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Efficacy of tocilizumab therapy in severe COVID-19 pneumonia patients and determination of the prognostic factors affecting 30 days mortality

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ABSTRACT

Objective: In coronavirus disease – 19 (COVID-19) patients, cytokine storm develops due to the increase of pro-inflammatory cytokines. Tocilizumab (TCZ), has been used in the treatment of COVID-19 patients and successful results have been obtained. The aim of this study was to determine the efficacy of TCZ and also investigate the prognostic factors affecting the success of treatment and mortality in COVID-19 patients treated with TCZ.

Patients and Methods: Between March 2020 and August 2021, a total of 326 confirmed severe COVID-19 pneumonia patients, treated in the intensive care unit, were included in the study.

Results: The mean age of the patients was 63.02±11.58 years, and 203 (62.3%) of the patients were male. Patients treated with TCZ had a longer survival time compared with the standard therapy (p=0.012). It was found that type of respiratory support (HR:2.19, CI:1.10-4.36, p=0.025) and hyperlactatemia on the day of TCZ therapy admission (HR:2.93 CI:1.53-5.64, p=0.001) were the significant and independent prognostic factors of survival in severe COVID-19 pneumonia patients treated with TCZ.

Conclusion: Tocilizumab therapy improved 30-days survival in critically ill COVID-19 pneumonia patients. Also, among the patients with TCZ, types of respiratory support and hyperlactatemia on the day of TCZ admission were the independent prognostic factors.

Keywords: SARS-CoV-2, COVID-19, Tocilizumab, Viral pneumonia, Cytokine storm, Prognostic factors

1. INTRODUCTION

The first cases of pneumonia caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) began to be seen at the end of 2019, in Wuhan, China, and subsequently, the novel coronavirus disease-2019 (COVID-19) spread the whole world and as a result of the rapid increase in the number of cases it was announced to be a pandemic [1-4].

Coronavirus disease-19 has a broad spectrum of clinical manifestations. In the majority of cases, the disease is mild to moderate, and the symptoms are similar to the typical symptoms of acute respiratory infection such as fever, cough, throat pain, and fatigue [5-7]. Although, it usually causes common cold symptoms, approximately 20% of the patients develop severe illness that requires supplemental oxygen therapy. Also, approximately 5% of patients develop critical illness with respiratory failure, which eventually progresses to multi-organ dysfunction and death [6-8].

In severe cases of COVID-19 pneumonia, the immune response to the viral induction plays a key role in the rapid progression of the disease to respiratory distress syndrome (ARDS) and multi-organ dysfunction [7, 9]. This uncontrolled response is defined as a cytokine storm and thought to result from the uncontrolled release of inflammatory cytokines. The clinical features of this hyper-inflammation process include, persistent fever, high levels of IL-6 and ferritin, gradually increasing C-reactive protein (CRP), D-dimer elevation, and increased liver enzymes [6, 9]. Since, COVID-19-related cytokine storm is associated with

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increased mortality and morbidity, early diagnosis of it is of considerable importance [9, 10].

In studies conducted in the early period of the pandemic, the treatment with tocilizumab (TCZ), which is an IL-6 receptor antagonist, has been reported to be effective on mortality in cases of severe COVID-19 pneumonia and provided significant clinical recovery; although, it is not a specific treatment for the COVID-19-related cytokine storm [9-13]. However, in the studies conducted later in the pandemic process, it has been reported that TCZ treatment had no effect on survival and the need for mechanical ventilation in severe COVID-19 pneumonia cases [14, 15]. Therefore, clinicians need to know which patient group will benefit from TCZ treatment in cases of severe COVID-19 pneumonia.

The aim of the present study was to evaluate the efficacy of TCZ treatment in the critically ill COVID-19 pneumonia patients and also determine the prognostic factors for 30 days mortality to better select the most appropriate patients for the TCZ treatment.

2. PATIENTS AND METHODS

Patients and data

Between March 2020 and August 2021, a total of 326 confirmed severe COVID-19 pneumonia patients treated in intensive care units were included into the study.

The data were obtained from the hospital's medical record system. The demographic and clinical data, laboratory findings, the number of days between the onset of symptoms and the initiation of TCZ treatment, types of respiratory support, length of stay in the ICU, outcomes, scores on the Acute Physiology and Chronic Health Evaluation II (APACHE II) [16] and Sequential Organ Failure Assessment (SOFA) [17] were recorded. All data and scores reported in this study were collected within the first 24 hours following the admission of the intensive care unit (ICU).

