Turk Thorac J 2022; 23(3): 225-230 DOI: 10.5152/TurkThoracJ.2022.21179

Original Article

Clinical Predictors of Response to Tocilizumab: A Retrospective Multicenter Study

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Cite this article as: Ercan S, Ergan B, Özuygur SS, et al. Clinical predictors of response to tocilizumab: A retrospective multicenter study. *Turk Thorac J.* 2022;23(3):225-230.

Abstract

OBJECTIVE: A substantial number of patients with coronavirus disease-2019 (COVID-19) demonstrate severe infection. Cytokine storm is an underlying condition that worsens clinical outcomes. As an interleukin-6 receptor antagonist, tocilizumab is a promising treatment option for COVID-19. This study aimed to evaluate the clinical predictors of mortality for critically ill COVID-19 patients receiving tocilizumab therapy.

MATERIAL AND METHODS: The retrospective cohort study was conducted in 4 centers' both wards and intensive care units between March 20 and May 20, 2020. Demographic, clinical, and laboratory data were consecutively drawn from medical records. The primary endpoint was in-hospital mortality.

RESULTS: In this study, 39 patients (28.2% female) were included, and the mortality rate was 25.6% (n = 10). There was statistically significant difference between survivor and non-survivor groups regarding age (53.0 (46.5-65.0) vs. 75.0 (68.25-81.25), respectively, $P = .001$), CALL score (8.0 (7.0-10.0) vs. 12.0 (9.75-13.0), $P = .001$), GRAM score (119.5 (99.5-142.0) vs. 155.0 (129.8-226.0), $P = .004$), and white blood cell count (k/mL) (5.6 (3.8-8.6) vs. 8.0 (7.6-9.3), $P = .003$). The patients who were on invasive mechanical ventilation at the time of tocilizumab administration had a higher mortality rate (100% vs. 25.9%, $P < .001$). Besides, arterial partial pressure of oxygen/fraction of inspiratory oxygen (PaO_2/FiO_2) ratio on day 7, but not on days 0, 1, and 3 of tocilizumab therapy, was associated with mortality. C-reactive protein (mg/dL) tended to be lower in the survivor group; however, it was not statistically significant (68.4 (32.7-157.5) vs. 113.5 (77.7-219.0), $P = .058$).

CONCLUSION: This study demonstrated that advanced age, increased leukocyte count, higher CALL and GRAM scores, and the need for invasive mechanical ventilation revealed a worse prognosis after tocilizumab treatment.

KEYWORDS: Tocilizumab, COVID-19, mortality, biomarkers, CALL score
Received: *July 17, 2021* ***Accepted:*** *January 3, 2022* ***Available Online:*** *April 13, 2022*

INTRODUCTION

The first cases of the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) were reported in December 2019.[1] Patients with coronavirus disease-2019 (COVID-19) manifest a wide spectrum of clinical presentations. Most patients display mild-to-moderate symptoms, while a number of patients suffer from severe illness.[2] These patients can quickly progress to acute respiratory distress syndrome (ARDS), septic shock, and multiorgan failure. Cytokine storm is the main underlying pathophysiological mechanism in patients with a severe clinical course.[2]

Cytokine storm is associated with widespread endothelial-barrier damage in the lungs, leading to ARDS.[2] Elevated levels of ferritin and interleukin-6 (IL-6) are considered to be significant characteristics of the cytokine storm; hence, IL-6 has become a therapeutic target in COVID-19 research.[3] Tocilizumab (TCZ) is a recombinant monoclonal antibody against the IL-6 receptor.[4] Recent data revealed that response to TCZ therapy is variable.[4,5] These contradictory results from different studies suggest that not all patients benefit from anti-IL-6 treatment and that there may be a subgroup who would be more likely to respond.

Hereby, in this multicenter study, we evaluated the treatment response to TCZ therapy in critically ill patients with COVID-19 pneumonia and aimed to investigate clinical predictors of mortality in patients who received TCZ. Furthermore, since CALL and GRAM scores have been validated for the assessment of the severity of COVID-19 pneumonia, we hypothesized that these scores and inflammatory biomarkers at hospital admission could be relevant in predicting response to TCZ treatment.[6,7]

MATERIAL AND METHODS

This retrospective study included patients from 3 different tertiary-care hospitals and one private hospital.

