NEÜ PRESS

MEVLANA TIP BİLİMLERİ
MEVLANA MEDICAL SCIENCES
eISSN:2757-976X

ARAŞTIRMA MAKALESİ/RESEARCH ARTICLE

DOI:http:/dx.doi.org/10.56752/Mevmedsci.2023.34
Mev Med Sci, 2023; 3(2): 66-71

# Interplay of Tocilizumab in Critical COVID-19 Cases

## Tocilizumab'ın Kritik COVID-19 Vakalarındaki Etkileşimi

Hilal Akay Cizmecioglu[1], Mevlut Hakan Goktepe[1], Halil Ibrahim Bayraktar[1], Ahmet Cizmecioglu[2]

[1]Necmettin Erbakan University, Meram Medical Faculty, Department of Internal Medicine, Konya, Turkey
[2]Selcuk University, Medical Faculty, Department of Internal Medicine, Konya, Turkey

**Makale Tarihleri/Article Dates:**
**Geliş Tarihi/Received:** 11 Nisan 2023
**Kabul Tarihi/Accepted:** 7 Ağustos 2023
**Yayın Tarihi/Published Online:** 15 Ağustos 2023

**Sorumlu Yazar/Corresponding Author:**
Ahmet Cizmecioglu,
Selcuk University, Medical Faculty, Department of Internal Medicine, Konya, Turkey
**e mail:** mdahmet2002@gmail.com

**Açıklama/Disclosure:** Yazarların hiçbiri, bu makalede bahsedilen herhangi bir ürün, aygıt veya ilaç ile ilgili maddi çıkar ilişkisine sahip değildir. Araştırma, herhangi bir dış organizasyon tarafından desteklenmedi. Yazarlar çalışmanın birincil verilerine tam erişim izni vermek ve derginin talep ettiği takdirde verileri incelemesine izin vermeyi kabul etmektedirler.

**ÖZET**

**Amaç:** Tocilizumab (TCZ), Corona Virüs 2019 (COVID-19) pandemisi sırasında uygulanan tedavi rejimleri arasında öne çıkan bir antikor tabanlı terapötik seçenek haline gelmiştir. Bu çalışmanın amacı, TCZ uygulanan COVID-19 hastalarında laboratuvar değişikliklerini, prognostik laboratuvar biomarkerlerini ve TCZ uygulama zamanlamasının mortalite üzerindeki etkilerini değerlendirmektir.
**Yöntemler:** Bu retrospektif, kesitsel çalışma, ek TCZ bazlı tedavi alan COVID-19 hastaları ile yapılmıştır. TCZ dozu, 8 mg/kg/gün olarak uygulanmıştır. Hastaların verileri, takip kayıtlarından ve dijital hastane bilgi sisteminden toplanmıştır.
**Bulgular:** Toplamda 64 hastanın verileri değerlendirmeye tabi tutulmuştur. Hastaların yaş ortalaması 62.43 ± 14.2 idi. Yoğun bakım ünitesinde yatan hastaların yarısı invaziv solunum desteği almıştı. Tüm hastalar favipiravir, hidroksiklorokin ve konvalesan plazma temelli tedavi almışlardı. TCZ uygulama süresi genellikle hastaneye yatıştan 7 gün sonra yapılmıştı. Genel olarak, ferritin ve d-dimer seviyeleri, laboratuvar sonuçları arasında prognostik biyobelirteçler olarak öne çıkmaktaydı, ancak lenfopenik hastalarda akut faz reaktanları ön plandaydı. Komorbiditelerin varlığı, hastanede kalış süresi ve mortalite artışı ile ilişkiliydi. TCZ'nin erken uygulandığı hastalarda mortalitenin arttığı görülmüştür.
**Sonuç:** Çalışmamızda da önceden ele alınan prognostik biyobelirteçler dikkat çekiciydi. Ancak literatürde de erken dönemde TCZ kullanımının riskli olduğu ve mortaliteyi artırabileceği belirtilmektedir. Bu nedenle, erken dönemde uygulama konusunda dikkatli olunmalıdır.

