Original Article

Access this article online
Quick Response Code:

Website:
https://eurasianjpulmonol.org
DOI:
10.14744/ejp.2023.4009

Tocilizumab in hospitalized patients with severe COVID-19 pneumonia: A single-center observational study

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Abstract:

BACKGROUND AND AIM: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a novel coronavirus, has caused a pandemic with a clinical course ranging from asymptomatic infection to pneumonia, Acute Respiratory Distress Syndrome (ARDS), and death. This study analyzes the effectiveness of tocilizumab (TCZ) in treating hospitalized Coronavirus Disease 2019 (COVID-19) patients.

METHODS: We included 141 patients with Macrophage Activation Syndrome (MAS) admitted to our hospital and treated with tocilizumab in addition to standard care. We examined laboratory parameters before and after TCZ treatment and assessed changes in clinical and radiological images.

RESULTS: The median time to start TCZ treatment was 6.5 days post-admission. Eighty patients received the first dose of TCZ within 6.5 days post-admission, while 61 patients received it after 6.5 days post-admission. Among the group who received TCZ within 6.5 days, 22 (27.5%) out of 80 patients died, whereas 30 (49.3%) out of 61 patients died in the group who received TCZ after 6.5 days post-admission (p=0.008). According to the laboratory results on the first day of hospitalization, the day of TCZ initiation, and the third and fifth following days; the median C-Reactive Protein (CRP), lymphocyte, and fibrinogen levels of patients returned to normal after TCZ treatment.

CONCLUSIONS: Several risk factors, such as older age and comorbidities, can cause mortality in severe COVID-19 patients. We observed that administering TCZ in the early stages of MAS decreased the necessity for both invasive and non-invasive mechanical ventilation, assisted in clinical recovery, and lowered the mortality rate.

Keywords:

COVID-19, macrophage activation syndrome, SARS-CoV-2, tocilizumab treatment

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Received: 27-04-2023
Revised: 12-06-2023
Accepted: 11-11-2023
Published: 09-02-2024

Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus was first detected in China in late December 2019 and has since spread to more than 200 countries worldwide, leading to a pandemic that has caused

How to cite this article: Kaya H, Öksüzler Kızılbay G, Ilgazlı AH, Özgür EG. Tocilizumab in hospitalized patients with severe COVID-19 pneumonia: A single-center observational study. Eurasian J Pulmonol 2024;26:41-50.

770,437,327 people to become ill and 6,956,900 people to die as of September 6, 2023.[1] The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic infections to flu-like symptoms, from pneumonia to Acute Respiratory Distress Syndrome (ARDS), multi-organ failure, and death. About 20% of patients develop severe Coronavirus Disease 2019 (COVID-19) pneumonia, which is characterized by increasing shortness of breath and oxygen requirements. Healthcare systems around the world have had difficulty providing the necessary amount of invasive mechanical ventilators and intensive care unit beds due to the pandemic.[2,3]

The course of the disease is characterized by an acute stage with flu-like symptoms and a cytokine storm caused by Macrophage Activation Syndrome (MAS), which can be prominent in some patients.[4] Increases in inflammatory cytokines and biomarkers correlate with the extent of lung damage. Treatments aim to reduce lung damage and prevent death.[5,6]

Tocilizumab (TCZ) is a recombinant humanized anti-interleukin-6 receptor (IL-6R) antibody, approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. Studies suggest that it can be an effective treatment for critical cases suffering from a cytokine storm caused by COVID-19 pneumonia.[7,8]

In this study, we aim to present our analysis of the efficacy of TCZ in the treatment of COVID-19 patients who have been hospitalized and monitored in our hospital since the beginning of the pandemic.

Materials and Methods

We examined the severe and critical SARS-CoV-2 patients who were hospitalized and received TCZ between March 20, 2020 and August 15, 2022. This study is single-center, retrospective, and observational. The treatment modality was determined based on the guidelines published by the Ministry of Health of the Republic of Turkiye, national and international journals, and clinical experience.[9] This study was approved by the Ethics Committee in accordance with the Declaration of Helsinki.

Study design

This study included hospitalized COVID-19 patients aged 18 years and older who received TCZ treatment in addition to standard treatment for MAS. All patients included in the study were informed about TCZ treatment, and informed consent was obtained prior to treatment. The diagnosis of COVID-19 was confirmed by SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) test or by clinical findings, laboratory results, and radiological imaging inpatients who tested negative. The typical radiological imaging findings are peripheral, bilateral, multifocal, commonly located in the lower, posterior lobes, ground-glass opacities, consolidations, crazy paving pattern, and inverted halo sign.

