was found to be significantly higher in group 1 compared to groups 2 and 3 ($p<0.001$) (Table 1). The number of patients undergoing noninvasive and invasive mechanical ventilation was significantly lower in group 1 compared to groups 2 and 3 ($p<0.001$) (Table 1). When groups 2 and 3 were compared, the number of patients undergoing noninvasive and invasive mechanical ventilation was significantly lower in group 3 ($p<0.001$) [5].

When comparing the number of patients in each group falling into one of the KDIGO stages after anticytokine therapy, it was observed that the number of patients in stage I was significantly higher in both group 1 and group 3 compared to group 2 ($p=0.003$) (Table 1). The number of patients in stage II was significantly lower in group 1 compared to groups 2 and 3, and it was also significantly lower in group 3 compared to group 2 ($p=0.003$) (Table 1). The number of patients in stage III was found to be significantly lower in group 1 compared to groups 2 and 3, and it was also significantly lower in group 3 compared to group 2 ($p=0.003$) (Tables 1 and 2).

TABLE 1
Comparison of blood groups, oxygen intake patterns, KDIGO stages and demographic data of the patients included in the groups

	Groups			Total	p
	1	2	3		
ABO blood group					
A	49 (44.5%)	32 (29.1%)	29 (26.4%)	110 (100%)	0.286
B	15 (30.6%)	16 (32.7%)	18 (36.7%)	49 (100%)	
AB	2 (13.3%)	6 (40.00%)	7 (46.7%)	15 (100%)	
O	20 (37.7%)	16 (30.2%)	17 (32.1%)	53 (100%)	
Total	87 (100%)	70 (100%)	70 (100%)	227 (100%)	
Rh blood group					
Rh(-)	9 (42.9%)	6 (28.6%)	6 (28.6%)	21 (100%)	0.885
Rh(+)	77 (37.9%)	64 (30.8%)	65 (31.6%)	206 (100%)	
Mortality					
Mortal	56 (54.3%)	7 (6.8%)	40 (38.9%)	103	<0.001*
Nonmortal	31 (25%)	63 (50.9%)	30 (24.1%)	124 (100%)	
Oxygen uptake before antistokine treatment					
Nasal and room air	8 (40.0%)	5 (25.0%)	7 (35.0%)	20 (100%)	0.921
Free oxygen and mask with reservoir	47 (39.8%)	38 (32.2%)	33 (28.0%)	118 (100%)	
HF	11 (37.9%)	10 (34.5%)	8 (27.6%)	29 (100%)	
Noninvasive and invasive mechanical ventilation	21 (35.0%)	17 (28.3%)	22 (36.7%)	60 (100%)	
Oxygen uptake before antistokine treatment					
Nasal and room air	9 (36%)	5 (20.0%)	11 (44%)	25 (100%)	<0.001*
Oxygen uptake before antistokine treatment	40 (58.0%)	11 (25.9%)	18 (26.1%)	69 (100%)	
HF	9 (45%)	5 (25%)	6 (30%)	20 (100%)	
Noninvasive and invasive mechanical ventilation	29 (25.7%)	49 (43.4%)	35 (31.1)	113 (100%)	
KDİGO staging after antistokine treatment					
Stage I	14 (45.2%)	7 (22.6%)	10 (32.3%)	31 (100%)	0.003*
Stage II	5 (19.2%)	14 (53.8%)	7 (26.9%)	26 (100%)	
Stage III	6 (16.7%)	16 (44.4%)	14 (38.9%)	36 (100%)	
Number of days of stay in the intencive care unit (Days)	10 (2-52)	11 (4-75)	11 (4-75)		0.374
Number of days to give medication (Days)	4 (1-11)	4 (1-11)	4 (1-11)		0.581
Age (Years)	69 (65-95)	69 (65-95)	69 (65-95)		0.741
Gendle (Male/Female)	60 (69 %)/27 (31%)	44 (62.9%)/26 (37.1%)	40 (57.1%)/30 (42.9%)		0.308
Radiological course Negative/Positive/Neutral	40 (46%)/25 (28.7%)/ 22 (25.3%)	42 (60%)/17 (24.3%)/11 (15.7%)	32 (47.1%)/27 (38.6)/11 (14.3%)		0.122

TABLE 2
Comparison of clinical and laboratory values of the patients included in the groups

Parameters	Group 1	Group 2	Group 3	p
SOFA-B	4 (1-11)	4 (2-9)	5 (2-16)	0.051
SOFA-A	4 (0-11)	9 (2-11)	7 (0-17)	<0.001*
p	0.067	<0.001•	0.006•	-
GKS-B	15 (10-15)	15 (10-15)	15 (10-15)	0.056
GKS-A	15 (3-15	6 (5-15)		<0.001*
p	<0.001•	<0.001•	<0.001•	-
Temperature-B	38.2 (36-39.8)	38.6 (36.8-39.9)	38.2 (36.6-39.7)	0.052
Temperature-A (ºC)	36.7 (36-39.1)	36.7 (36-39)	36.7 (35.9-38.1)	0.195
p	<0.001•	<0.001•	<0.001•	-
HR-B	102 (58-146)	98.5 (11-130)	97.5 (54-150)	0.053
HR-A (Rate/Minute)	92 (54-150)	88.5 (45-156)	90 (49-155)	0.554
p	0.077	0.572	0.545	-
Systolic blood pressure-B	131 (81-190)	131 (100-180)	130 (90-180)	0.119
Systolic blood pressure-A (mmHg)	130 (80-187)	130 (63-170)	120 (60-170)	0.010*
p	0.972	0.015•	0.007•	-
Diastolic blood pressure-B	33 86-45)	73 (43-100)	72 (50-100)	0.845
Diastolic blood pressureı-A (mmHg)	75 (40-103)	72.5 (35-100)	70 (20-115)	0.005*
p	0.808	0.965	0.013•	-
RR-B	33 (6-45)	30 (16-44)	31 (16-36)	0.051
RR-A (RR/Minute)	28 (16-45)	24 (18-38)	26 (6-44)	<0.001*
p	<0.001•	<0.001•	0.013•	-
SpO_2-B	88 (60-98)	88 (70-99)	88 (81-99)	0.059
SpO_2-A (%)	94 (43-100)	90 (30-100)	92 (60-99)	0.460
p	0.02•	0.297	0.503	-
PO_2/FiO_2-B	83.33 (45-452.38)	80 (38-300)	80 (38-434)	0.133
PO_2/FiO_2-A	70 (21-255)	70 (24-100)	70 (21-100)	0.021*
p	0.001•	0.034•	<0.001•	-
PaO_2-B	54 (36-132)	56 (38-150)	62 (28-136)	0.059
PaO_2-A (mmHg)	70 (21-255)	65 (33-190)	86.5 (34-159)	0.215
P	<0.001•	0.003•	0.016•	
FiO_2-B	60 (21-100)	60 (21-100)	60 (21-100)	0.710
FiO_2-A (%)	80 (21-100)	90 (24-100)	80 (21-100)	0.021*
p	0.0125*	0.0210*	0.038*	-
Lactate-B	2 (1.5-4)	2(1-4)	2 (1-4)	0.087
Lactate-A mMol/L	5 (3-16)	8 (5-27)	7 (5-19)	0.001*
p	0.011	0.025	0.028	-
Ferritin-B	992 (35-6598)	978.5 (29-9744)	980.5 (29-8700)	0.057
Ferritin-A (mcg/L)	1456 (138-2050)	1509.5 (18-13875)	1452.5 (69-1630)	0.087
p	0.007•	0.026•	0.008•	
CRP-B	159.8 (40.6-349.2)	157.95 (29.7-332)	158.4 (2-317)	0.051