**Anahtar Kelimeler:** COVID-19, hastalık şiddeti, interlökin 6, mortalite, tosilizumab

**ABSTRACT**

**Aim:** Tocilizumab (TCZ) has become a prominent antibody-based therapeutic option among treatment regimens during the Corona Virus 2019 (COVID-19) pandemic. This study aimed to evaluate laboratory changes, prognostic laboratory biomarkers, and the effects of the timing of TCZ application on mortality in COVID-19 patients who underwent TCZ.
**Methods:** This retrospective, sectional study was conducted with COVID-19 patients received additional TCZ-based treatment. TCZ was administered at a dose of 8 mg/kg/day. The patients' data were recruited from their follow-up records and the digital hospital information system.
**Results:** The data of 64 patients have been subjected to evaluation. The mean age of all patients was 62.43 ± 14.2. Half of the patients who placed in the intensive care unit had received invasive respiratory support. All patients had received favipiravir, hydroxychloroquine, and convalescent plasma-based therapy. The mean time of TCZ administration was 7 days after hospitalization. In general, ferritin and d-dimer levels stood out as prognostic biomarkers among the laboratory results, whereas in lymphopenic patients, the acute-phase reactants were favored. The presence of comorbidities was associated with an increase in hospital stay and mortality. Mortality was found to increase in patients who received early administration of TCZ.
**Conclusion:** Prognostic biomarkers previously addressed were also prominent in our study. Considering that early TCZ administration is deemed risky in the literature and may increase mortality, caution should be exercised in its early application.

**Key words:** COVID-19, disease severity, interleukin-6, mortality, tocilizumab

**Atıf yapmak için/ Cite this article as:** Akay Cizmecioglu H, Goktepe MH, Bayraktar HI, Cizmecioglu A. Interplay of Tocilizumab in Critical COVID-19 Cases. Mev Med Sci. 2023;3(2): 66-71

## INTRODUCTION

In the last three-year period, the COVID-19 pandemic has gradually disoriented its mortality; hence the medical world has begun to evaluate the applicability or necessity of the treatment scenarios. Although these remedies applied during the pandemic, which the virus effects were not comprehensibly known, and there was not even a vaccine yet, sometimes seem adequate, we can evaluate their efficacy and complications more objectively with the current data.

The COVID-19 treatment regimens that are sometimes given for palliative purposes, but some of which are aimed to be targeted, could be roughly grouped as follows. Antivirals, including antibody products, immunomodulators, antithrombotic therapies, supplements and miscellaneous drugs (1,2). Here, Tocilizumab (TCZ), which is included in antibody-mediated therapy, is a recombinant, humanized IgG1 monoclonal antibody against the interleukin-6 (IL-6) receptor that leads to immunosuppressant outcomes (3). TCZ targets and binds to both the soluble and the membrane-bound form, thereby preventing the junction of IL-6 to its receptor (4). This prevention disrupts IL-6-mediated signalling (3, 4). IL-6, which has been found to have biphasic effects, is in the interleukin pathway as a pro-inflammatory and myokine as an anti-inflammatory (5-7).

In the COVID-19 arena, IL-6 was frequently used to predict the cytokine storm (8). In addition, elevated IL-6 levels were reported to be linked to the disease severity of COVID-19 (9). Furthermore, after the TCZ administration, laboratory improvements in IL-6 levels and related clinical healing were demonstrated in severe COVID cases (10, 11). Many studies and reviews have been published on applying TCZ, in particular, on the effectiveness of TCZ in preventing cytokine storms in COVID-19 patients. Relatedly, this article presents a single-center experience on TCZ effectiveness in line with the literature findings.

## METHODS

This retrospective, sectional study was conducted with COVID-19 patients between 2020 and 2021. Concerted study protocol was approved by the Ethics Committee of Necmettin Erbakan University Medical Faculty (2022/3980). Among the patients with PCR-identified COVID-19 positivity, those of received additional TCZ-based regimens (a single infusion of 8 mg/kg/day) were analyzed. Patients under 18 years old and hospitalized in clinics other than the internal medicine department were excluded from the study. Maximum attention was paid to the inclusion of patients with the following characteristics: with respiratory distress, with a respiratory rate of 30 breaths per minute or higher, $SpO_2$ (peripheral oxygen saturation) less than 90% on room air, $PaO_2$ (arterial oxygen partial pressure) to $FiO_2$ (fraction of inspired oxygen) ratio less than 300 mmHg (12).

The most predictive laboratory tests for COVID-19 (absolute neutrophil count, absolute lymphocyte count, C-reactive protein (CRP), procalcitonin, erythrocyte sediment rate (ESR), ferritin, fibrinogen, d-dimer, IL-6) (13) taken at admission and after TCZ administration, the day of TCZ infusion, and the number of days started from TCZ administration to discharge or death time were retrieved from the digital hospital system. Involvement in pulmonary CTs performed at admission, recorded oxygen saturation and respiratory rates, or hospitalization place were also noted.