In this study, severe COVID-19 pneumonia was defined according to the presence of fever, nausea, diarrhea, cough, muscle and joint pain, ≥30 breaths/minute, Peripheral Capillary Oxygen Saturation (SpO_2) ≤90%, and bilateral, diffuse pneumonic involvement on chest X-ray and/or non-contrast thorax Computed Tomography (CT) images.

Treatment and follow-up

According to the Ministry of Health's COVID-19 guidelines, patients were initially treated with hydroxychloroquine (HCQ) and then favipiravir (FVP) at the start of the pandemic. Patients requiring oxygen support were started on 6 mg of dexamethasone or the equivalent of 40 mg of methylprednisolone, and all patients received enoxaparin, unfractionated heparin, or fondaparinux for thromboprophylaxis. Patients with clinical, laboratory, and radiological findings suggestive of bacterial infection received empirical antibiotics based on laboratory culture results.

Continuous fever, persistently elevated C-reactive protein (CRP), ferritin >700 μg/L, elevated D-dimer, lymphopenia, thrombocytopenia, neutrophilia, and impaired liver function were the criteria used to diagnose MAS, and patients diagnosed with MAS received additional pulse steroid therapy (250 mg of methylprednisolone) for a maximum of three days. Patients who did not respond to pulse steroid therapy for at least three days and had persistently elevated inflammatory markers and progressive MAS cases with increased oxygen requirements or radiological findings progression were started on TCZ. Patients with no contraindications to TCZ and who weighed more than 50 kg received 400 mg intravenously on the first day of treatment. Those who did not respond to the first dose according to clinical and laboratory results received a repeat dose of 200 mg or, in most cases, 400 mg of TCZ.

Table 1: Clinical analysis of patients

Variable	Alive		Deceased		p
	n	%	n	%	
Age					
Under 65 years	69	74.2	24	25.8	<0.001*
65 years and older	20	41.7	28	58.3	
Sex					
Female	22	59.5	15	40.5	0.591
Male	67	64.4	37	35.6	
Length of stay (days)	12 (8–17)		15.5 (11–26.75)		0.002*
Fever >37°C	38	76.0	12	24.0	0.019*
O_2 requirement	73	58.4	52	41.6	0.001*
Mechanical ventilation	2	4.2	46	95.8	<0.001*
ICU requirement	17	25.0	52	70	<0.001*
Timing of TCZ administration (days)					
Before 6.5 days	58	72.5	22	27.5	0.008*
After 6.5 days	31	50.8	30	49.2	
Duration of treatment (days)	6 (4–11)		7 (3.25–15.5)		0.578
Lung involvement on radiological imaging					
Unilateral	5	55.6	4	44.4	0.576
Bilateral	73	62.4	44	37.6	
Normal	5	83.3	1	16.7	
Severity of involvement					
Mild	6	66.7	3	33.3	0.237
Moderate	53	66.3	27	33.7	
Severe	18	50.0	18	50.0	
CAD	8	42.1	11	57.9	0.041*
COPD	1	14.3	6	85.7	0.01*
Cancer	7	41.2	10	58.8	0.046*

*: Statistically significant. ICU: Intensive care unit, TCZ: Tocilizumab, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease

All patients included in our study received at least one dose of TCZ and were followed up daily by a COVID-19 team consisting of pulmonologists, infectious disease specialists, clinical microbiologists, internal medicine, and intensive care specialists.

The patients included in our study were analyzed with regard to demographic characteristics, comorbidities, laboratory results (CRP, creatinine, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), procalcitonin, D-dimer, fibrinogen, ferritin, leukocyte, neutrophil, lymphocyte, hemoglobin, platelet), radiological imaging findings, clinical complaints, oxygen, invasive mechanical ventilation, and Intensive Care Unit (ICU) requirements, length of hospital stay, and time of TCZ onset. Patients were then divided into two groups, those who died and those who survived, and comparisons were made between the two groups according to the above criteria.