CRP-A (mg/L)	48.9 (2-311.4)	68.85 (2-350)	42.2 (2-350)	0.079
p	<0.001•	<0.001•	<0.001•	
D-Dimer-B	943 (113-48644)	945.5 (75-19729)	953.5 (88-30829)	0.051
D-Dimer-A (ng/mL)	1836 (7.31-43497)	1885 (347-35935)	1818 (85-27110)	0.104
p	<0.001•	<0.001•	<0.001•	-
PCT-B	0.18 (0.01-0.18)	0.15 (0.03-0.153)	0.145 (0.01-0.236)	0.052
PCT-A (mcg/mL)	0.195 (0.01-100)	0.14 (0.01-94.71)	0.165 (0.01-94.71)	0.002*
p	0.620	0.968	<0.001•	
WBC-B	10.57 (2.01-12.6)	11.455 (0.95-35.792)	10.93 (1.13-39.6)	0.051
WBC-A (103 UL)	9.83 (2.12-53.42)	11.79 (0.77-33.917)	10.74 (1.87-29.1)	<0.001*
p	0.256	0.574	0.003•	-
Number of the neutrophil-B	9.75 (0.78-21.88)	10.37 (0.63-31.07)	9.25 (0.66-21.48)	0.068
Number of the neutrophil-A (10^3 UL)	9.38 (1.02-30.40)	9.75 (0.08-53.03)	6.55 (1.49-28.01)	<0.04*
p	0.215	0.512	0.003•	-
Number of the lymphocyte-B	0.79 (0.29-30.57)	0.78 (0.21-34.08)	0.82 (0.21-18.40)	0.051
Number of the lymphocyte-A (%)	0.71 (0.17-43.69)	0.68 (0.11-32.04)	0.61 (0.12-29.70)	<0.001*
p	0.577	0.041•	0.008•	-
N/L oranı-B	12.34 (0.31-36.4)	13.29 (0.03-51.67)	11.28 (0.38-59.20)	0.087
N/L oranı-A (%)	10.65 (0.20-55.27)	15.11 (0.03-19.35)	19.63 (0.39-92.58)	0.046*
p	0.238	0.053	0.008•	
Number of the platelet-B	228 (65-393)	211 (48-530)	235.5 (41-750)	0.404
Number of the platelet-A (10^3 UL)	252 (29-587)	158.5 (8-489)	321 (59-534)	<0.001*
p	<0.001•	0.001•	<0.001•	-
Total bilirubin-B	0.69 (0.15-2.07)	0.59 (0.27-2.9)	0.685 (0.14-2.80)	0.479
Total bilirubin-A (mg/dL)	0.7 (0.25-2.23)	0.765 (0.25-4.69)	0.65 (0.28-5.70)	0.394
p	0.921	0.004•	0.233	-
LDH-B	533 (219-1476)	528 (164-1733)	531 (116-12000)	0.059
LDH-A (U/L)	680 (289-4500)	627.5 (118-16372,2)	526 (169-4500)	0.055
p	<0.001•	0.015•	0.031•	-
SGOT-B	42 (14-457)	40.5 (9-1265)	38.5 (9-4200)	0.057
SGOT-A (U/L)	43 (12-4202)	60.5 (12-4202)	38.5 (9-4202)	0.138
p	0.179	0.001•	0.017•	
SGPT-B	31 (7-320)	31 (6-943)	25.5 (6-1300)	0.141
SGPT-A (U/L)	34 (12-3758)	40.5 (6-3512)	46.5 (7-2955)	0.478
p	0.040•	0.007•	0.001•	-
CK-B	99.6 (10-4267)	98.5 (18-2281)	96.7 (11-4267)	0.057
CK-A (IU/L)	113 (17-3772)	125 (18-4267)	140.5 (10-3678)	0.653
p	0.112	0.171	0.091	-
Ure-B	47.5 (10-195)	48.5 (11-241)	46.5 (13-206)	0.054

Ure-A (mg/dL)	52 (11-255)	108 (21-267)	68.5 (7-247)	<0.001*
p	0.001•	<0.001•	<0.001•	-
Cr-B	0.905 (0.42-1.4)	0.94 (0.55-1.2)	0.83 (0.35-1.52)	0.268
Cr-A (mg/dL)	0.84 (0.13-4.12)	1.135 (0.5-7.54)	1.025 (0.39-5.20)	0.012*
p	0.256	0.001•	0.006•	-
e-GFR-B	86 (21-90)	76.5 (5-90)	85 (9-90)	0.116
e-GFR-A (mL/minute/1.73 m^2)	87 (8-90)	61 (5-267)	64.5 (8-90)	0.001*
p	0.675	0.002•	<0.001•	-