Primarly, patients were evaluated in two groups according to their health status, survivors and deceased ones. The data were also evaluated per comorbidities and hospitalization location.

***Statistical analysis:*** The data were evaluated using SPSS version 21.0 (SPSS, Inc., Chicago, IL). The Pearson correlation test was used for regularly distributed data, and the Spearman test was used for skewed data to evaluate correlations. Due to the decrease in patients in group evaluations, non-parametric tests were chosen. In this context, the Wilcoxon signed-rank test was used in repetitive data, and the Man-Whitney U test was used in grouped data. Chi-square or Fisher's exact test was used to evaluate categorical data. The binary logistic regression test was preferred to evaluate IL-6 levels and TCZ application days on mortality. Kaplan-Meirer and Gehan-Breslow-Wilcoxon tests did the survival evaluation, and hazard ratios were calculated by the Mantel-Haenszel calculation method. In all calculations, $p < 0.05$ was accepted as meaningful.

## RESULTS

A total of 64 patients were evaluated in our retrospective study; 54 (84.4%) were male. In general, while the mean age was 62.43±14.2, it was 62.96±15.34 for males and 59.6±4.09 for females, respectively. Thirty-four (53.1%) patients were treated in the internal medicine ward, and 30 (46.9%) were in the intensive care unit (ICU). Thirty Sixteen (53.3%) of ICU patients were intubated. The first three rows in blood group determinations were A Rh+ with 30 patients (46.9%), 0 Rh+ with 16 patients (25%), and B Rh+ with ten patients (15.6%). Two patients (3.1%) were mild, 4 (6.3%) moderate, and 58 (90.6%) they had severe pneumonia in the involvements of thorax CTs performed at admission. All patients received favipiravir, 46 (71.9%) received hydroxychloroquine, and 54 (84.4%) received convalescent plasma therapy (Table 1).

In total, the mean hospitalization time was 15.9±8.52 days. Due to clinical progression, the mean time of the decision of tocilizumab administration was 7.40±4.35 days. In addition, the mean time to discharge or exitus was 10.84±7.14 days after tocilizumab administration. This period was 10.76±5.38 in

**Table 1.** Characteristics and laboratory results of the patients.

| | Survivors | Deceased | p value |
|---|---|---|---|
| Female/Male, n (%) | 10 (24) / 32 (76) | 0 (0) / 22 (100) | 0.078 |
| Comorbidities,n(%) | | | |
| (CAD, CKD, CLD, COPD, DM, HT) | 26 (61.9) | 18 (81.8) | 0.248 |
| Hospitalization day, n (%) | 15.71±7.0 | 16.27±11.27 | 0.696 |
| Hospitalization in the ICU, n (%) | 12 (28.6) | 18 (81.8) | 0.004* |
| Entubation, n (%) | 0 (0) | 16 (72.7) | 0.001* |
| Treatment regimen | | | |
| Favipiravir, 1200 mg/day | 42 (100) | 22 (100) | na |
| Hydroxychloroquine, 400 mg/day | 32 (76.2) | 14 (63.6) | 0.453 |
| Convalescent plasma, single dose | 38 (90.5) | 16 (72.7) | 0.189 |
| The median day of TCZ admission | 7 (5-10) | 5 (3-7) | 0.123 |
| Time passed after TCZ admission | 10 (7-12) | 8 (4 - 11) | 0.347 |
| Absolute neutrophil count, x109/L | 6.18±3.87 | 5.82±3.24 | 0.639 |
| Absolute lymphocyte count, x109/L | 0.90±0.50 | 0.67±0.48 | 0.133 |
| Platelet, x109/L | 225.10±125.62 | 186.5±97.99 | 0.558 |
| Erythrocyte sediment rate, mm/h | 62.71±28.75 | 66.09±33.83 | 0.785 |
| C-Reactive protein, mg/dL | 82 (48–175) | 116 (81–185) | 0.434 |
| Procalcitonin, ng/mL | 0.31 (0.09–1.61) | 1.63 (0.23–6.01) | 0.223 |
| Ferritin, ng/mL | 1032 (556-1651) | 1942 (1374-3393) | 0.025* |
| Fibrinogen, mg/dL | 581.61±171.99 | 485.0±162.94 | 0.208 |
| D-dimer, ng/mL | 446 (170.5-886) | 1054 (328-1450) | 0.031* |
| Interleukin 6, pg/ml | 36.56±14.78 | 45.57±16.06 | 0.155 |