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Patient Characteristics

All adult (age > 18 years) ward and ICU patients (n = 39) who received TCZ for COVID-19 pneumonia between March 20, 2020, and May 20, 2020, were included. Pneumonia was confirmed with computerized tomography (CT). They were diagnosed by either positive reverse transcriptase-polymerase chain reaction (RT-PCR) test (n = 37) or chest CT findings that were characteristic of COVID-19 infection, that is peripheral ground-glass opacities and/or patchy consolidations[8] (n = 2). Demographic, clinical, and laboratory data were recorded from the medical records. The first result of each laboratory variable in days 0-3 of hospital admission was used. Disease severity was assessed with CALL (comorbidity, age, lymphocyte, lactate dehydrogenase (LDH)) and GRAM scores.[6,7] Escalation of respiratory support was defined as stepping up oxygen support with a nasal cannula to high-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV) or stepping up HFNO/NIV support to invasive mechanical ventilation (IMV).

TCZ Administration

The decision to give TCZ treatment was made according to The Turkish Ministry of Health COVID-19 Guideline for Anticytokine, Anti-inflammatory Treatments, and Management of Coagulopathy.[9,10] Briefly, since April 2020, the Turkish Ministry of Health COVID-19 Guideline for Adult Patients Treatment recommends TCZ therapy for severe COVID-19 patients who have a rapid clinical progression and are unresponsive to corticosteroid treatment.[8] Thus, the patients were treated with a dose of 8 mg/kg with a maximum dose of 800 mg. The first dose was either 400 mg or 800 mg depending on the patient's weight and the physician's decision.[10] A second dose of 200-400 mg was used within 12-24 hours only in patients who had initially received 400 mg and were accepted as unresponsive to treatment according to clinical and biochemical values.[10]

Statistical Analysis

The primary endpoint was in-hospital mortality. All categorical variables were expressed as numbers and percentages, and continuous variables were expressed as median and interquartile range. Categorical variables between groups were compared with chi-square or Fisher's exact test, continuous variables were compared with Mann–Whitney *U*-test. A two-tailed *P*-value of <.05 was considered statistically significant. Statistical analysis was performed using Statistical Package for the Social Sciences, version 24.0 software (IBM Corporation, Armonk, NY, USA).

MAIN POINTS

- Tocilizumab (TCZ) is a recombinant monoclonal antibody against the interleukin-6 receptor which is a therapeutic target in the cytokine storm of coronavirus disease-2019 (COVID-19) infection.
- Controversial data are present about the response to TCZ treatment in COVID-19.
- In this retrospective study, advanced age increased leukocyte count, higher CALL and GRAM scores, and the need for invasive mechanical ventilation revealed a worse prognosis after TCZ treatment.

Ethical Approval

Ethical approval was obtained from Ege University medical research ethics committee (approval number: E.122881) after the Permission of the Ministry of Health was given. The requirement for informed consent was waived due to the retrospective design of the study.

RESULTS

A total of 39 patients (11 females and 28 males) were included in the study. The median age was 62 years, and the most common comorbidities were hypertension (35.9%) and diabetes mellitus (17.9%) (Table 1). The most common symptoms at the time of admission were high body temperature (>37.5°C) (89.7%), dyspnea (69.2%), and dry cough (51.3%).

Table 1. Patient's Baseline Demographics and Clinical Characteristics (n = 39)