Statistical analysis

In this study, IBM Statistical Package for the Social Sciences (SPSS) 20.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Normal distribution was evaluated using the Kolmogorov-Smirnov test. Numeric variables that are normally distributed were presented as mean±standard deviation, and those that were not normally distributed as median (25^{th}-75^{th} percentile). Categorical variables were shown as frequencies (percentages). When there were only two groups, the difference between the groups was tested with the Mann-Whitney U test for numeric variables that are not normally distributed. The difference between medical tests when there were more than two groups was evaluated with the Friedman test for numeric variables that are not normally distributed. For the relationships between categorical variables, Pearson's chi-squared test and Fisher's exact test were used. Statistical significance was set at $p<0.05$.

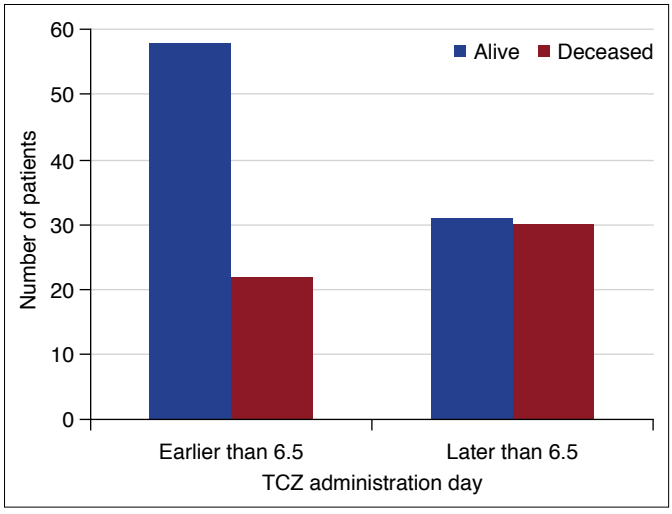

Figure 1: Timing of TCZ administration and mortality y: number of patients. x: timing of administration (days) earlier than 6.5 – later than 6.5

TCZ: Tocilizumab

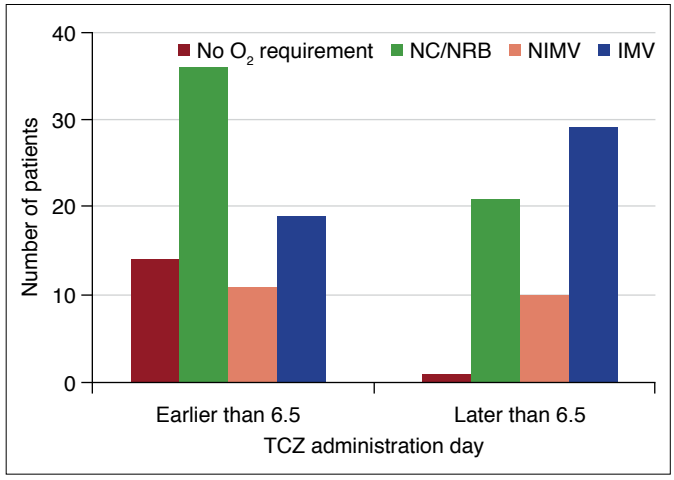

Figure 2: Oxygen requirement. Non-invasive mechanical ventilation (NIMV) requirement and invasive mechanical ventilation (IMV) requirement based on timing of TCZ administration: No O_2 requirement

NC/NRB: Nasal Cannula/Non-rebreather mask

Results

The study included a total of 141 patients, 104 (73.8%) males and 37 (26.2%) females. The median age of all patients was 57.9 (±13.8); 57.4 (±13.5) for males and 59.5 (±14.8) for females. The median length of hospital stay was 16 (2–68) days. For surviving patients, the median length of hospital stay was 12 days, and for those who died, it was 15.5 days. Fifty (35.5%) patients had a fever on hospital admission. A fever of more than 37°C at the time of admission was statistically significant in deaths. Our patients had hypertension in 36%, diabetes mellitus in 23%, Coronary Artery Disease (CAD) in 13%, Congestive Heart Failure (CHF) in 2%, Chronic Obstructive Pulmonary Disease (COPD) in 5%, asthma in 2%, cancer in 12%, Chronic Kidney Disease (CKD) in 6%, and other underlying diseases in 24%. The mortality rate was significantly higher in patients with cancer (p=0.046), COPD (p=0.01), and CAD (p=0.041).