Data are expressed as mean ± standard deviation or median and percentiles. P values are the comparison of the groups by the Mann Whitney U, the Chi-square test and the Fisher's Exact Test; CAD, Coronary artery disease; CKD, Chronic kidney disease; CLD, Chronic liver disease; COPD, Chronic obsructive lung disease; DM, Diabetes mellitus; HT, Hypertension; TCZ, Tocilizumab; na, not applicable.

patients who could be discharged. During the follow-up, 42 patients (65.6%) were discharged, while 22 (34.4%) died. The effect of the interval from diagnosis to TCZ application on mortality was shown in Figure 1a (AUC = 0.670, SE = 0.071, 95% CI = 0.529 to 0.809), and the salvation outcomes of TCZ application on mortality is given in Figure 1b.

As a main subgroup comparison, patients were evaluated according to the discharge status, the deceased patients had higher age (p = 0.001, $\eta^2$ = 0.205), ferritin (p = 0.025, $\eta^2$ = 0.080), and d-dimer (p = 0.031, $\eta^2$ = 0.074) levels than the survivor ones (Figure 2). In addition, being treated in ICU (p = 0.004), being intubated (p = 0.001), and having other malignancies (p = 0.020) were more common in deceased

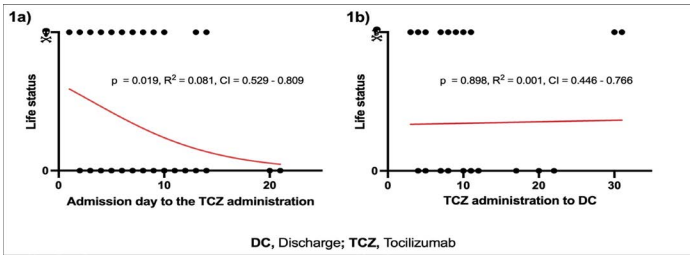


**Figure 1. a.** Patients' mortality rates during the time period prior to the administration of TCZ; **b.** Mortality rates during the period from the administration of TCZ to hospital discharge.

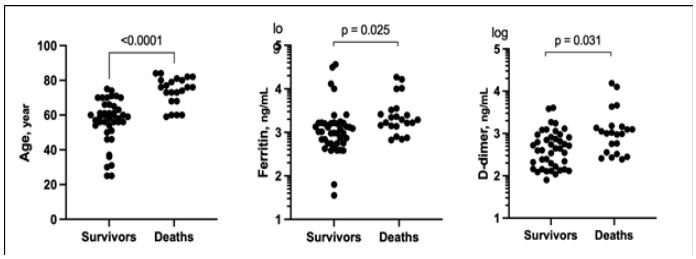


**Figure 2.** Comparison of prognostic laboratory values between survivors and non-survivors.

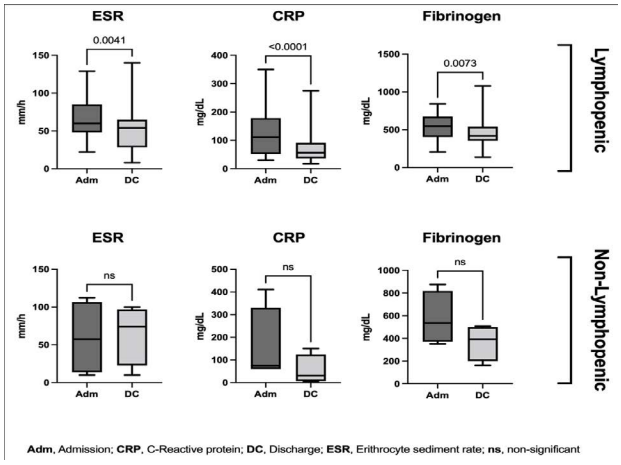


**Figure 3.** Comparison of changes in acute phase reactants between lymphopenic and non-lymphopenic patients during hospitalization using the Wilcoxon signed-rank test.