The patients were divided into two groups as survivors and non-survivors. The clinical and laboratory data of the patients in both groups at the time of TCZ treatment administration were evaluated and compared.

Definitions

Confirmed COVID-19 case was defined as a clinical suspect case with positive SARS-CoV-2 real-time reverse transcription polymerase chain reaction (RT-PCR) from the upper respiratory sample (nasopharyngeal and/or oropharyngeal swab) or lower respiratory tract sample (tracheal aspirate). And, the COVID-19 pneumonia case was defined as a confirmed COVID-19 case that has pulmonary infiltrates in thorax computed tomography.

Tocilizumab treatment was administered intravenously at a dose of 8 mg / kg (to a maximum dose of 800 mg per infusion); it was administered 400 mg or 800 mg IV, depending on the severity of the patient's symptoms. When the first dose was administered as 400 mg, the dose was repeated as 200-400 mg for 24 hours, taking into account the changes in clinical and laboratory findings. Indications of the TCZ treatment in severe COVID-19 pneumonia patients have included clinical worsening due to COVID-19 pneumonia (persistent or increasing oxygen demand and fever), and high inflammatory biomarkers (elevated level of serum CRP, LDH, D-dimer and ferritin, decreased lymphocyte count and serum albumin level). Standard therapy defined as the patients received standard care according to national practice guidelines that include the concomitant use of antiviral treatment (hydroxychloroquine, azithromycin and favipiravir), antibiotics and supportive care.

APACHE-II and SOFA scores of the patients were used for the assessment of the severity of illness. The APACHE-II score is a number between 0 and 71 that is calculated based on current physiologic measures, age, and previous medical history; higher scores indicate more severe disease and a higher risk of mortality. The SOFA score is used to monitor a patient's organ dysfunction while in an ICU. This scoring system is composed of six independent scores for the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems, with one score for each. The average and highest scores are the most accurate predictors of mortality. These scores were calculated based on the worst clinical and laboratory findings of the patients observed during the first 24 h following the admission to the ICU [16, 17].

All patients were followed during their ICU stay or until death and mortality was defined as death within 30 days after the ICU admission. Mortality data of the patients were collected from the hospital medical record system.

Statistical analysis

After the data obtained from the hospital database they were arranged and transferred to Microsoft Excel tables. The data compatible with normal and homogeneous distribution were expressed as mean ± standard deviation and data without normal or homogeneous distribution were expressed as min-max values by numbers and percentages. The distribution of the variables was controlled by the Skewness-Kurtosis. In the comparison of two independent groups, the independent samples t test was used for independent variables for the analysis of the parametric data, the Mann-Whitney-U test was used for the analysis of non-parametric data, and the chi-square test was used for the analysis of categorical data. The Kaplan-Meier method was used for the survival curve of the patients and the log-rank test was used to calculate the differences in survival between the groups. Independent variables associated with mortality in the univariate analysis were evaluated with multivariate Cox regression models. Results were evaluated at 95% CI and a value of $p < 0.05$ was accepted as statistically significant. SPSS (Statistical Package for Social Sciences) for Windows 25.0 program was used for statistical analysis.

3. RESULTS

Baseline characteristics of the study population

Between March 2020 and August 2021, a total of 326 severe COVID-19 pneumonia patients, treated at our intensive care unit, were included into the study. The mean age of the patients was 63.02±11.58 years, and 203 (62.3%) of the patients were male. We found that 264 (81.0%) patients had at least one comorbid disease. The most frequent comorbid diseases were hypertension (71.2%), diabetes mellitus (42.6%), and coronary artery disease (35.0%). The baseline characteristics of the study population are summarized in Table I.