Eighty (64%) patients had bilateral and moderate lung involvement on radiological examination, while 36 (28.8%) patients had severe involvement (Table 1). One hundred twenty-five (88.7%) patients required oxygen support on admission or subsequently, and, as expected, the percentage of patients requiring oxygen support was significantly higher in the fatal cases (p=0.001). In total, 52 (36%) patients died, and 89 (64%) were discharged from the hospital. Twenty-four (25.8%) of 93 patients under 65 years of age and 28 (58.3%) of 48 patients over 65 years of age died despite the treatment. The mortality rate in patients over 65 years of age was significantly higher than in those under 65 years of age. Sixty-eight (48.2%) patients required ICU care, and 48 (70%) of these patients were followed up with mechanical ventilation (Table 1). Fifty-two (70%) patients died in the ICU. The median age of patients requiring ICU follow-up was 60.2 years, while it was 55.8 years for those not requiring ICU follow-up. 60.4% of patients over 65 years of age needed ICU care, and this rate was statistically significant. The number of male patients was higher among those who died, but the mortality rate between male and female patients was not statistically significant.

The median time to start TCZ treatment was 6.5 days after admission. Eighty patients received the first dose of TCZ within 6.5 days post-admission, while 61 patients received it after 6.5 days post-admission. Among the group who received TCZ within 6.5 days, 22 (27.5%) out of 80 patients died, whereas 30 (49.3%) out of 61 patients died in the group who received TCZ after 6.5 days post-admission (p=0.008) [Fig. 1] (Table 1). Oxygen requirements were significantly higher in patients who started TCZ after 6.5 days [Fig. 2]. The number of patients receiving mechanical ventilation support in the ICU was higher in those who received their first dose of TCZ after 6.5 days compared to those who started receiving it before 6.5 days; however, this difference was not statistically significant.

The median duration of TCZ treatment resulting in either discharge or death was seven days. The median length of hospital stay was six days for patients who survived and seven days for those who died.