**Table 2.** Characteristics of Patients with and without Lymphopenia.

| | Lympopenic (n = 56) | Non-Lymphopenic (n = 8) | p value |
|---|---|---|---|
| Gender, Female/Male, % | 8 (14) / 48 (86) | 2 (25) / 6 (75) | 0.581 |
| Age, year | 61.92±14.52 | 65.50±12.83 | 0.891 |
| TCZ administration day | 6.5 (4-10) | 8.5 (5.5-13) | 0.332 |
| Hospitalization, day | 14 (11-16.7) | 18.5 (11.2-32.5) | 0.491 |
| Survivor, n (%) | 36 (64) | 6 (75) | 0.673 |
| Mortality, % | 36 | 25 | 0.999 |

Data are expressed as mean±standard deviation or median and percentiles. P values obtained by the Mann Whitney U, the Fisher's Exact Test; TCZ, Tocilizumab.

patients.

When the laboratory results of the patients at hospitalization and after TCZ administration were compared, a Wilcoxon signed-rank test stated that while there were significant improvements in prognostic markers other than ESR in survivors ($p < 0.05$). However, there was no statistically significant contribution of prominent markers to disease progression except for ESR in those who died ($p = 0.020$). Besides ESR, CRP and fibrinogen levels were crucial in lymphopenic patients. Accordingly, ESR ($t(27) = 3.3$, $p = 0.004$), CRP ($t(27) = 4.2$, $p = 0.001$), and fibrinogen ($t(27) = 2.7$, $p = 0.007$) levels in lymphopenic patients were less decreased or even in a rise compared to non-lymphopenic ones (Figure 3). In addition, mortality rates did not differ in lymphopenic patients (Table 2).

In another subgroup evaluation based on hospitalization location, patients were differentiated regarding hospitalization days, ferritin levels, and discharge status. Accordingly, those administered in ICU had higher hospitalization days ($p = 0.049$), ferritin levels ($p = 0.020$), and mortality rates ($p = 0.004$) than those in the services.

Final finding was that patients with chronic diseases were lower in rank than those without comorbidities regarding age, TCZ-caused time to discharge, total hospitalization days, CRP and D-Dimer levels, and CT involvements ($p < 0.05$) (Table 3).

The convenient correlations that could be considered logical were the following. Hospitalization location was positively correlated with hospitalization day ($p = 0.044$, $r = 0.358$), patient comorbidities were positively correlated with the duration after TCZ ($p = 0.041$, $r = 0.363$), and associated hospitalization day ($p = 0.015$, $r = 0.426$).

## DISCUSSION

This retrospective study evaluated the TCZ administration process and related alterations in the prognostic laboratory results of COVID-19 patients. Per the results, TCZ was adequate for orienting disease progression. In line with the previous literature outcomes, markers attributed to disease severity had been linked to prognosis. In lymphopenic cases, ESR, CRP, and fibrinogen levels predominated during disease progression. As an unlike finding, early application of TCZ may increase mortality rates.

As TCZ is a monoclonal antibody that targets and inhibits

**Table 3.** Comparison of Patients Based on Chronic Diseases.

| | Patients having CD (n = 44) | Patients without CD (n = 20) | p value |
|---|---|---|---|
| Gender, Female/Male, % | 8 (18) / 36 (82) | 2 (10) / 18 (90) | 0.555 |
| Age, year | 67.68±9.99 | 50.90±15,70 | 0.003 |
| Intubation, n (%) | 12 (27) | 4 (20) | 0.660 |
| TCZ administration day | 6.5 (3.75-10.5) | 7 (4.75-10) | 0.920 |
| Hospitalization, day | 12.92±5.51 | 11.0±2.82 | 0.018 |
| Survivor/Deceased, n (%) | 26 (59) / 18 (41) | 16 (80) / 4 (20) | 0.425 |
| Interleukin-6, pg/ml | 40.88±16.50 | 36.97±13.80 | 0.675 |
| C-Reactive protein, mg/dL | 148 (76-187) | 67 (46-121) | 0.025 |
| Erithrocyte Sediment Rate, mm/h | 67.63±29.04 | 55.6±32.24 | 0.269 |
| Ferritin, ng/ml | 1651 (688-2692) | 1098 (657-1456) | 0.251 |
| D-dimer, ng/ml | 886 (506-1273) | 209 (128-296) | 0.001 |
| Fibrinogen, mg/dl | 573.54±157.38 | 428.5±199.97 | 0.287 |
| Absolute neutrophil count, x109/L | 6.30±3.94 | 5.52±2.92 | 0.535 |
| Neutrophil to Lymphocyte Ratio | 8.47 (4.26-12.26) | 4.58 (2.91-14.77) | 0.646 |
| Platelet, x109/L | 218.81±126.05 | 196.31±97.26 | 0.889 |
| Procalcitonin, ng/ml | 0.95 (0.23-3.73) | 0.11 (0.07-1.45) | 0.058 |