Table I. *Baseline demographic characteristics of the patients*

		All patients (n=326)
Mean age, years (Mean ± SD)		63.02±11.58
Age	≥ 65 years	168 (51.5%)
	< 65 years	158 (485%)
Gender	Male, (%)	203 (62.3%)
	Female, (%)	123 (37.7%)
At least one comorbidity	Yes, (%)	264 (81.0%)
	No, (%)	62 (29%)
Comorbid diseases	Hypertension, (%)	232 (71.2%)
	Diabetes mellitus, (%)	139 (42.6%)
	Coronary artery disease, (%)	114 (35.0%)
	Chronic obstructive pulmonary disease, (%)	55 (16.9%)
	Chronic heart failure, (%)	38 (11.7%)
	Alzheimer disease, (%)	36 (11.0%)
	Cerebrovascular disease, (%)	19 (5.8%)
	Chronic kidney disease, (%)	14 (4.3%)
	Rheumatologic disease, (%)	8 (2.5%)
	Malignancy, (%)	8 (2.5%)
SOFA score, (Min-Max)		4 (2-9)
APACHE-II score, (Mean ± SD)		17.32±4.20

SOFA: sequential organ failure assessment, APACHE-II: acute physiology assessment and chronic health evaluation II, Min: minimum, Max: maximum, SD: standard deviation

Comparison of the baseline laboratory findings between patients treated with TCZ and patients treated with standard therapy

The patients were grouped as TCZ therapy group (n=110) and standard therapy group (n=216). We found that, mean age of the standard therapy group significantly higher compared with TCZ therapy group (59.86±10.91 vs 64.63±11.61, p<0.001), and also proportion of the patients with ≥65 years old higher in standard therapy group (44 (40.0%) vs 124 (57.4%), p=0.003).

Baseline laboratory parameters of the two groups on the day of ICU admission are summarized in Table II. We found that serum levels of LDH, CRP, PCT, ALT, ferritin and D-dimer on the day of ICU admission were respectively significantly higher in TCZ therapy group (p=0.004, p=0.004, p=0.001, p=0.001, p=0.002, p=0.045, respectively). And, counts of the lymphocytes were significantly lower in TCZ therapy group (p=0.015)

Table II. *Baseline laboratory findings of the patients*

	All patients (n=326)	TCZ therapy group (n=110)	Standard therapy group (n=216)	P value
White blood cells, mm³ (Mean±SD)	11791±5693	12444±5255	11459±5888	0.140**
Neutrophils, mm³ (Mean±SD)	10483±4876	10833±4468	10305±5072	0.356**
Lymphocytes, mm³ (Mean±SD)	852±669	726±333	916±780	**0.015****
Urea, mg/dL (min-max)	51 (14-263)	49 (15-213)	52 (14-263)	0.298*
Creatinine, mg/dL (min-max)	0.85 (0.36-9.29)	0.81 (0.36-3.64)	0.88 (0.41-9.29)	**0.016***
AST, U/L (min-max)	45 (10-1672)	48 (12-426)	43 (10-1672)	0.317*
ALT, U/L (min-max)	33 (8-814)	38 (7-265)	31 (6-814)	**0.001***
LDH, IU/L (min-max)	564 (14-1900)	618 (126-1604)	530 (14-1900)	**0.004***
Albumin, g/dL (Mean±SD)	2.74±0.45	2.74±0.44	2.74±0.47	0.975**
Ferritin, ng/dL (Mean±SD)	916±636	1067±581	839±651	**0.002****
D-Dimer, µg/mL (Mean±SD)	3.11±4.71	3.81±5.86	2.75±3.96	**0.045****
Fibrinogen, ng/dL (Mean±SD)	503±189	505±177	503±194	0.935**
CRP, mg/dL (Mean±SD)	13.18±8.12	14.98±7.16	12.26±8.44	**0.004****
PCT, ng/mL (Mean±SD)	0.60±1.18	0.76±1.42	0.30±0.27	**0.001****
pH, (Mean±SD)	7.42±0.07	7.44±0.05	7.42±0.07	**0.020****
pO_2, mmhg (min-max)	74.30 (47-205)	68.97 (47-195)	79.45 (52-205)	**<0.001***
pCO_2, mmhg (min-max)	35.20 (18-99)	40.92 (24-62)	34.30 (18-99)	0.006*
Lactate, mmol/L (Mean±SD)	2.11±1.26	2.10±0.95	2.12±1.40	0.923**

TCZ: tocilizumab, AST: aspartate aminotransferase, ALT: alanine transaminase, LDH: lactate dehydrogenase, CRP: C-reactive protein, PCT: procalcitonin, Min: minimum, Max: maximum, Me: mean, Std: standard deviation
** Mann–Whitney U test*
*** Independent samples t test*

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There were statistically significant differences between the groups in terms of O_2 requirements and the Horowitz index (the ratio of partial pressure of oxygen in blood (PaO_2) and the fraction of oxygen in the inhaled air (FiO_2)), on the day of ICU admission. Baseline O2 requirements has been found to be higher in TCZ therapy group (91.74±13.46 vs 85.81±20.94, p=0.008), and Horowitz index has been found to be lower in TCZ therapy group compared with standard therapy (0.82±0.27 vs 1.13±0.58, p<0.001).