Note: *Kruskal Wallis H test, statistically sinificant; •Wilcoxon test, statistically sinificant; B: Before not starting antistokine theraphy; A: 7 Days after starting antistokin theraphy; SOFA: Sequential Organ Failure Assessment; GKS: Glasgow Coma Scale; HR: Heart Rate; RR: Respiratory Rate; SpO_2: Periperal oxygen saturation; FiO_2: Inspired free oxygen; PCT: Procalcitonin; N/L: Neutrophil Lymphocyte ratio; E-GFR: Estimated Glomerular Filtration Rate; Cr: Creatinine; CK: Creatine Kinase

Comparison of groups after receiving anticytokine therapy

When comparing the SOFA scores among the three groups, statistically significant differences were observed (p<0.001). The median SOFA score was 4 (0-11) in group 1, 9 (2-11) in group 2, and 7 (0-17) in Group 3. The median SOFA score was significantly higher in both Group 2 (p<0.001) and group 3 (p=0.009) compared to group 1 (Table 2). When comparing the GCS scores among the three groups, statistically significant differences were observed (p<0.001). The median GCS score was 15 (3-15) in group 1, 6 (5-15) in group 2, and 9 (2-15) in group 3. The median GCS score was significantly higher in group 1 compared to group 2 (p<0.001) and group 3 (p=0.010) and it was also significantly lower in group 2 compared to group 3 (p<0.001).

When the patients included in the groups were compared in terms of systolic blood pressure, there was a statistically significant difference between the groups (p=0.010). The median systolic blood pressure was 130 (80-187) mmHg in group 1, 130 (63-130) mmHg in group 2 and 120 (60-120) mmHg in group 3. The median systolic blood pressure was significantly lower in group 3 compared to group 2 (p=0.036) and group 1 (p=0.003) (Table 2). When comparing the diastolic blood pressures among the three groups, statistically significant differences were observed (p=0.005). The median diastolic blood pressure was 75 (40-103) mmHg in group 1, 72.5 (35-100) mmHg in group 2 and 70 (20-115) mmHg in group 3. The median diastolic blood pressure was significantly lower in group 3 compared to group 2 (p=0.04) and group 1 (p=0.004) [6].

There was a statistically significant difference when the patients included in the groups were compared in terms of respiratory rate (RR) (p<0.001). The median RR was 28 (16-45) breaths/min in group 1, 24 (18-38) breaths/minute in group 2 and 26 (6-44) breaths/minute in group 3. The median RR was significantly higher in group 1 compared to group 2 (p<0.001) (Table 2). When the PO_2/FiO_2 ratios of the patients included in the groups were compared, a statistically significant difference was observed between group 2 and group 3 (p=0.021). The median PO_2/FiO_2-S ratio was 70 (21-255) in group 1, 70 (24-100) in group 2 and 70 (21-100) in group 3. The median PO_2/FiO_2-S ratio was significantly lower in group 3 compared to both group 1 (p=0.008) and group 2 (p=0.006) (Table 2). When the patients included in the groups were compared in terms of FiO_2 value, there were statistically significant differences (p=0.021). The median FiO_2-S was 80% (21-100) in group 1, 90% (24-100) in group 2, and 80% (21-100) in group 3. The median FiO_2 was significantly higher in group 2 compared to both group 1 and group 3 (p=0.028 and p=0.001). When the patients included in the groups were compared in terms of lactate values, there were statistically significant differences. The median lactate value was 5 (3-16) in group 1, 8 (85-27) in group 2, and 7 (5-19) in group 3. The median lactate value was significantly lower in group 1 compared to both groups 2 and 3 (p=0.011 and p=0.002) [7].

When the patients included in the groups were compared in terms of PCT value, there was a statistically significant difference between the groups (p=0.002). The median PCT was 0.195 (0.01-100) ng/mL in group 1, 0.14 (0.01-94.71) ng/mL in group 2 and 0.165 (0.01-94.71) ng/mL in group 3. The median PCT values was significantly higher in group 1 compared to group 2 (p<0.001) (Table 2). When the White Blood Cell count (WBC) was compared among the patients included in the groups, there were statistically significant differences between the three groups (p<0.001). The median WBC count was 9.83 (2.12-53.42) in group 1, 11.79 (0.77-33.917) in group 2 and 10.74 (1.87-29.100) in group 3. The median WBC count was significantly lower in group 1 compared to group 2 (p=0.005) and group 3 (p<0.001) (Table 2). When the neutrophil counts of the patients included in the groups were compared, there were statistically significant differences between the three groups (p<0.04). The median neutrophil count was 9.38 (0.78-21.88) in group 1, 9.75 (0.08-53.0.3) in group 2, and 6.55 (1.49-28.01) in group 3. The median neutrophil count was significantly lower in group 3 compared to group 1 (p=0.004) and group 2 (p<0.001) (Table 2). When the patients included in the groups were compared in terms of lymphocyte count, there was a statistically significant difference between the groups (p<0.001). The median lymphocyte count was 0.71 (0.17-43.69) in group 1, 0.68 (0.11-32.04) in group 2 and 0.61 (0.12-29.70) in group 3.

The median lymphocyte count was significantly lower in group 3 compared to groups 1 and 2 (p<0.001 and p<0.001). The median lymphocyte count was also significantly higher in group 1 compared to group 2 (p<0.001). When the patients included in the groups were compared in terms of Neutrophil-to-Lymphocyte (N/L) ratio, there was a statistically significant difference between the groups (p=0.046). The median N/L ratio was 10.65 (0.20-55.27) in group 1, 15.11 (0.03-19.35) in group 2 and 19.63 (0.39-92.58) in group 3. The median N/L ratio was significantly lower in group 1 compared to group 2 (p=0.016) and Group 3 (p=0.034). The median N/L ratio was also significantly lower in group 2 compared to group 3 (p=0.041) (Table 2). When the platelet (PLT) counts of the patients included in the groups were compared, there were statistically significant differences between the three groups (p<0.001). The median PLT count was 252 (29-587) in group 1, 158.5 (8-489) in group 2 and 321 (59-534) in group 3. The median PLT count was significantly lower in group 2 compared to group 1 (p<0.001) and group 3 (p<0.001) and it was also significantly lower in group 1 compared to group 3 (p=0.016) (Table 2) [8].