Age (years)	62 (49-74)
Female/male	11 (28.2)/28 (71.8)
Healthcare worker	6 (15.4)
Comorbidities	
Hypertension	14 (35.9)
Diabetes mellitus	7 (17.9)
Coronary artery disease	5 (12.8)
Asthma	2 (5.1)
Other*	2 (5.1)
Active immunosuppression	2 (5.1)
Admission symptoms	
High body temperature (>37.5°C)	35 (89.7)
Dyspnea	27 (69.2)
Cough	20 (51.3)
Weakness	15 (38.5)
Sputum production	5 (12.8)
Nausea/vomiting	3 (7.7)
Sore throat	2(5.1)
Diarrhea	2(5.1)
Nasal discharge	1(2.6)
Myalgia	1(2.6)
Headache	1(2.6)
Admission vital signs	
Blood pressure-systolic (mmHg)	120 (112-136)
Blood pressure-diastolic (mmHg)	77 (70-83)
Pulse (beats/min)	100 (88-108)
Respiratory rate (/m)	20 (17-26)
Body temperature (°C)	38.2 (38.0-38.3)
SaO_2/FiO_{22}	309.5 (172.7-400.0)
PaO_2/FiO_2 δ_2	186.5 (121.8-294.8)
CALL score	9.0 (7.0-11.5)
GRAM score	131.0 (101.3-155.5)
Vital signs before tocilizumab therapy	
Blood pressure-systolic (mmHg)	123 (101-144)
Blood pressure-diastolic (mmHg)	72 (56-79)
Pulse (beats/min)	99(84-113)
Respiratory rate (/m)	24 (22-28)
Body temperature (°C)	38.1-(36.8-38.6)

All values are expressed as n (%) or median (IQR).
*Other diseases were rheumatoid arthritis in one patient and chronic renal failure in another patient. δData available only in 22 patients
PaO_2, arterial partial pressure of oxygen; FiO_2, fraction of inspiratory oxygen; SaO_2, pulse oximetric saturation.

Patients were mainly treated with hydroxychloroquine and favipiravir, and one-third of the patients concurrently received corticosteroids (n = 13). All patients received low-molecular-weight heparin therapy. Vitamin C was administered intravenously (1-3 g/day, n = 17) or orally (low dose, n = 4). The median duration between symptom onset and hospital admission was 4 (2.5-7.0) days. The median (IQR) length of stay prior to the administration was 3 days (2-6). A second dose was given in 10 patients according to the guideline recommendation.

All patients received conventional oxygen therapy at the time of hospital admission aiming for oxygen saturation > 92%. Six patients were already on IMV during TCZ therapy. The frequency of HFNC (high-flow nasal cannula), NIV (mostly CPAP), and IMV use were 24.3%, 66.7%, and 45.9%, respectively, at the time of TCZ admission. Fifteen patients (38.5%) needed to step up respiratory support after TCZ therapy (Figure 1).

The mortality rate was 25.6% (n = 10). There were statistically significant difference between survivor and non-survivor groups regarding age (53.0 (46.5-65.0) vs. 75.0 (68.25-81.25), *P* = .001), CALL score (8.0 (7.0-10.0) vs. 12.0 (9.75-13.0), *P* = .001), GRAM score (119.5 (99.5-142.0) vs. 155.0 (129.8-226.0), *P* = .004), and white blood cell count (WBC) (K/mL) (5.6 (3.8-8.6) vs. 8.0 (7.6-9.3), *P* = .003) (Table 2).

There was no significant difference between survivors and non-survivors in terms of lymphocyte count (k/mL) (1.12 (0.80-1.40) vs. 0.73(0.56-1.30), *P* = .112), procalcitonin (ng/mL) (0.18 (0.08-0.38) vs. 0.15 (0.13-0.83), *P* = .956), D-dimer (ng/mL) (658 (443-1516) vs. 699 (2.6-2723), *P* = .887), ferritin (622.0 (426.3-1013.7) vs. 616.0 (528.7-881.5), *P* = 1.000), and lactate dehydrogenase (LDH) (313.0 (241.3-492.0) vs. 342.0 (251.5-539.0), *P* = .931, respectively) at the time of hospital admission. C-reactive protein (CRP, mg/dL) levels tended to be lower in the survivor group; however, this failed to reach statistical significance (68.4 (32.7-157.5) vs. 113.5 (77.7-219.0), *P* = .058).

PaO_2/FiO_2 levels remained mostly unchanged in non-survivors, whereas there was a consistent improvement following TCZ administration in survivors, which reached statistical significance on day 7 (199.0 (119.5-284.3) vs. 122.0 (67.5-177.0), *P* = .050) (Table 2). The patients who were on IMV at the time of TCZ administration had a higher mortality (n = 10 (100%) vs. n = 7 (25.9%), *P* < .001).