Efficacy of tocilizumab therapy

When we evaluated the impact of the TCZ therapy on 30-days survival, we found that patients with treated TCZ therapy had a longer survival time compared with the standard therapy (p=0.012) (Figure 1). Also, 30-days mortality rate of the overall study population was %49.1, and 30-days mortality rate has been found to be significantly lower in the TCZ treatment group compared with standard therapy group (40.9% vs 53.2%, p=0.035).

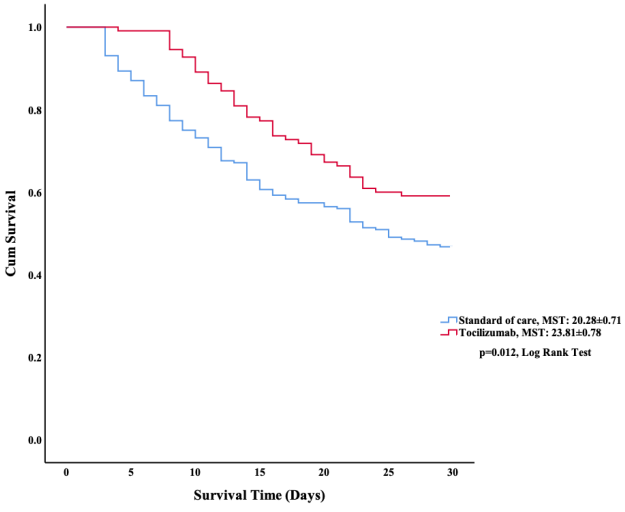

Figure 1. *Kaplan–Meier curves of survival for severe COVID-19 pneumonia patients. Effect of TCZ therapy on 30-days mortality. P values calculated using the Log-rank test. MST: mean survival time*

General characteristics of tocilizumab therapy patients and predictors of 30-days mortality in TCZ therapy

Patients treated with TCZ were grouped as survivors (n=65) and non-survivors (n=45). The mean age of the patients significantly higher in non-survivors, and proportion of the patients 65 years old higher in non-survivors (p=0.010, p=0.048). Percentage of hypertension and diabetes mellitus were significantly higher in non-survivor patients (p=0.003, p=0.007, respectively). In addition, we found that SOFA and APACHE-II scores were significantly higher in those who died within 30 days (p<0.001, p<0.001, respectively). Comparison of the baseline demographic characteristics of the two groups are summarized in Table III.

Table III. *Baseline demographic characteristics of the tocilizumab therapy*

		All patients (n=110)	Survivors (n=65)	Non-survivors (n=45)	P value
Mean age, years (Mean±SD)		63.02±11.58	57.66±12.06	63.04±8.09	**0.010**
Age	≥ 65 years	44 (40.0%)	21 (32.3%)	23 (51.1%)	**0.048**
	< 65 years	66 (60.0%)	44 (67.7%)	22 (49.9%)	
Gender	Male, (%)	75 (68.1%)	45 (69.2%)	32 (71.1%)	0.832
	Female, (%)	35 (31.9%)	20 (30.8%)	13 (29.9%)	
At least one comorbidity	Yes, (%)	83 (75.4%)	44 (67.6%)	39 (86.6%)	**0.023**
	No, (%)	27 (24.6%)	21 (32.4)	6 (13.4%)	
Comorbid diseases	DM, (%)	49 (44.5%)	22 (33.8%)	27 (60.0%)	**0.007**
	COPD (%)	15 (13.6%)	8 (12.3%)	7 (15.5%)	0.626
	HT, (%)	73 (66.3%)	36 (55.3%)	37 (82.2%)	**0.003**
	CHF, (%)	6 (5.4%)	4 (6.1%)	2 (4.4%)	0.698
	CAD, (%)	28 (25.4%)	14 (21.5%)	14 (31.1%)	0.257
Days between the onset of symptoms and TCZ treatment initiation		9.66±2.22	9.63±2.08	9.71±2.43	0.853
SOFA score, (Min-Max)		4 (3-9)	4 (3-7)	5 (3-9)	**<0.001**
APACHE-II score, (Mean±SD)		17.32±4.20	15.89±3.68	18.96±3.69	**<0.001**

DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, HT: hypertension, CHF: chronic heart failure, CAD: coronary artery disease, SOFA: sequential organ failure assessment, APACHE-II: acute physiology assessment and chronic health evaluation II, Min: minimum, Max: maximum, SD: standard deviation

Baseline laboratory parameters of the patients that were treated with TCZ were summarized in Table IV. We found that blood levels of LDH, D-dimer, procalcitonin and lactate on the day of TCZ admission were respectively significantly higher in non-survivors (p=0.030, p=0.038, p=0.034, p<0.001), And, counts of the lymphocytes were lower in non-survivors (p=0.030).