When the urea values of the patients included in the groups were compared, there was a statistically significant difference between the three groups (p<0.001). The median urea level was 52 (11-255) in group 1, 108 (21-267) in group 2 and 68.5 (7-247) in group 3. The median urea level was significantly lower in group 1 compared to group 2 (p<0.001) and group 3 (p=0.006), and it was also significantly higher in group 2 compared to group 3 (p=0.001) (Table 2). When the patients included in the groups were compared in terms of Creatinine (Cr) values, there was a statistically significant difference between group 1 and group 2 (p=0.012). The median Cr value was 0.84 (0.13-4.12) in group 1, 1.135 (0.5-7.54) in group 2 and 1.025 (0.39-5.20) in group 3. The median Cr value was significantly lower in group 1 compared to group 2 (p=0.001) and group 3 (0.025) (Table 2). When the estimated Glomerular Filtration Rates (eGFR) of the patients

included in the groups were compared, there were statistically significant differences between the three groups (p=0.001). The median eGFR was 87 (8-90) in group 1, 61 (5-267) in group 2, and 64.5 (8-90) in group 3. The median eGFR was significantly higher in group 1 compared to group 2 (p<0.001) and group 3 (p=0.017) (Table 2) [9].

Comparison of the parameters of the patients in the groups before and after receiving anticytokine therapy

When evaluating the efficacy of anticytokine therapies administered to the patients in group 1: The median GCS was 15 (10-15) before anticytokine therapy and 15 (3-15) after anticytokine therapy and the median GCS was significantly higher before the anticytokine therapy (p<0.001). The median body temperature was 38.2 (36-39.8) before anticytokine therapy and 36.7 (36-39.1) after anticytokine therapy and the median body temperature was significantly higher before anticytokine therapy (p<0.001). The median RR was 33 (6-45) before anticytokine therapy and 28 (16-45) after anticytokine therapy and the median RR was significantly higher before anticytokine therapy (p<0.001).The median SpO_2 was 88 (60-98) before anticytokine therapy and 94 (43-100) after anticytokine therapy, and the median SpO_2 was significantly higher after anticytokine therapy (p=0.02) (Table 2). The median PO_2 was 54 (36-132) before anticytokine therapy and 70 (21-255) after anticytokine therapy and the median PO_2 was significantly higher after anticytokine therapy.

The median PO_2/FiO_2 ratio was 83.33 (45-452.38) before anticytokine therapy and 70(21-255) after anticytokine therapy and the median PO_2/FiO_2 ratio was significantly lower after anticytokine therapy (p=0.001). The median FiO_2 was 60 (21-100) before anticytokine therapy and 80 (21-100) after anticytokine therapy and the median FiO_2 was significantly higher after anticytokine therapy (p=0.0125). The median lactate value 2 (1.5-4) before anticytokine therapy and 5 (3-16) after anticytokine therapy and the median lactate value was significantly higher after anticytokine therapy (p=0.011).The median ferritin was 992 (35-6,598) before anticytokine therapy and 1,456 (138-2,050) after anticytokine therapy and the median ferritin value was significantly higher after anticytokine therapy (p=0.007). The median C-Reactive Protein (CRP) level was 159.8 (40.6-349.2) before anticytokine therapy and 48.9 (2-311.4) after anticytokine therapy and the median CRP value was significantly higher before anticytokine therapy (p<0.001). The median D-dimer value was 943 (113-48,644) before anticytokine therapy 1,836 (7.31-43,497) after anticytokine therapy and the median D-dimer value was significantly higher after anticytokine therapy (<0.001). The median platelet count was 228 (65-393) before anticytokine therapy and 252 (29-587) after anticytokine therapy and the median platelet count was significantly higher after anticytokine therapy (p<0.001). The median LDH value was 533 (219-1,476) before anticytokine therapy and 680 (289-4,500) after anticytokine therapy and the median LDH value was significantly higher after anticytokine therapy (p<0.001) [10].

The median Alanine Transaminase (ALT) value was 31 (7-320) before anticytokine therapy and 34 (12-3,758) after anticytokine therapy and the median ALT value was significantly higher after anticytokine therapy (p=0.040). The median urea value was 47.5 (10-195) before anticytokine therapy and 52 (11-255) after anticytokine therapy and the median urea value was significantly higher after anticytokine therapy (p=0.001) (Table 2).

When evaluating the efficacy of anticytokine therapies administered to the patients in group 2: The median SOFA score 4 (2-9) before anticytokine therapy and 9 (2-11) after anticytokine therapy and the median SOFA score significantly higher after anticytokine therapy (p<0.001) (Table 2). The median GCS score was 15 (10-15) before anticytokine therapy and 6 (5-15) after anticytokine therapy and the median GCS score significantly higher before anticytokine therapy (p<0.001). The median body temperature was 38.6 (36.8-39.9) before anticytokine therapy and 36.7 (36-39) after anticytokine therapy and the median body temperature was significantly higher before anticytokine therapy (p<0.001) (Table 2).

The median systolic blood pressure was 131 (100-180) before anticytokine therapy and 130 (63-170) after anticytokine therapy and the median systolic blood pressure was significantly higher before anticytokine therapy (p=0.015). The median RR was 30 (16-44) before anticytokine therapy and 24 (18-38) after anticytokine therapy and the median RR was significantly higher before anticytokine therapy (p<0.001). The median PO_2 was 56 (38-150) before anticytokine therapy and 70 (24-100) after anticytokine therapy and the median PO_2 was significantly lower after anticytokine therapy (p=0.003) (Table 2). The median PO_2/FiO_2 ratio was 80 (38-300) before anticytokine therapy and 70 (24-100) after anticytokine therapy, and the median PO_2/FiO_2 ratio was significantly lower after anticytokine therapy (p=0.034). The median FiO_2 was 60 (21-100) before anticytokine therapy and 90 (24-100) after anticytokine therapy, and the median FiO_2 was significantly higher after anticytokine therapy (p=0.0210). The median lactate value was 2 (1-4) before anticytokine therapy and 8 (5-27) after anticytokine therapy, and the median lactate value was significantly higher after anticytokine therapy (p=0.025). The median ferritin value was 978.5 (29-9,744) before anticytokine therapy and 1,509.5 (18-13,875) after anticytokine therapy, and the median ferritin value was significantly higher after anticytokine therapy (p=0.026) [11].