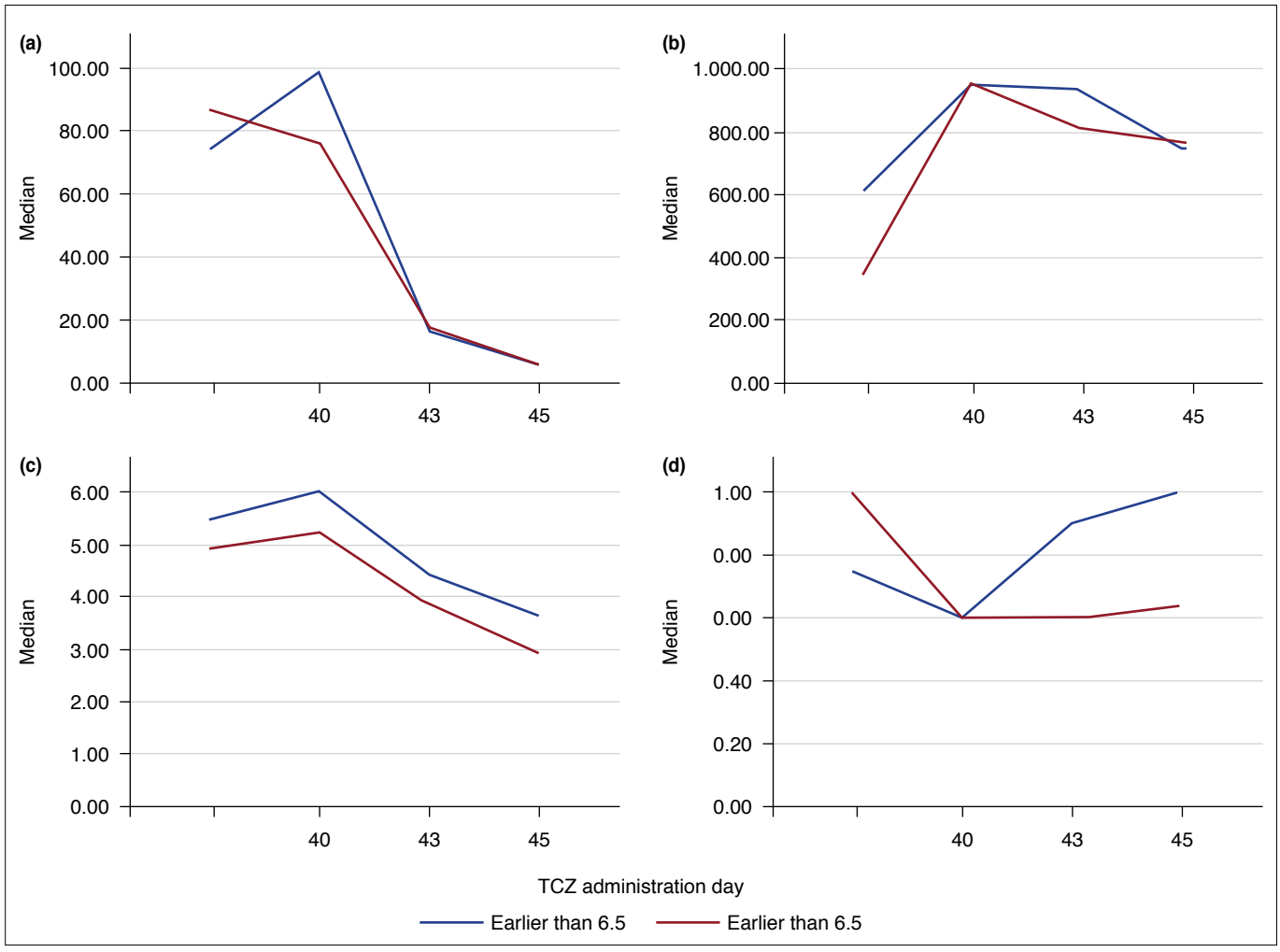

Figure 3: Change in laboratory results after the initial dose of TCZ. (a) CRP level. (b) Ferritin level. (c) Fibrinogen level. (d) Lymphocyte level

CRP: C-reactive protein

Upon examining the CRP levels of the patients, the median CRP level was found to be 78 on admission and 91 on the first day of TCZ administration. After the use of TCZ, the median CRP level decreased to 17 on the third day and 6 on the fifth day of treatment. Median creatinine, White Blood Cell (WBC), Neutrophil (NEU), Hemoglobin (HGB), and Platelet (PLT) levels were all within the reference ranges, eliminating the need for statistical comparison. Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) levels appeared to increase in the follow-ups, but this was not statistically significant. There was a decrease in Lymphocyte (LYM) levels on the first day of TCZ administration as expected, compared to the day of admission. After the use of TCZ, the levels appeared to return to normal. The difference in ferritin levels between the admission day and the TCZ administration day was significant, but this appeared to regress in the follow-ups after TCZ use. Procalcitonin was higher only on the first day of TCZ administration; the admission and follow-up levels were similar. There was a progression in D-dimer levels from the day of admission and they did not decrease after TCZ use. Fibrinogen increased from the day of admission to the TCZ administration day, but it returned to normal in the follow-ups [Figs. 3, 4 and Table 2].

CRP, WBC, LYM, procalcitonin, and ferritin levels were higher in patients with fever compared with those without fever. Although patients who required ICU after admission had higher procalcitonin levels both on admission at the hospital and on the day of TCZ administration than those who did not require ICU, this was not statistically significant.

Significant results in deceased and surviving cases were analyzed using univariate and multivariate logistic regression.