When we evaluated the prognostic factors affecting the 30-days mortality in the patients treated with TCZ therapy, we found that patients with diabetes mellitus and hypertension had significantly shorter survival times (p=0.029, p=0.047, respectively). In addition, patients with hyperlactatemia (blood lactate level >2 mmol/L) on the day of TCZ therapy admission had a significantly shorter survival time (p=0.002). Also, patients receiving invasive mechanical ventilation on the day of TCZ therapy admission had a significantly shorter survival time compared with patients receiving non-invasive mechanical ventilation (p=0.007).

The factors detected in the univariate survival analysis were included in the Cox regression analysis for the multivariate analysis of factors affecting the survival of patients. Univariate and multivariate survival analysis of the patients receiving TCZ therapy are presented in Table V. According to the Cox regression model, it was found that type of respiratory support (HR:2.19, CI:1.10-4.36, p=0.025) and hyperlactatemia on the day of TCZ therapy admission (HR:2.93 CI:1.53-5.64, p=0.001) were the significant and independent prognostic factors of survival in severe COVID-19 pneumonia patients treated with TCZ.

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Table IV. *Baseline laboratory findings of the TCZ therapy patients*

	All patients (n=110)	Survivors (n=65)	Non-survivors (n=45)	P value
White blood cells, mm³ (Mean±SD)	12444±5255	12566±5029	12267±5618	0.771**
Neutrophils, mm³ (Mean±SD)	10833±4468	10528±3873	11274±5224	0.391**
Lymphocytes, mm³ (Mean±SD)	726±333	738±367	643±259	**0.030****
Urea, mg/dL (min-max)	49 (15-213)	48(15-98)	50 (17-213)	0.116*
Creatinine, mg/dL (min-max)	0.80 (0.36-3.64)	0.78 (0.36-1.60)	0.86 (0.55-3.64)	0.088*
AST, U/L (min-max)	49 (12-426)	45(12-146)	52 (12-426)	0.657*
ALT, U/L (min-max)	38 (7-265)	38 (12-178)	37 (7-265)	0.990*
LDH, IU/L (min-max)	617 (126-1604)	589 (281-1604)	718 (126-1339)	**0.030***
Albumin, g/dL (Mean±SD)	2.74±0.44	2.76±0.47	2.70±0.38	0.515**
Ferritin, ng/dL (Mean±SD)	1067±581	1039±572	1107±599	0.550**
D-Dimer, µg/mL (Mean±SD)	3.81±5.86	2.85±4.49	5.21±7.24	**0.038****
Fibrinogen, ng/dL (Mean±SD)	505±177	527±472	472±182	0.108**
CRP, mg/dL (Mean±SD)	14.98±7.16	14.96±7.17	15.02±7.23	0.963**
PCT, ng/mL (Mean±SD)	0.30±0.27	0.25±0.24	0.36±0.30	**0.034****
pH, (Mean±SD)	7.44±0.05	7.44±0.04	7.43±0.07	0.593**
pO_2, mmhg (min-max)	68.97 (47-195)	69.45 (52-146)	66.00 (47-195)	0.534*
pCO_2, mmhg (min-max)	36.60 (24-62)	37.65 (24-55)	36.00 (27-62)	0.114*
Lactate, mmol/L (Mean±SD)	2.10±0.95	1.83±0.26	2.50±1.06	**<0.001****

AST: aspartate aminotransferase, ALT: alanine transaminase, LDH: lactate dehydrogenase, CRP: C-reactive protein, PCT: procalcitonin, Min: minimum, Max: maximum, Std: standard deviation
** Mann–Whitney U test*
*** Independent samples t test*

Table V. *Univariate and multivariate survival analysis of the patients receiving TCZ therapy*

