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ORIGINAL PAPER

Infectious diseases

Low-dose tocilizumab is associated with improved outcome and a low risk of secondary infection in severe COVID-19 pneumonia

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Abstract

Background: Respiratory failure and death are the leading causes of severe Coronavirus disease 2019 (COVID-19). Hyper-inflammation and cytokine storm cause lung damage. This study aimed to compare the low-dose and high-dose effects of tocilizumab, an IL-6 receptor antagonist.

Method: Patients with severe pneumonia and hyper-inflammation signs because of COVID-19 were included in this retrospective study. Patients receiving tocilizumab <200 mg intravenously were classified as the low-dose group, and receiving ≥200 mg as the high-dose group, and those not treated with tocilizumab as the control group. Demographic and clinical data of patients who died and survived in both low-high dose and control patients were compared. According to symptom day and radiological infiltration, patients with tocilizumab were also evaluated in two groups as early and late periods at tocilizumab administration time.

Results: A total of 160 patients were included in the study; 70 were treated with a low dose and 50 with high-dose tocilizumab. Forty patients were in the control group. Age, comorbidity and clinical features were similar in the control, low-dose tocilizumab and high-dose tocilizumab groups. The mortality rate (12.9%, 30.0%, 37.5, $P = .008$) was less in the low-dose tocilizumab group. The secondary infection rate was higher in the high-dose group than in the low-dose tocilizumab and control groups (44.0%, 10.0%, 10.0%, $P < .001$). Distinguishing between those patients who died and survived, age (OR: 1.1589, $P < .001$), higher APACHE II scores (OR: 1.225, $P = .001$) and needs for non-invasive mechanical ventilation (OR: 14.469, $P < .001$) were the most critical risk factors. Low-dose tocilizumab was associated with a lower mortality rate (OR: 0.244, $P = .012$).

Conclusion: The use of tocilizumab at a low dose is associated with lower secondary infections and mortality.

Ilhami Celik and Esma Eryilmaz-Eren contributed equally.

1 | INTRODUCTION

Globally, there have been more than 188 million confirmed cases of Coronavirus disease 2019 (COVID-19), with more than 4 million deaths have been reported from the first COVID-19 case was identified.[1] The most common symptoms of patients with COVID-19 are fever, cough and dyspnoea. Patients may have severe pneumonia, which leads to respiratory failure and death.[2] Severe COVID-19 patients are known to have cytokine release syndrome (CRS). IL-6, IL-2, IL-7, IL-10 and tumour necrosis factor (TNF) levels were higher in patients who need intensive care.[3] IL-6 levels were correlated with poor clinical outcome and SARS-CoV-2 RNAaemia in severely ill patients.[4]

Tocilizumab (TCZ) is an anti-interleukin-6-receptor (IL-6R) monoclonal antibody used in rheumatological diseases. The first case in which TCZ was found effective was reported, in February 2020, in China.[5] Guaraldi et al treated 33 patients with severe pneumonia associated COVID-19, with TCZ and reported a positive effect on survival and respiratory function compared with the control group.[6] There are also reports claiming that the use of TCZ in the treatment of severe COVID-19 is ineffective for survival.[7] There is no consensus yet in the literature and there are different results.[8] TCZ-related side effects have also been reported.[9,10] As a result of multiple side effects, especially secondary bacterial infections, low-dose TCZ recommendations have been attracting interest.[11,12] Here, we aimed to evaluate the efficacy on clinical outcome and 28-day mortality, and side effects of low-dose TCZ compared with high doses.

What's known

Many patients with COVID-19 have acute lung damage and hypoxic respiratory failure, possibly caused by hyper-inflammation. Interleukin-6 (IL-6) blockade was found to be beneficial in this process, but the most important disability of anti-inflammatory treatments are secondary infections.

What's new

The appropriate dose of tocilizumab in the COVID19 environment is unknown. In this study, we evaluated different doses of tocilizumab in COVID-19 patients. Randomised controlled trials of tocilizumab, including a low-dose tocilizumab, are ongoing in this patient population. Based on the results of our study, low-dose acute hyper-inflammatory tocilizumab may reduce secondary infection and improve survival. Under normal conditions, the application of interventional pharmacoeconomics can help control drug costs through a reduction in the units used. This study shows how the interventional pharmacoeconomics principles can be applied to drug shortages in a global pandemic.

2 | METHODS

2.1 | Study design and patients

This retrospective study was carried out in a tertiary hospital with a 1607 bed capacity, and 253 intensive care beds. Adult patients (>18 years old) treated with intravenous TCZ because of severe COVID-19 from 1 April 2020 to 31 December 2020 were included in this study.

TCZ treatment indications were determined as follows: lymphopenia (lymphocyte count, <0.80, $\times 10^9$/L), high CRP levels (>40 mg/dL) and high D-dimer and ferritin levels.