Data are expressed as mean±standard deviation or median and percentiles. P values are the comparison of the groups by the Mann Whitney U, the Chi-square test and the Fisher's Exact Test; CD, Chronic disease; TCZ, Tocilizumab.

the activity of IL-6 receptor, in conditions where IL-6 levels are abnormally high, such as in autoimmune diseases or cytokine release syndrome (CRS) associated with COVID-19, TCZ can help reduce inflammation and improve symptoms (14). Therefore, TCZ, which has already completed its 20th year on several diseases, has become one of the drugs approved during COVID-19 (15).

However, as with any medication, TCZ is associated with several potential side effects, which can vary depending on the patient's underlying disease, the dose, dose timing and duration of treatment. The increased risk of infections, particularly serious or opportunistic infections, are one of the most significant risks associated with TCZ. Patients taking TCZ are, therefore, more susceptible to infections such as pneumonia, sepsis, and tuberculosis (16). Our data withal revealed that patients with comorbidities had worsened prognostic laboratory results. In addition, they also had higher pulmonary involvements, resulting in longer hospitalization days. Among them, diabetic cases had more sequels.

Lymphopenia is acknowledged as a notable determinant of mortality in COVID-19 pneumonia (17). However, within the scope of our investigation, no statistical significance was discerned concerning mortality in the context of lymphopenia-based evaluations, encompassing both samples obtained during the initial diagnosis and subsequent to TCZ (Tocilizumab) administration.

Lowering high levels of IL-6 via TCZ would be clinically beneficial in an autoimmune or inflammation state; nevertheless, the anti-inflammatory effects of IL-6 would also be suppressed. It can be expected that the levels of cytokines, such as Interleukin-10 and Suppressor of Cytokine Signaling 3, which are increased by IL-6, will decrease, and the Nuclear factor-κβ signaling pathway, inhibited by IL-6, will be activated (18, 19). In addition, the suppression of Type 1 T helper, which causes an increase in the inflammatory response, and the suppression of the response of Type 2 T helper, which reduces inflammation, can also be anticipated (18, 20). These cascades for reducing inflammation can unintentionally be blocked by administering TCZ. In this scenario, the expectation of ambiguity in achieving an appropriate inflammatory response may not warranted. In our cases, we did not have values indicative of decreases or increases that could be a scale of TCZ blockade. However, the higher mortality in patients with early TCZ administration may indirectly indicate that anti-inflammatory steps are also inhibited. Based on our data, we can even say that TCZs administrated in the first week of hospitalization are associated with mortality.

Another consideration may be the duration of the effect after the TCZ administration. Fundamentally, giving precise timing for initiating the TCZ effect is rough. The duration of action depends on several factors, including disease severity, comorbidities, the dose of TCZ and the route of administration. The literature revealed that the effect of TCZ starts within a few days after intravenous administration and reaches the climax influence within 1-2 weeks (21, 22). Correspondingly, our patients with comorbidities or poor laboratory had a longer median time to discharge/death than those without. In contrast, complications caused by the potential systemic inflammation triggered by COVID-19 may be responsible for mortality, rather than the complications caused by drugs during the disease.

The major limitation of our study was the relatively small sample size of the study population. Nevertheless, the inclusion of patients who met the pre-specified enrollment criteria, albeit from a single center, may provide sufficient experiential evidence. Secondly, obtaining a second result of IL-6 was not feasible for the entire cohort of patients enrolled in the study, which would have allowed for a more accurate interpretation of the anti-inflammatory efficacy of IL-6.

In conclusion, this study evaluated single-center experience in TCZ administration in COVID-19 cases. In the context of applying TCZ, ferritin and d-dimer levels may be regarded as prioritized prognostic criteria among laboratory tests. In lymphopenic patients, acute phase reactants (such as ESR, fibrinogen, and CRP) appear to exhibit more significant discriminative potential in demonstrating prognosis. Comorbidities, as observed in many infectious diseases, exert an adverse effect on the recovery time from infection. As an unlike finding, we can say that early TCZ administration seemed to increase mortality rates.