		Univariate analysis*		Multivariate analysis**	
		MST days	P value	HR (95% CI)	P value
Age	≥ 65 years	21.56±1.31	**0.029**	1.74 (0.93-3.25)	0.079
	< 65 years	25.31±0.92			
At least one comorbidity	Absent	25.85±1.54	**0.045**	0.49 (0.09-2.70)	0.416
	Present	23.15±0.89			
Diabetes mellitus	Absent	25.13±1.02	**0.012**	1.65 (0.81-3.34)	0.162
	Present	22.18±1.16			
Hypertension	Absent	26.32±1.22	**0.007**	2.16 (0.49-9.55)	0.307
	Present	22.54±0.96			
Type of respiratory support	IMV	20.23±1.71	**0.007**	**2.19 (1.10-4.36)**	**0.025**
	NIMV	24.66±0.85			
Blood lactate level	< 2 mmol/L	25.83±0.98	**0.002**	**2.93 (1.53-5.64)**	**0.001**
	≥ 2 mmol/L	21.56±1.16			

MST: mean survival time, HR: hazard ratio, CI: confidence interval, IMV: invasive mechanical ventilation, NIMV: non-invasive mechanical ventilation
** Log rank test*
*** Cox regression*

4. DISCUSSION

In the present study, we evaluated the efficacy of the TCZ therapy in severe COVID-19 pneumonia patients and prognostic factors affecting 30 days mortality in severe COVID-19 pneumonia patients treated with TCZ. We found that patients receiving TCZ therapy had a significantly longer survival time compared with the usual care (patients not received TCZ therapy). Also, type of respiratory support and hyperlactatemia on the day of TCZ therapy admission were the significant and independent prognostic factors of survival in severe COVID-19 pneumonia patients treated with TCZ.

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Cytokine storm is the clinical picture characterized by excessive and uncontrolled release of pro-inflammatory cytokines such as IL-1, IL-2, IL-6, IL-7, IL-10, TNF-α, granulocyte-colony-stimulating factor (G-CSF), and interferon. Cytokine storm syndrome may be caused by a variety of infectious and rheumatic diseases or cancer immunotherapy. Since, cytokine storm is a life-threatening critical condition, it requires follow up in the intensive care unit and in clinical practice it is commonly characterized with increased systemic inflammation and may lead to multi-organ dysfunction [18-20].

In studies, it has been shown that a high cytokine profile can develop in some serious COVID-19 cases, which is also observed in severe acute respiratory syndrome associated coronavirus (SARS-CoV) and middle-east respiratory syndrome-coronavirus (MERS-CoV) infections. High serum levels of IL-6, TNF-α, IL-1β, IL-8, and IL-2R have been detected in cases of severe COVID-19 pneumonia. However, the levels of cytokines were found to be significantly higher in patients with severe disease compared to those with mild disease [18, 19, 21, 22]. In addition, it has been shown that the frequency of ARDS and mortality are higher in cases of COVID-19 pneumonia, in which inflammation-related biomarkers such as CRP and ferritin are elevated as well as cytokines [23-25].

In the studies conducted, it has been stated that in patients with COVID-19, a rapid deterioration of the clinical picture can be observed especially within the second week of the disease. This hyper-inflammation is usually manifested by an unexpected aggravation of symptoms such as high fever and respiratory distress and is associated with an increase in acute phase reactants (erythrocyte sedimentation rate (ESR), CRP, and ferritin), coagulation factors (D-dimer), and intracellular lysis markers (lactate dehydrogenase (LDH), creatine kinase (CK)) [2, 4, 26, 27]. Increased cytokine levels observed in the COVID-19-related cytokine storm, unlike other pneumonitis species, leads to the development of organ dysfunction and the need for intensive care [28]. In our study, in accordance with the literature, it was observed that cases of severe COVID-19 pneumonia, cytokine storm or COVID-19-associated hyperinflammatory syndrome developed within the second week of the disease. Similarly, in our study, the levels CRP, ferritin, LDH, CK, and D-dimer were well above the normal values.

Another important finding of cytokine storm is an increase in the number of neutrophils and a decrease in the number of lymphocytes, monocytes and basophils, in the peripheral blood. In the COVID-19-related cytokine storm, increased inflammatory cytokines generally cause a decrease in the number of all T cells and impair their functions. In the studies conducted, it has been shown that, as the number of lymphocytes decreases, the severity of the disease, the rate of the development of septic shock, and mortality increase, in COVID-19 cases [5, 29, 30]. Similarly, in our study, there was lymphopenia (852±669/mm^3) in cases with severe COVID-19 pneumonia associated cytokine storm. Also, in patients receiving TCZ therapy, the counts of the lymphocytes were lower in the non-survivors' group compared to the survivors' group, and the difference was statistically significant (738±367/mm^3 vs 643±259/mm^3, p=0.030).