The median CRP value was 157.95 (29.7-332) before anticytokine therapy and was 68.85 (2-350) after anticytokine therapy, and the median CRP value was significantly higher before anticytokine therapy (p<0.001). The median D-dimer value was 945.5 (75-19,729) before anticytokine therapy and 1,885 (347-35,935) after anticytokine therapy, and the median D-dimer value was significantly higher after anticytokine therapy (p<0.001). The median lymphocyte count was 0.78 (0.21-34.08) before anticytokine therapy and 0.68 (0.11-32.04) after anticytokine therapy, and the median lymphocyte count was significantly lower after anticytokine therapy (p=0.041). The median platelet count was 211 (48-530) before anticytokine therapy and 158.5 (48-530) after anticytokine therapy, and the median platelet count was significantly higher before anticytokine therapy (p=0.001). The median bilirubin value was 0.59 (0.27-2.9) before anticytokine therapy and 0.765 (0.25-4.69) after anticytokine therapy, and the median bilirubin value was significantly higher after anticytokine therapy (p=0.004).

The median LDH value was 528 (164-1,733) before anticytokine therapy and 627.5 (118-16,372.2) after anticytokine therapy, and the median LDH value was significantly higher after anticytokine therapy (p=0.015). The median aspartate transaminase (AST) value was 40.5 (9-1,265) before anticytokine therapy and 60.5 (12-4,202) after anticytokine therapy and the median AST value was significantly higher after anticytokine therapy (p=0.001). The median ALT value was 31 (6-943) before anticytokine therapy and 40.5 (6-3,512) after anticytokine therapy and the median ALT value was significantly higher after anticytokine therapy (p=0.007). The median urea value was 48.5 (11-241) before anticytokine therapy and 108 (21-267) after anticytokine therapy, and the median urea value was significantly higher after anticytokine therapy (p<0.001). The median Cr value was 0.94 (0.55-1.2) before anticytokine therapy and 1.135 (0.5-7.54) after anticytokine therapy, and the median Cr value was significantly higher after anticytokine therapy (p=0.001). The median eGFR was 76.5 (5-90) before anticytokine therapy and 61 (5-267) after anticytokine therapy, and the median eGFR was significantly higher before anticytokine therapy (p=0.002) (Table 2).

When evaluating the efficacy of anticytokine therapies administered to the patients in group 3: The median SOFA score was 5 (2-16) before anticytokine therapy and 7 (0-17) after anticytokine therapy and the median SOFA score was significantly higher after anticytokine therapy (p=0.006). The median GCS score was 15 (10-15) before anticytokine therapy and 9 (2-15) after anticytokine therapy and the median GCS score was significantly higher before anticytokine therapy (p<0.001) (Table 2). The median body temperature was 38.2 (36.6-38.7) before anticytokine therapy and 36.7 (35.9-38.1) after anticytokine therapy and the median body temperature was significantly higher before anticytokine therapy (p<0.001). The median systolic blood pressure was 130 (90-180) before anticytokine therapy and 120 (60-170) after anticytokine therapy and the median systolic blood pressure was significantly higher before anticytokine therapy (p=0.007). The median diastolic blood pressure was 75 (50-100) before anticytokine therapy and 70 (20-115) after anticytokine therapy and the median diastolic blood pressure was significantly lower before anticytokine therapy (p=0.013). The median RR was 31 (16-36) before anticytokine therapy and 26 (6-44) after anticytokine therapy and the median RR was

significantly higher before anticytokine therapy (p=0.013). The median PO_2 was 62 (28-136) before anticytokine therapy and 86.5 (34-159) after anticytokine therapy and the median PO_2 was significantly higher after anticytokine therapy (p=0.016) (Table 2). The median PO_2/FiO_2 ratio was 80 (38-434) before anticytokine therapy and 70 (21-100) after anticytokine therapy, and the median PO_2/FiO_2 ratio was significantly lower after anticytokine therapy (p<0.001). The median FiO_2 was 60 (21-100) before anticytokine therapy and 80 (21-100) after anticytokine therapy, and the median FiO_2 was significantly higher after anticytokine therapy (p=0.038). The median lactate value was 2 (1-4) before anticytokine therapy and was 7 (5-19) after anticytokine therapy, and the median lactate value was significantly higher after anticytokine therapy (p=0.028) [12].

The median ferritin value was 980.5 (29-8,700) before anticytokine therapy and 1,452.5 (69-1,630) after anticytokine therapy and the median ferritin value was significantly higher after anticytokine therapy (p=0.008). The median CRP value was 158.4 (2-317) before anticytokine therapy and 42.2 (2-350) after anticytokine therapy and the median CRP value was significantly higher before anticytokine therapy (p>0.001). The median D-dimer value was 953.5 (88-30,829) before anticytokine therapy and 1,818 (85-27,110) after anticytokine therapy and the median D-dimer value was significantly higher after anticytokine therapy (p<0.001). The median PCT value was 0.145 (0.01-0.236) before anticytokine therapy and 0.165 (0.01-94.71) after anticytokine therapy and the median PCT value was significantly higher after anticytokine therapy (<0.001). The median WBC count was 10.93 (1.13-39.6) before anticytokine therapy and 10.74 (1.87-28.1) after anticytokine therapy and the median WBC count was significantly lower after anticytokine therapy (p=0.003). The median neutrophil count was 9.25 (0.66-21.48) before anticytokine therapy and 6.55 (1.49-28.01) after anticytokine therapy and the median neutrophil count was significantly lower after anticytokine therapy (p=0.001).