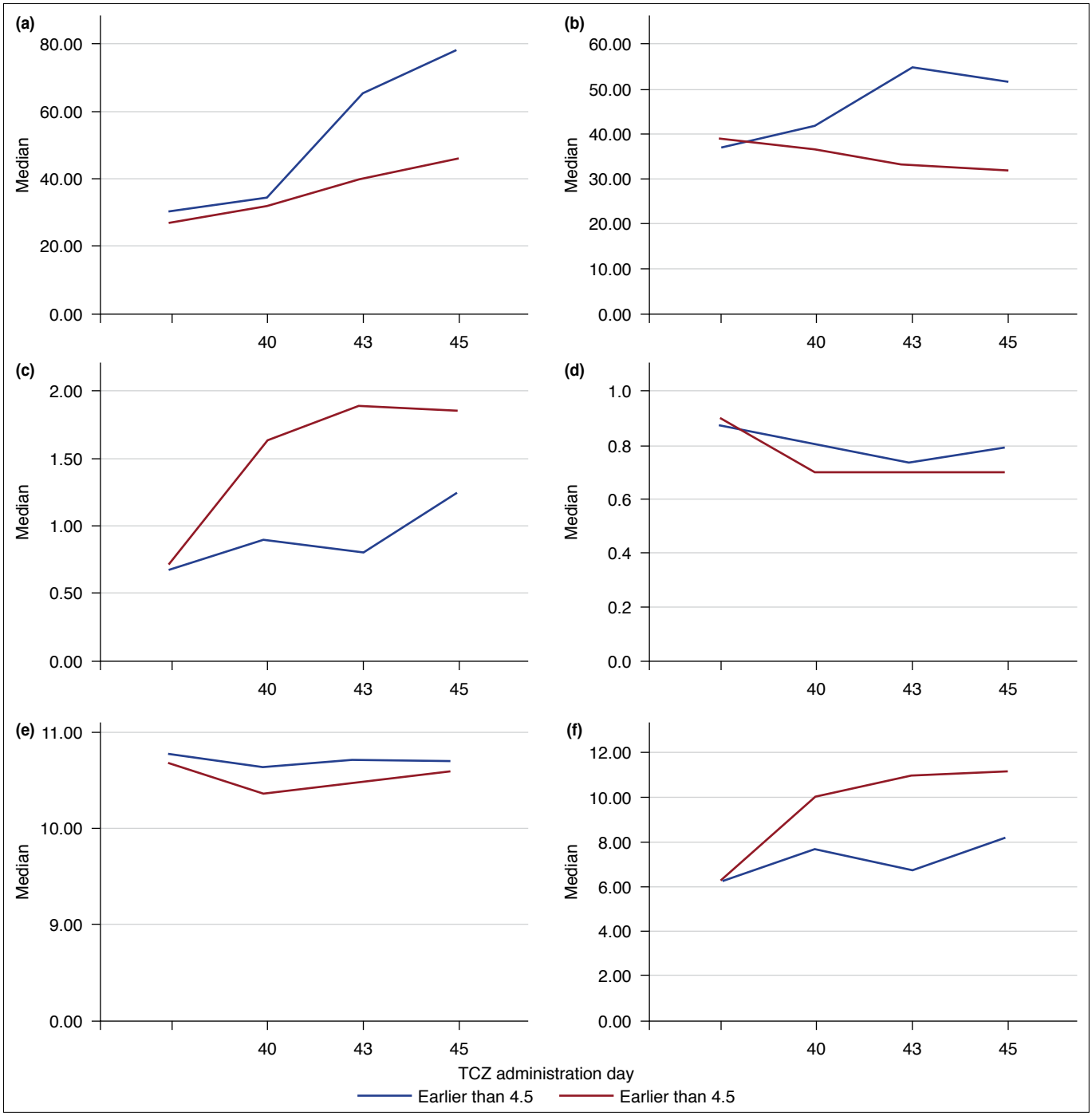

Figure 4: Change in laboratory results after the initial dose of TCZ. (a) ALT level. (b) AST level. (c) D-dimer level. (d) Creatinine level. (e) Hemoglobin level. (f) WBC level

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, WBC: White blood cell

Variables with a p-value up to 0.020 in the univariate analysis were included as variables in the multiple logistic regression analysis. As a result of the analysis, age and length of hospital stay were statistically significant ($p<0.05$). O_2 requirement, mechanical ventilation, and intensive care unit stay variables were not included in the model because the relationship between them negatively affected the multiple logistic model.

Patients aged 65 years and older had a 2.920 times higher mortality rate than patients not aged 65 years and older ($p=0.014$). Increasing the length of hospital stay by one day increased the mortality rate 1.053 times.