In severe COVID-19 pneumonia, it has been shown that the host immune response is responsible from the cytokine storm or COVID-19-associated hyperinflammatory syndrome. Although, not specific for COVID-19-related cytokine storms, it is considered that anti-inflammatory treatment approaches may be useful. It was thought that blocking the overproduction of IL-6, which plays a key role especially in the cytokine storm, could be beneficial in the COVID-19-related cytokine storm [9, 12, 26, 27].

In studies evaluating the effects of TCZ treatment on clinical improvement, the need for mechanical ventilation, and survival in severe COVID-19 cases with cytokine storm conflicting results have been reported [10, 31, 32]. In a study conducted in China in the first period of the pandemic, it was found that TCZ treatment in severe COVID-19 pneumonia cases provided a decrease in oxygen demand in 75% of the patients, improvement in thoracic CT findings in 90%, and an increase in lymphocyte count in 52.6% of the patients. Moreover, it was found that all patients treated with TCZ were recovered [33]. Similarly, in two studies conducted in Italy, it has been shown that TCZ treatment provided a fast and permanent clinical improvement in severe COVID-19 pneumonia cases, decreased the need for invasive mechanical ventilation and more importantly reduced mortality [13, 34]. In the present study, we found that severe COVID-19 pneumonia patients treated with TCZ had a statistically significant longer survival time compared with patients treated with standard therapy (p=0.012).

In a systematic meta-analysis in which Tleyjeh et al., evaluated the efficacy and safety of TCZ treatment in COVID-19 cases, it was found that TCZ treatment did not reduce the risk of short-term mortality although, it reduced the need for mechanical ventilation in COVID-19 cases [35]. In addition, in a randomized placebo-controlled double-blind study, it was shown that TCZ therapy was not effective in preventing the need for invasive mechanical ventilation and mortality compared to standard therapy in patients hospitalized with moderate COVID-19 [15]. However, a recently published randomized controlled RECOVERY trial showed that tocilizumab improved survival and clinical outcomes in hospitalized COVID-19 pneumonia patients with hyperinflammation. In addition, it was shown that TCZ therapy was effective in preventing the need for invasive mechanical [36].

We think that it is very important for clinicians to predict which cases will benefit from treatment, before the decision for TCZ treatment in severe COVID-19 pneumonia patients. However, there are a limited number of studies evaluating prognostic factors in severe cases of COVID-19 pneumonia treated with TCZ. In a retrospective cohort study in which Lohse et al., evaluated prognostic factors in patients with severe COVID-19 pneumonia associated cytokine storm treated with TCZ, it was found that patients with severe lymphopenia, increased oxygen demand, low fibrinogen level, and increased serum aspartate aminotransferase (AST) levels did not benefit from TCZ treatment [27].

In the present study, among the patients treated with TCZ therapy, we found that levels of LDH, PCT, D-dimer and lactate

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were significantly higher in non-survivors' patients. And counts of the lymphocytes were significantly lower in non-survivor patients. We also found that the presence of comorbidities such as HT and DM were other risk factors for poor prognosis in patients receiving TCZ therapy. More importantly, patients receiving invasive mechanical ventilation on the day of TCZ therapy admission had a significantly shorter survival time compared with patients receiving non-invasive mechanical ventilation.

The present study has some limitations. First, this is a retrospective, small sample size cohort study, conducted in a single center. Second, IL-6, which is the most important biomarker of cytokine storms, was not evaluated in the study.

In conclusion, TCZ therapy improved 30-days survival in critically ill COVID-19 pneumonia patients with hyperinflammation. And, patients receiving invasive mechanical ventilation and hyperlactatemia on the day of TCZ admission were less likely to benefit from TCZ treatment. We believe that more clinical studies are needed to predict which patients will benefit from TCZ therapy.

Compliance with Ethical Standards

Ethical Approval: The present study protocol was approved by the Clinical Ethics Committee of Inonu University School of Medicine (2020/164). Due to the retrospective nature of the study, the written informed consent form was not obtained.

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