The median lymphocyte count was 0.82 (0.21-18.40) before anticytokine therapy and 0.61 (0.12-29.70) after anticytokine therapy and the median lymphocyte count was significantly higher before anticytokine therapy (p=0.008). The median N/L ratio was 11.28 (0.38-59.20) before anticytokine therapy and 19.63 (0.39-92.58) after anticytokine therapy and the median N/L ratio was significantly higher after anticytokine therapy (p=0.008). The median platelet count was 235.5 (41-750) before anticytokine therapy and 321 (59-534) after anticytokine therapy and the median platelet count was significantly higher after anticytokine therapy (<0.001). The median LDH value was 531 (116-12,000) before anticytokine therapy and 526 (169-4,500) after anticytokine therapy and the median LDH value was significantly higher after anticytokine therapy (p=0.031). The median AST value was 38.5 (9-4,200) before anticytokine therapy and 38.5 (9-4,202) after anticytokine therapy and the median AST value was significantly higher after anticytokine therapy (p=0.017). The median ALT value was 25.5 (6-1,300) before anticytokine therapy and 46.5 (7-2,955) after anticytokine therapy and the median ALT value was significantly higher after anticytokine therapy (p=0.001). The median urea value was 46.5 (13-206) before anticytokine therapy and 68.5 (7-247) after anticytokine therapy and the median urea value was significantly higher after anticytokine therapy (p<0.001). The median Cr value was 0.83 (0.35-1.52) before anticytokine therapy and 1.025 (0.39-5.20) after anticytokine therapy and the median Cr value was significantly higher after anticytokine therapy (p=0.006). The median eGFR was 85 before anticytokine therapy and 64.5 (8-90) after anticytokine therapy and the median eGFR was significantly higher before anticytokine therapy (p<0.001) [13].

When comparing the gender distribution of the patients included in the groups, the groups were found to have homogeneous gender distribution (p=0.122) (Tables 1-3). Among the patients included in the study, records of thoracic CT scans taken in the emergency department were inaccessible for 20 patients. It was determined that these patients had their initial thorax CT scans performed outside the hospital setting. When comparing the number of improved, worsened, or unchanged AP-chest x-rays taken 7 days after anticytokine therapy, the groups were found to have homogeneous distribution (p=0.308) [14].

DISCUSSION

The criteria for cytokine release syndrome have been defined consistently in classical literature and various articles. The release of proinflammatory cytokines plays a significant role in contributing to the mortality rate of patients. IL-6 has been identified as a key molecule in cytokine release syndrome and the markers of the disease have been extensively described. However, the exact pathology underlying cytokine release syndrome remains unclear. In the present study, cytokine storm was diagnosed based on clinical and laboratory parameters in critically ill COVID-19 patients who were hospitalized in the ICU. Elderly patients and those receiving immunosuppressive therapies are more susceptible to the manifestations of COVID-19. In these individuals, thoracic CT scans often reveal abnormal findings associated with the disease. All of the patients included in our study were individuals over the age of 65 who were critically ill with COVID-19 developed ARDS and sepsis. The patients in our study were divided into groups, with each group receiving a different anticytokine therapy. When these groups were compared in terms of the number of non-survivors at 28 days, it was found that the number of non-survivors was statistically significantly higher (n=63, 50.9%) and the number of survivors was significantly lower (n=7, 6.8%) in group 2 (p<0.001) (Table 1). This finding suggests that the administration of Intravenous Immunoglobulin (IV-IG) therapy as an anticytokine therapy in group 2 resulted in an increased number of non-survivors. This observation could potentially be attributed to the fact that the IV-IG preparations utilized in the study were not derived from a community that had been immunized against COVID-19.

There was no statistically significant difference between Group 1 and Group 3 in terms of the number of non-survivors (Table 1). The combined utilization of antiviral agents and immunomodulatory agents plays a crucial role in preventing acute respiratory collapse, reducing the need for mechanical ventilation, and decreasing morbidity and mortality. Antiviral therapy was used as the standard of care in patients with cytokine storm. COVID-19 is clinically divided into two phases. Lymphopenia, lymph node involvement and atrophy of lymphatic tissue in organs such as the spleen, which are commonly observed in severe COVID-19 patients, are explained by cytokine storm. Cytokine-mediated damage has been described in detail in various publications. The present study did not assess the levels of proinflammatory cytokines; instead, we focused on evaluating the clinical and laboratory findings resulting from the effects of proinflammatory cytokines released by the SARS-CoV-2, which is responsible for the disease. Following anticytokine therapy, group 3 demonstrated a statistically significant increase in the number of patients breathing with a nasal cannula and on room air when compared to groups 1 and 2 (p<0.001) (Table 1). Group 1 exhibited a significant increase in the number of patients receiving oxygen supplementation *via* a face mask or a reservoir mask compared to groups 2 and 3 (p<0.001) (Table 1).

The number of patients receiving high-flow oxygen was found to be significantly higher in group 1 compared to groups 2 and 3 (p<0.001) (Table 1). The number of patients undergoing noninvasive and invasive mechanical ventilation was significantly lower in group 1 compared to groups 2 and 3 (p<0.001) (Table 1). When comparing groups 2 and 3, group 3 showed a significantly lower number of patients requiring noninvasive and invasive mechanical ventilation (p<0.001) (Table 1). This suggests that spontaneous respiration was more effective in groups 1 and 3 compared to group 2. The need for mechanical ventilation was higher in group 2. This finding suggests that the effectiveness of anticytokine therapy employed in group 2 patients was insufficient. However, when comparing the AP-lung x-rays of the patients across the groups, there was no statistically significant difference in the number of patients with recovering lung. This led the authors to contemplate that any improvement in lung appearance may require a significant amount of time to become apparent [15].

When comparing the number of patients in each group falling into one of the KDIGO stages after anticytokine therapy, it was observed that the number of patients in stage I was significantly higher in both group 1 and group 3 compared to group 2 (p=0.003) (Table 1). The number of patients in Stage II was significantly lower in group 1 compared to groups 2 and 3, and it was also significantly lower in group 3 compared to group 2

(p=0.003) (Table 1). The number of patients in stage III was found to be significantly lower in group 1 compared to groups 2 and 3, and it was also significantly lower in group 3 compared to group 2 (p=0.003) (Table 1). This suggests that in group 2 patients, the renal function deteriorated further due to the low effectiveness of IV-IG therapy in inhibiting cytokine activity. In addition to the limited effectiveness of IV-IG as anticytokine therapy, the authors also posit that the development of acute renal damage in group 2 patients may be attributed to the impact of sepsis. Similarly, the authors consider that the lower extent of acute renal damage observed in groups 1 and 3 could be attributed to both the inadequate effectiveness of anticytokine therapies and the influence of sepsis. SOFA score, GCS score, systolic blood pressure, diastolic blood pressure, RR, PO_2/FiO_2 ratio, FiO_2, lactate, PCT, WBC, neutrophil count, lymphocyte count, N/L ratio, platelet count, urea, Cr and eGFR values after receiving anticytokine therapy did not significantly differ among the groups (Table 2).