Two patients had increased liver function tests after TCZ therapy. Six patients (15.4%) developed ventilator-associated pneumonia and 2 patients (5.1%) developed catheter-related urinary tract infection. Septic shock was present in 2 patients before TCZ therapy and in 8 patients within the first week of TCZ therapy.

DISCUSSION

In this multicenter study, we have addressed the clinical course of the COVID-19 pneumonia patients who received TCZ and compared the characteristics of survivors and non-survivors. We have demonstrated that patients who were older, had increased leukocyte count, higher CALL and GRAM scores, and the need for IMV revealed a worse prognosis after TCZ treatment.

Several studies investigating the efficacy of TCZ treatment have been published with controversial results. A multicenter observational study suggested TCZ was associated with an improvement in-hospital-related mortality, especially in patients who were younger than 65 years and intubated at the time of TCZ administration.[11] Biran et al[11] claimed that TCZ might reduce the intensive care requirement and mortality. On the other hand, a randomized, controlled trial showed no benefit in patients with severe disease.[12] TCZ also seems relatively safe since virus-specific antibody responses

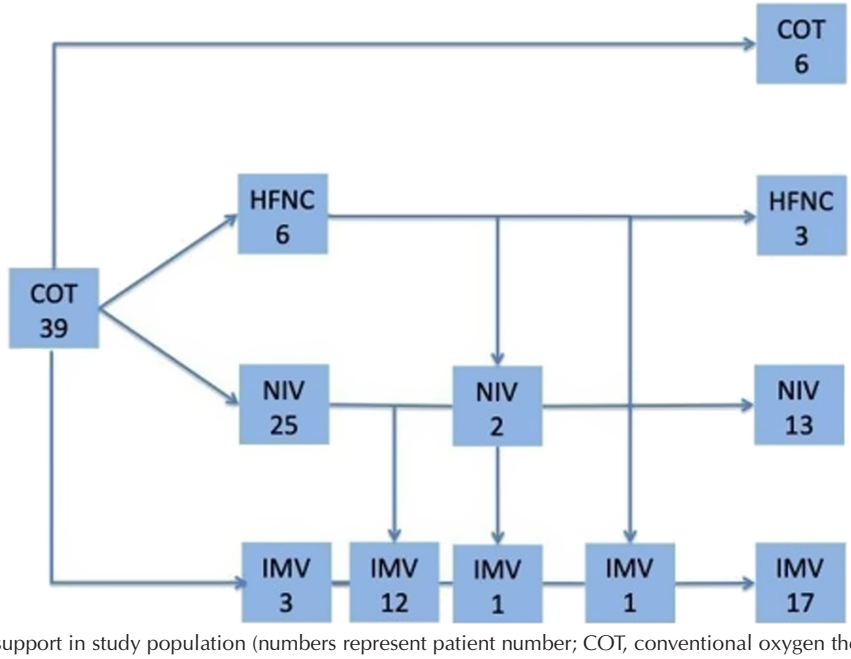

Figure 1. Respiratory support in study population (numbers represent patient number; COT, conventional oxygen therapy; HFNC, high-flow nasal cannula; IMV, invasive mechanical ventilation; NIV, non-invasive mechanical ventilation).