Table 2: Laboratory parameters before and after TCZ

Variable	Total	Alive	Deceased	p
CRP				
Admission	78 (31–141)	81.73 (20–119)	132.34 (53–177)	<0.001*
0-Day	91 (36–150.5)	63 (28.75–145.50)	114 (74–174.25)	0.002*
3-Day	17.3 (8–31)	12.9 (6.25–25)	22.95 (16–46.25)	<0.001*
5-Day	6 (2.9–10.75)	5 (2–9)	8.2 (3.95–16.55)	0.004*
WBC				
Admission	6.2 (4.55–8.6)	6.18 (4.55–7.75)	6.53 (452–10.90)	0.346
0-Day	9.5 (4.8–13.6)	8.29 (4.30–11.58)	10.75 (7.67–16.39)	0.003*
3-Day	8.3 (4.6–13.1)	6.94 (3.85–9.45)	14 (10.09–22.22)	<0.001*
5-Day	9.3 (6.7–14.9)	8.1 (5.9–11.18)	16.35 (10.1–16.62)	<0.001*
NEU				
Admission	4.2 (3–7.25)	4.17 (2.85–5.95)	4.90 (3.30–9.45)	0.108
0-Day	8.5 (4–12.25)	7.15 (3.60–10.30)	10.25 (7.55–14.52)	<0.001*
3-Day	6.6 (3.1–11.37)	5.37 (2.30–7.75)	12.46 (9.59–20.22)	<0.001*
5-Day	7.8 (5.3–12.87)	6.3 (3.9–8.8)	13.8 (8.92–18.77)	<0.001*
LYM				
Admission	0.88 (0.53–1.30)	1 (0.6–1.3)	0.7 (0.42–1.1)	0.045*
0-Day	0.6 (0.34–0.96)	0.7 (0.5–1)	0.39 (0.22–0.6)	<0.001*
3-Day	0.7 (0.5–1.2)	1 (0.6–1.35)	0.56 (0.38–0.7)	<0.001*
5-Day	0.74 (0.5–1.3)	1.1 (0.6–1.6)	0.48 (0.28–0.70)	<0.001*
Ferritin				
Admission	501.5 (208–933)	469.5 (165–781)	531 (245–1.210.50)	0.182
0-Day	955 (555–1.423)	864 (440–1.346)	1.018.5 (741.75–2.285)	0.010*
3-Day	826 (424–1.300)	768.5 (354–1.173)	931 (596.25–1.856.25)	0.008*
5-Day	747 (444–1.219)	690 (407–1.056)	933 (589.75–2.227.25)	0.012*
Procalcitonin				
Admission	0.11 (0.10–0.27)	0.11 (0.09–0.17)	0.24 (0.11–0.41)	0.001*
0-Day	0.14 (0.11–0.31)	0.11 (0.09–0.23)	0.24 (0.011–0.42)	<0.001*
3-Day	0.11 (0.06–0.18)	0.11 (0.04–0.11)	0.20 (0.10–0.41)	<0.001*
5-Day	0.11 (0.04–0.14)	0.10 (0.03–0.11)	0.13 (0.10–0.43)	<0.001*
D-Dimer				
Admission	0.70 (0.40–1.39)	0.65 (0.40–1.16)	0.90 (0.55–1.52)	0.039*
0-Day	1.13 (0.57–2.6)	0.85 (0.45–1.50)	2.17 (1.02–6.5)	<0.001*
3-Day	1.39 (0.59–4.53)	0.76 (0.48–1.53)	4.64 (1.92–10.32)	<0.001*
5-Day	1.51 (0.52–4.21)	0.78 (0.41–1.60)	3.91 (2–10.32)	<0.001*
Fibrinogen				
Admission	5.3 (4.2–6.4)	5.2 (4.24–6.31)	5.62 (4.27–6.83)	0.272
0-Day	5.6 (4.91–6.9)	5.59 (5–6.81)	5.77 (4.55–7.15)	0.651
3-Day	4.2 (3.4–5.1)	4.51 (3.8–5.3)	3.68 (2.78–4.80)	0.005*
5-Day	3.3 (2.59–4.3)	3.38 (2.86–3.99)	2.83 (1.78–4.38)	0.259

*: Statistically significant. CRP: C-reactive protein, WBC: White blood cell, HGB: Hemoglobin, NEU: Neutrophil, LYM: Lymphocyte

None of the patients showed signs of TCZ-related adverse events.

Discussion

COVID-19 is a disease that can cause various serious complications such as pneumonia and hypoxemia. The cause of death in most patients is macrophage activation syndrome, which causes damage to various organs, especially the lungs.[10] The basic pathology of MAS occurring in COVID-19 disease is an excessive increase in various inflammatory cytokines and suppression of the anti-inflammatory process. In most patients, this cytokine release is controlled, and the disease undergoes spontaneous remission. However, the disease may progress in some patients. Several predisposing or protective factors are thought to be involved in this inflammatory process.[11–15]

Many studies have been conducted worldwide on potential drugs that can be used for the treatment of

COVID-19 disease. However, to date, no definitive antiviral agent has been found that can cure COVID-19 disease.[16] While the primary aim of treatment is to suppress the replication of the virus in the early stages, another aim in severe cases is to control the cytokine storm caused by MAS. In severe cases, the choice of drug and the timing of administration are very critical. One of the pro-inflammatory cytokines that causes the cytokine storm is IL-6. TCZ is a monoclonal antibody developed against IL-6, an anti-inflammatory agent with the potential to help treat cytokine storm.[17,18]