GCS score after anticytokine therapy was significantly higher in group 1 than in groups 2 and 3. It was also significantly lower in group 2 than in group 3. There was a statistically significant difference in RR among the study groups. RR after anticytokine therapy was significantly higher in group 1 than in group 2. When comparing PO_2/FiO_2-S ratio, a statistically significant difference was observed among the groups. PO_2/FiO_2 ratio after anticytokine therapy was significantly lower in group 3 compared to groups 1 and 2. When the patients included in the groups were compared in terms of FiO_2 values after anticytokine therapy, a statistically significant difference was observed. FiO_2 value after anticytokine therapy was significantly higher in group 2 compared to groups 1 and 3. WBC count and neutrophil count, N/L ratio, urea, and Cr after anticytokine therapy were significantly lower in group 1 compared to groups 2 and 3. N/L ratio was also significantly lower in group 2 than in group 3. PLT count after anticytokine therapy was also significantly lower in group 1 than in group 3. Urea value was also significantly higher in group 2 than in group 3. When comparing lymphocyte count after anticytokine therapy, a statistically significant difference was observed among the groups. Lymphocyte count after anticytokine therapy was significantly lower in group 3 compared to groups 1 and 2. It was significantly higher in group 1 than in group 2. eGFR value after anticytokine therapy was significantly higher in group 1 compared to groups 2 and 3 [16].

SOFA scores after anticytokine therapy were significantly higher in groups 2 (9 (2-11)) and 3 (7 (0-17)) compared to group 1 (4 (0-11)). The lactate value was significantly lower in group 1 (5 (3-16)) compared to groups 2 (8 (5-27)) and 3 (7 (5-19)). Systolic and diastolic blood pressures after anticytokine therapy were significantly lower in group 3 compared to groups 1 and 2. When comparing the groups in terms of PCT values after anticytokine therapy, the median PCT value was significantly higher in group 1 (0.195 (0.01-100)) compared to groups 2 (0.14 (0.01-94.71)) and 3 (0.165 (0.01-94.71)). Based on sepsis markers, it was determined that patients in all groups were experiencing sepsis prior to anticytokine therapy and this septic condition persisted in all groups even after receiving anticytokine therapy. However, the markers were found to be significantly lower in group 1. This finding led the authors to contemplate that the course of sepsis was more severe in groups 2 and 3. However, it is believed that the effectiveness of anticytokine therapy was lower in groups 2 and 3. The PCT value after anticytokine therapy was higher in group 1, indicating that the effectiveness of anticytokine therapy utilized in group 1 was higher. However, it also suggests that bacterial infection was more prominent in group 1 [17].

When assessing the efficacy of anticytokine therapy by comparing FiO_2 values before and after treatment, a significant difference was observed in FiO_2 values before and after receiving anticytokine therapy in groups 1, 2, and 3. FiO_2 values after anticytokine therapy were found to be higher in all three groups. When comparing PO_2 values before and after anticytokine therapy, PO_2 value after anticytokine therapy was significantly higher in group 1 ($p<0.001$). PO_2 value after anticytokine therapy was significantly higher in group 2 (p=0.003). PO_2 value after anticytokine therapy was significantly higher in group 3 (p=0.016). However, when comparing the three groups after anticytokine therapy, group 2 exhibited a significantly higher FiO_2 value compared to groups 1 and 3 (p=0.012-0.024). This observation suggests that patients in group 2 require a higher FiO_2 level in order to achieve sufficient PO_2 values. In all three groups, it was observed that there was an increased requirement for FiO_2 in order to raise the PO_2 values. When comparing the PO_2/FiO_2 ratios before and after anticytokine therapy, it was found that the PO_2/FiO_2 ratio decreased significantly in all three groups after receiving anticytokine therapy. When comparing the groups in terms of PO_2/FiO_2 values after anticytokine therapy, a statistically significant difference was observed among the three groups (p=0.021). The PO_2/FiO_2 ratio was significantly lower in group 2 compared to groups 1 and 3 (p=0.002-0.24). Patients in all three groups continued to experience ARDS even after receiving anticytokine therapy. Patients in all three groups exhibited severe ARDS prior to anticytokine therapy, and there was no statistically significant difference in the PO_2/FiO_2 ratio between the groups before receiving anticytokine therapy. The decrease in the PO_2/FiO_2 ratio of patients following anticytokine therapy was evident in the number of patients who did not survive. In group 2, there was a statistically significant rise in the requirement for FiO_2 compared to groups 1 and 3. Additionally, the decrease in the PO_2/FiO_2 ratio was significantly associated with the number of patients who did not survive. This observation suggests that IV-IG alone is not sufficient to cease cytokine storm and prevent death. In groups 1 and 3, a statistically significant decrease in the PO_2/FiO_2 ratio was observed after patients underwent anticytokine therapy. This decrease was reflected in the fact that there was no statistically significant difference between groups 1 and 3 in terms of the number of patients who died. The presence of bacterial and fungal agents in tracheal aspirate cultures from all deceased patients suggests that superinfections may have played a role in their fatal outcomes. The patients being in a state of sepsis both before and after anticytokine therapy indicates that ARDS may be caused by sepsis, in addition to the potential ineffectiveness of anticytokine therapy. Anticytokine therapy alone proved inadequate in preventing lung injury and may have exacerbated the septic condition [18].