Table 2. Bivariate Analysis Between Survivors and Non-survivors

	Survivors (29)	Non-survivors (10)	*P*
Age (years)(n = 39)	53.0 (46.5-65.0)	75.0 (68.25-81.25)	.001
Hospital day of TCZ administration (n = 20)	3 (3.00-3.75)	4 (3.25-11.5)	.095
PaO_2/FiO_2 on TCZ therapy day 0 (n = 16)	135.4 (116.75-184.50)	132.0 (84.5-256.0)	.716
PaO_2/FiO_2 on TCZ therapy day 1 (n = 16)	152.0 (118.0-192.0)	121.0 (78.0-261.0)	.335
PaO_2/FiO_2 on TCZ therapy day 3 (n = 20)	166.0 (118.75-230.75)	115.0 (85.75-160.0)	.094
PaO_2/FiO_2 on TCZ therapy day 7 (n = 15)	199.0 (119.5-284.25)	122.0 (67.5-177.0)	.050
High-flow nasal oxygen (n = 37, %)	8 (28.6)	1 (11.1)	.403
NIV (n = 39, %)	20 (69.9)	6 (60.0)	.704
Invasive mechanical ventilation (n = 37, %)	7 (25.9)	10 (100.0)	<.001
Escalation of respiratory support after TCZ therapy (n = 39, %)	10 (34.5)	5 (50)	.418
Therapies for COVID-19			
Hydroxychloroquine (n = 39, %)	29 (100.0)	10 (100.0)	
Azithromycin (n = 39, %)	17 (58.6)	3 (30)	.115
Favipiravir (n = 39, %)	28 (96.6)	9 (90)	.452
Darunavir (n = 28, %)	5 (22.7)	0 (0)	.553
Corticosteroid (n = 28, %)	10 (45.5)	3 (50.0)	1.000
ICU admission (n = 24, %)	15 (83.3)	6 (100.0)	.546
Hospital length of stay (days) (n = 39)	18.0 (14.5-23.5)	10.0 (8.5-14.8)	.002
CALL score (n = 39)	8.0 (7.0-10.0)	12.0 (9.75-13.0)	.001
CALL score >9 (n = 39, %)	13 (44.8)	10 (100.0)	.002
GRAM score (n = 36)	119.5 (99.5-142.0)	155.0 (129.75-226.00)	.004
White blood cell count (k/mL) (n = 39)	5.80 (5.11-7.89)	9.18 (7.66-12.38)	.003
Lymphocyte count (k/mL) (n = 39)	1.12 (0.80-1.40)	0.73 (0.56-1.30)	.108
Hemoglobin (mg/dL) (n = 39)	13.0 (11.8-15.2)	13.55 (11.95-14.93)	.607
C-reactive protein (mg/dL) (n = 39)	68.36 (32.7-157.5)	113.5 (77.7-219.0)	.058
Procalcitonin (ng/mL) (n = 34)	0.18 (0.08-0.38)	0.15 (0.13-0.83)	.940
D-dimer (ng/mL) (n = 39)	658.0 (443.0-1516.0)	699.0 (2.6-2723.0)	.885
Ferritin (ng/mL) (n = 31)	622.5 (426.25-1013.65)	616.0 (528.65-811.50)	.965
LDH (U/L) (n = 37)	313.0 (241.25-492.0)	342.0 (251.5-539.0)	.915
Troponin (ng/L) (n = 35)	13.0 (13.0-25.0)	35.5 (14.1-183.05)	.024
Creatinine (mg/mL) (n = 39)	0.90 (0.74-1.07)	1.26 (1.02-3.33)	.007
AST (U/L) (n = 37)	40.0 (25.0-49.0)	36.0 (27.0-45.5)	.656
ALT (U/L) (n = 37)	32.0 (20.0-55.0)	22.5 (17.5-27.8)	.146

TCZ, tocilizumab; ICU, intensive care unit; COVID-19, coronavirus disease-2019; HFNO, High-flow nasal oxygen; NIV, non-invasive ventilation; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine transaminase; PaO_2, arterial partial pressure of oxygen; FiO_2, fraction of inspiratory oxygen.

are not affected; on the contrary, some evidence suggested that viral clearance may be delayed in cases treated with TCZ.[4,13] Guaraldi et al[14] demonstrated in a retrospective cohort study that TCZ might reduce the rates of IMV and mortality. Price et al[15] also showed that TCZ might improve oxygenation and survival. However, Veiga et al[16] reported that TCZ treatment had no clinical benefit to standard care at 15 days and that it might be associated with an increase in mortality. Similarly, Tsai et al[17] showed no difference in mortality when TCZ was used for cytokine storm.

These contradictory results may be associated with differences in patient populations, indications for TCZ use, level of inflammation, or timing of TCZ treatment. We used TCZ relatively earlier than most of the previous reports. In a previous study, Klopfenstein et al[18] administered TCZ relatively early, their hospital day of TCZ administration was 6.5 days (1-21), and similar to our results, the mortality rate was 25%.