**Etik Kurul:** The coordinated study protocol was approved by the Ethics Committee of Necmettin Erbakan University, Faculty of Medicine (2022/3980).

**Çıkar Çatışması:** Çalışmada herhangi bir çıkar çatışması yoktur.

**Finansal Çıkar Çatışması:** Çalışmada herhangi bir finansal çıkar çatışması yoktur.

**Sorumlu Yazar:** Ahmet Cizmecioglu, Selcuk University, Medical Faculty, Department of Internal Medicine, Konya, Turkey
**e-mail:** mdahmet2002@gmail.com

**REFERENCES**

1. Bartoli A, Gabrielli F, Alicandro T, et al. COVID-19 treatment options: A difficult journey between failed attempts and experimental drugs. Intern Emerg Med 2021;16(2):281-308.
2. COVID-19 treatment guidelines. https://www.covid19treatmentguidelines.nih.gov/therapies. Accessed on January 23th, 2023
3. Sheppard M, Laskou F, Stapleton PP, et al. Tocilizumab (ActeTCZ). Hum Vaccin Immunother 2017;13(9):1972-88.
4. Sebba A. Tocilizumab: The first interleukin-6-receptor inhibitor. Am J Health Syst Pharm 2008;65(15):1413-8.

5. Mima T, Nishimoto N. Clinical value of blocking IL-6 receptor. Curr Opin Rheumatol 2009;21(3):224-30.
6. Barbalho SM, Prado Neto EV, De Alvares Goulart R, et al. Myokines: A descriptive review. J Sports Med Phys Fitness 2020;60(12):1583-90.
7. Nara H, Watanabe R. Anti-Inflammatory Effect of Muscle-Derived Interleukin-6 and Its Involvement in Lipid Metabolism. Int J Mol Sci 2021;22(18).
8. Copaescu A, Smibert O, Gibson A, et al. The role of IL-6 and other mediators in the cytokine storm associated with SARS-CoV-2 infection. J Allergy Clin Immunol 2020;146(3):518-34 e1.
9. Potere N, Batticciotto A, Vecchie A, et al. The role of IL-6 and IL-6 blockade in COVID-19. Expert Rev Clin Immunol 2021;17(6):601-18.
10. Elahi R, Karami P, Heidary AH, et al. An updated overview of recent advances, challenges, and clinical considerations of IL-6 signaling blockade in severe coronavirus disease 2019 (COVID-19). Int Immunopharmacol 2022;105:108536.
11. Wei Q, Lin H, Wei RG, et al. Tocilizumab treatment for COVID-19 patients: a systematic review and meta-analysis. Infect Dis Poverty 2021;10(1):71.
12. COVID-19 treatment guidelines. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum. Accessed on February 2nd, 2023.
13. Tjendra Y, Al Mana AF, Espejo AP, et al. Predicting Disease Severity and Outcome in COVID-19 Patients: A Review of Multiple Biomarkers. Arch Pathol Lab Med 2020;144(12):1465-74.
14. Crisafulli S, Isgro V, La Corte L, et al. Potential Role of Anti-interleukin (IL)-6 Drugs in the Treatment of COVID-19: Rationale, Clinical Evidence and Risks. BioDrugs 2020;34(4):415-22.
15. Covid-19 update: Tocilizumab (ActeTCZ) FDA-approved for treatment of COVID-19. Med Lett Drugs Ther 2023;65(1667):e9.
16. Saki A, Rajaei E, Rahim F. Safety and efficacy of tocilizumab for rheumatoid arthritis: a systematic review and meta-analysis of clinical trial studies. Reumatologia 2021;59(3):169-79.
17. Ozer MR, Avci A, Baloglu I, et al. Factors Associated with Intensive Care Hospitalization in Patients with Covid-19. Selcuk Med J 2022;38(2): 76-81.
18. Karki R, Sharma BR, Tuladhar S, et al. Synergism of TNF-alpha and IFN-gamma Triggers Inflammatory Cell Death, Tissue Damage, and Mortality in SARS-CoV-2 Infection and Cytokine Shock Syndromes. Cell 2021;184(1):149-68 e17.
19. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol 2014;6(10):a016295.
20. Murakami M, Hirano T. The pathological and physiological roles of IL-6 amplifier activation. Int J Biol Sci 2012;8(9):1267-80.
21. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: Results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis 2008;67(11):1516-23.
22. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med 2020;383(24):2333-44.