TCZ is approved by the FDA as an IL-6 receptor blocker. In a study of fifteen critically ill COVID-19 patients, the mean CRP level decreased from 126.9 (10.7-257.9) to 11.2 (0.02-113.7) mg/L ($P<0.01$) after TCZ therapy. In a study conducted in China involving 21 severe or critically ill COVID-19 patients, it was demonstrated that TCZ resulted in the regression of pulmonary lesions, improvement in laboratory findings, a decrease in mortality, ventilator usage and oxygen requirement. In our patient population, 28.7% in group 1, 24.3% in group 2, and 38% in group 3 demonstrated improvement in AP-lung appearance. However, the difference between the groups in this regard was not statistically significant. None of our patients exhibited pleural effusion, mediastinal lymph node involvement or pulmonary embolism findings. Additionally, there was no evidence of heart failure detected during Echocardiography (ECHO). All of our patients exhibited severe diffuse lesions in both lungs. Although some of our patients showed improvement on AP-chest radiographs taken 7 days after the completion of anticytokine therapy compared to the ones taken before the therapy, none of them displayed completely normalized AP-chest images. However, these patients exhibited enhanced oxygenation and improved clinical parameters. This finding prompted the authors to contemplate that lung damage persisted for a certain duration in patients undergoing anticytokine therapy, which could explain the lack of improvement in the AP-lung image. However, they observed that the oxygenation of the surviving patients began to improve before any visible improvement in the AP-lung image occurred [19].

In the TESEO study and the randomized clinical trial CORIMUNO-TOCI, TCZ was found to be linked with reduced mortality and a decreased risk of requiring mechanical ventilation. However, it was also reported to increase the risk of developing candidemia. In our study, tracheal aspirate cultures from patients who died on the 7^{th} day after anticytokine therapy revealed the presence of both Candida species and various bacterial species. In our study, GCS scores, body temperature, RR, and CRP were significantly higher before anticytokine therapy in patients receiving TCZ. The decrease in these parameters after the administration of TCZ can be attributed to its anticytokine effect. However, the decrease in the GCS score may be a result of the impact of worsening sepsis on the central nervous system. In group 1, there is a statistically significant increase in FiO_2, PO_2 and SpO_2 values after anticytokine therapy, but there is a statistically significant decrease in PO_2/FiO_2 values after anticytokine therapy. The increase in PO_2 values did not lead to a statistically significant increase in the PO_2/FiO_2 ratio. When

comparing the SOFA scores before and after the use of TCZ, no statistically significant difference was observed. However, SOFA scores were 2 or higher in both cases conditions. After anticytokine therapy, lactate, ferritin, D-dimer, platelet count, LDH, ALT and urea values were significantly lower compared to before the use of TCZ. The observed elevations in these parameters after the use of TCZ suggest that despite anticytokine therapy, cell destruction continued, organ failure worsened and this condition persisted for at least up to the 7^{th} day following TCZ administration. It was thought that the ongoing sepsis may have contributed to the elevation of these parameters [20].

IV-IG controls systemic autoimmunity and inflammation through several mechanisms. Based on these mechanisms, patients are provided support to manage cytokine storm and ARDS. TCZ has been also employed in the treatment of H1N1, but studies have indicated that it did not result in a significant reduction in adult mortality. Similarly, no difference in mortality was observed between groups receiving Intravenous Immunoglobulin (IV-IG) and those not receiving it. As a result, most international organizations do not recommend IV-IG as a treatment for COVID-19. However, certain publications have suggested the combined use of IV-IG and dexamethasone in COVID-19 patients. In our study, it was observed that the SOFA score, PO_2, FiO_2, lactate, ferritin, D-dimer, bilirubin, LDH, ALT, AST, urea and Cr values after anticytokine therapy were significantly higher in patients who received IV-IG compared to the values before IV-IG administration. It was observed that the PO_2 values of the patients increased with the use of anticytokine therapy. However, the FiO_2 values also increased, and the increase in FiO_2 values was significantly higher in group 2 compared to groups 1 and 3. The PO_2/FiO_2 ratio decreased significantly after anticytokine therapy. The low GCS score, systolic blood pressure, lymphocyte count, platelet count and eGFR indicate that cell destruction and organ failure persist until day 7 following anticytokine therapy. The decrease in RR, body temperature and CRP values after anticytokine therapy is attributed to the anticytokine effect of IV-IG. However, this effect did not correspond to a significant difference in the number of surviving patients. The deepening of sepsis in patients also contributed to the increase in the number of deaths [21].

Corticosteroids, such as MP, are commonly used agents in the management of cytokine storms and their mechanisms of action have been explained. However, corticosteroid therapy is typically administered at high doses for extended durations, necessitating vigilant monitoring for potential side effects. Some publications advocate for its utilization, while others report no significant benefits. In our study, SOFA score, PO_2, FiO_2, lactate, ferritin, D-dimer, PCT, N/L ratio, platelet count, AST, ALT and urea values after anticytokine therapy were significantly higher in patients receiving MP. These findings suggest that cell destruction, sepsis and organ failure persist up to day 7 following anticytokine therapy. No statistically significant difference was observed in the number of non-survivors between patients treated with MP and patients treated with TCZ. Following administration of MP, there was a statistically significant increase in GCS score, body temperature, systolic blood pressure, diastolic blood pressure, CRP values and lymphocyte count compared to the values prior to MP administration. The decrease in body temperature and CRP values following MP administration suggests its anti-inflammatory effect. However, the decrease in lymphocyte and platelet counts indicates the persistence of the cytokine storm up to day 7 after anticytokine therapy. A decrease in the GCS score may indicate a deepening septic picture [22].

LIMITATION

First and foremost, it is important to note that our study was retrospective in nature. Additionally, the analysis of IL-6 blood levels was not conducted in the patients included in the study in the future, we highly recommend conducting prospective, randomized, double-blind clinical trials specifically targeting patients diagnosed with cytokine storm based on IL-6 blood levels.

CONCLUSION

In the treatment of cytokine storm in critically ill COVID-19 patients over 65 years of age with sepsis and ARDS hospitalized in the ICU, it was observed that both TCZ and MP do not demonstrate superiority over each other in terms of efficacy and number of deaths. Furthermore, it was observed that both agents can potentially exacerbate existing sepsis and ARDS in patients. Despite the anticytokine activity of IV-IG, it was observed that its use can lead to an increase in the number of non-survivors, a finding that can be attributed to the exacerbation of organ failure, deepening of ARDS and worsening of sepsis. The authors advocate that the use of IV-IG should be avoided in these patients.

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