When compared to survivors, non-survivors were older and more frequently needed IMV. As PaO_2/FiO_2 ratios were lower on TCZ day 7 in non-survivors, this may be used as a marker of clinical outcome during the follow-up. There were no statistically significant differences in terms of lymphocyte count, ferritin, D-dimer, and LDH values, which are suggested as prognostic markers for COVID-19 infection.[6,19] White blood cell was statistically higher in the non-survivor group. Anurag et al[20] also demonstrated that a high WBC count

might be associated with severe COVID-19, defined as the need for oxygen support. Additionally, Li et al[21] reported that both high CRP levels and WBC counts could be risk factors for severe disease. Interestingly, although being a widely used marker for COVID-19, we have not found statistical significance between survivors' and non-survivors' lymphocyte counts at their admission. Sarabia De Ardanaz et al[22] evaluated lymphocyte values of survivors and non-survivors who were given TCZ in their center. They reported that there was no statistically different lymphocyte count on the day of TCZ admission between these 2 groups. In contrast, survivors' lymphocyte increment response was significantly higher than non-survivors. On the other hand, Lakatos et al[23] have postulated in their prospective cohort that both baseline lymphocyte count and lymphocyte response to TCZ were significantly higher in the survivor group.

In the present study, as both groups received TCZ, we aimed to determine the parameters that could predict mortality following TCZ treatment. Non-survivor group had statistically significantly more severe disease with higher CALL and GRAM scores than the survivor group. CALL and GRAM scores are 2 validated scoring systems to determine COVID-19 severity. CALL score is easy-to-use and is convenient for outpatient management.[6,24] GRAM score aims a comprehensive evaluation with clinical, biochemical, and radiologic characteristics of patients with COVID-19.[7] Ucan et al[24] demonstrated that although GRAM score independently predicts mortality without age and comorbidity, CALL score is better in the prediction of disease's progression. An important contribution of the study is that, to the best of our knowledge, it is the first study that compares GRAM and CALL scores of both groups after TCZ administration and shows that these scores are associated with the risk of mortality.

Limitations of this study have to be taken into account. First, the study population had a limited size, but as this is an expensive treatment with relatively specific indications, it is used in a small proportion of patients only. Second, the data were collected in the first 3 months of the pandemic in Turkey. There was remarkable data loss based on the retrospective design as parameters had been noted previously and there were missed values. Third, concomitant treatments such as hydroxychloroquine and favipiravir may have affected the treatment outcomes. However, it is now established that hydroxychloroquine is ineffective for COVID-19 treatment and there is no clear evidence that favipiravir improves clinical outcomes.[25] Despite these limitations, this study underlines predictive factors for prognosis after TCZ treatment. Future studies may therefore consider including patient groups that are more likely to benefit from anti-cytokine treatment.

CONCLUSION

Effective treatment options of COVID-19 are the most attractive topic for the medical research area. Tocilizumab has become prominent as its pharmacokinetic was found to be related to COVID-19 cytokine storm; controversial results were found. A wide range of the TCZ study outcomes suggested that the response might be related to the clinical and biochemical profile of the patient. This study showed that patients with higher leukocyte count, older age, higher CALL and GRAM scores, and need for IMV are less likely to benefit from TCZ treatment. Since "the most effective treatment in the shortest time" is one of the vital aims in the treatment, this study might give a perspective for foreseeing treatment response a prognosis. More studies with larger patient groups are required to foresee patients' response to TCZ treatment.

Ethics Committee Approval: This study was approved by Ethics committee of Ege University, (Approval No: E.122881).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – O.K., A.S., B.E.; Design B.E.; Supervision O.K., A.S., O.E., M.A., M.S.T., O.K.B.; Data Collection and/or Processing – S.E., S.S.O.E.; Analysis and/or Interpretation B.E., S.E., S.S.O.E.; Literature Search – S.E.; Writing Manuscript – S.E., S.S.O.E.; Critical Review – O.K., A.S., M.S.T., O.K.B.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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