Although the effectiveness of TCZ in treating of COVID-19 was uncertain at the beginning of the pandemic, it has been shown in many recent studies to improve mortality, intensive care unit length of stay, and lung functions. As a result of these studies, the European Medicines Agency and the U.S. Food and Drug Administration have approved it for the treatment of COVID-19.[19–24]

Although the criteria of MAS differ in many studies, they generally include, after confirming a COVID-19 diagnosis and administering primary treatment, an increase in oxygen requirement, rapid progression in radiological findings, persistent fever, high CRP and ferritin levels, lymphopenia, thrombocytopenia, neutrophilia, impaired liver function, hypofibrinogenemia, or elevated triglycerides. The Ministry of Health of the Republic of Turkiye's COVID-19 infection guidelines recommend the use of TCZ for the treatment of COVID-19 pneumonia cases with MAS.[8,10,19,25]

Similar to the study by Uchiyama et al.,[26] the mortality rate was statistically higher in patients with fever during hospitalization in our study. Fever may be associated with an increase in acute phase reactants such as CRP, WBC, ferritin, and subsequent worsening of the MAS clinical picture. In our study, 141 patients with MAS were admitted, and the overall mortality rate was calculated as 36%. All patients who died had at least one comorbid disease. Our mortality rate was similar to many studies in patients with MAS who received TCZ treatment.[27–29]

Similar to the studies by Milošević et al.[30] and Yılmaz et al.,[31] our study also found a decrease in markers such as CRP, ferritin, fibrinogen, and D-dimer, and an increase in lymphocyte levels on the third and fifth days after the first dose of TCZ. Median levels of creatinine, WBC, procalcitonin, NEU, HGB, and PLT levels were all within the reference ranges, and were therefore not compared with TCZ treatment. In addition, similar to the studies by Lacedonia et al.[32] and Keske et al.,[8] clinical and radiological imaging findings improved after treatment in our study.

In the study by Salazar et al.,[33] TCZ administration within 48 hours and after 48 hours of hospital admission was compared, and early TCZ administration was shown to reduce mortality. In the study by San-Juan et al.,[34] the rate of significant clinical improvement (SCI) was found to be 70.2% in those who received TCZ in the first 48 hours, while it was 45.1% in those who received TCZ after the seventh day. Similarly, Schmidt et al.[35] reported that TCZ treatment was more beneficial in the early hyperinflammatory period before respiratory failure developed. Consistent with the literature, our study found that the oxygen requirement was significantly higher in patients who started TCZ treatment more than 6.5 days after admission. Additionally, 22 (27.5%) of the patients who received TCZ within the first 6.5 days of admission died, whereas 30 (49.2%) of the patients who received TCZ after 6.5 days died. This difference was statistically significant (p=0.008).

Studies indicate that TCZ can have various side effects, particularly bacterial and fungal infections.[2,36] Hermine et al.[19] reported that 32% of 131 patients in the TCZ group experienced side effects. However, in our study, similar to the findings by Ghosn et al., no major TCZ-related side effects were observed.[37]

This study has some limitations. First, although TCZ is an anti-IL-6 receptor monoclonal antibody, we could not assess the IL-6 levels of the patients in our hospital laboratory before and after treatment. Second, our clinical observations suggest that in the early stages of the pandemic, TCZ was mainly used for patients in intensive care. We believe that after its application in general patient services, fewer patients required intensive care. However, a statistical comparison of this situation could not be made. Another limitation is that our study cannot be classified as a randomized blinded trial due to its retrospective nature and the absence of a control group.

In conclusion, various risk factors such as male gender, advanced age, and comorbidities may lead to death in patients with severe COVID-19. The use of TCZ treatment in the early stages of MAS has been shown to reduce the mortality rate.

Ethics Committee Approval

The study was approved by the Kocaeli University Faculty of Medicine Ethics Committee (No: 2021/270, Date: 23/09/2021).

Authorship Contributions

Concept – H.K., G.Ö.K., A.H.I.; Design – H.K., G.Ö.K.; Supervision – A.H.I., E.G.Ö.; Data collection &/or processing – H.K., G.Ö.K.; Analysis and/or interpretation – E.G.Ö.; Literature search – H.K., G.Ö.K., A.H.I.; Writing – H.K., G.Ö.K., E.G.Ö.; Critical review – H.K., G.Ö.K., A.H.I., E.G.Ö.

Conflicts of Interest

There are no conflicts of interest.

Use of AI for Writing Assistance

Not declared.

Financial Support and Sponsorship

Nil.

Peer-review

Externally peer-reviewed.

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