The case group was defined as patients who received TCZ in addition to antiviral and supportive treatment. The age- and gender-matched control group consisted of the severe COVID-19 pneumonia patients who were followed up in the same period as the patients in the study group and had hyper-inflammation but did not use TCZ. Only antiviral and supportive treatments were given to the control group.

COVID-19 pneumonia was defined as I. SARS-CoV-2 PCR positivity in the upper respiratory tract samples and bilateral peripheral ground glass infiltration (typical for COVID-19) in the thorax computerised tomography (CT); or II. The rapid antibody test was positive and typical infiltration for COVID-19 in thorax CT.[13] Severe COVID-19 pneumonia was defined as fever and respiratory tract infection findings and the presence of one of the following: respiratory rate >30/min, defined as severe respiratory distress (dyspnoea, use of extra respiratory muscles), presence of oxygen saturation <90% in room air (PaO_2/FiO_2 < 300 in the patient receiving oxygen).[14] Antiviral treatments were used for five days as a standard. Their doses were, respectively, favipiravir; 3200 mg loading dose followed by 1600 mg/day maintenance dose, hydroxychloroquine; 400 mg/day following 800 mg loading dose and 100 mg/day following remdesivir 200 mg loading dose. Dexamethasone 8 mg/day and methylprednisolone 1 mg/kg were administered.

Patients with absolute contraindications (neutrophils $<1 \times 10^9$/L, platelets $<100 \times 10^9$/L, aspartate aminotransferase (AST) >3 × upper limit of normal or severely active bacterial or opportunistic infection) were not treated with TCZ.

The patients diagnosed with cancer, undergoing any immunosuppressive therapy, mild or moderate COVID-19 clinic and intubated with COVID-19 were excluded from this study.

2.2 | TCZ use

During the pandemic, a 400 mg vial of TCZ was used. The physicians determined the dose of TCZ. Each vial was divided into two to five patients, used with a 1-hour infusion in 100 cm^3 0.9% saline. Each vial was consumed within 24 hours of opening the vial. After administration of 80 or 100 mg, a further 80 or 100 mg repeat dose was administered within 24-48 hours.

TCZ doses <200 were considered a low dose, and ≥200 as a high dose.[12] TCZ administration time was determined according to thorax CT imaging and duration of symptoms. If there was ground glass and duration of symptoms <7 days, it was defined as early period; if there was paving stone or fibrotic band and duration of symptoms >7 days, it was considered the late period.[15]

TABLE 1 Comparison and outcomes of survivor and non-survivor patients

	Total n = 160 (%)	Survivor n = 121 (%)	Non-survivor n = 39 (%)	*P*	Multivariate analysis OR (95% CI) *P*
Age -median (min-max)	53 (24-65)	51 (24-65)	58 (44-65)	.002	1.158 (1.066-1.257) < 0.001
Male gender	105 (65.6)	78 (64.5)	27 (69.2)	.699	
Comorbidities					
Hypertension	53 (33.1)	36 (29.8)	17 (43.6)	.121	
Diabetes mellitus	38 (23.8)	30 (24.8)	8 (20.5)	.669	
Coronary artery disease	19 (11.9)	11 (9.1)	8 (20.5)	.084	
Asthma	16 (10.0)	14 (11.6)	2 (5.1)	.361	
Chronic obstructive pulmonary disease	9 (5.6)	6 (5.0)	3 (7.7)	.689	
Symptoms					
Dyspnoea	104 (65.0)	76 (62.8)	28 (71.8)	.340	
Cough	103 (64.4)	79 (65.3)	24 (61.5)	.703	
Myalgia	48 (30.0)	40 (33.1)	8 (20.5)	.162	
Fever	54 (33.8)	41 (33.9)	13 (33.3)	1.000	
APACHE II	8 (3-31)	7 (3-29)	12 (3-31)	<.001	1.225 (1.092-1.375) 0.001
Infiltration					
Ground glass opacity (early-acute)	121 (75.6)	98 (81.0)	23 (59.0)	.009	
Intralobular lines-fibrosis (late-chronic)	39 (24.4)	23 (19)	16 (41.0)		
Antiviral treatment					
Hydroxychloroquine	3 (1.9)	3 (2.5)	—	1.000	
Remdesivir	2 (1.3)	1 (0.8)	1 (2.6)	.429	
Favipiravir	155 (96.8)	117 (96.7)	38 (97.4)	1.000	
Corticosteroid	148 (92.5)	113 (93.4)	35 (89.7)	.488	
Methylprednisolone	83 (51.9)	65 (53.7)	18 (46.2)	.463	
Dexamethasone	65 (40.6)	48 (39.7)	17 (43.6)	.710	
Respiratory support					
High flow O_2	34 (21.3)	23 (19.0)	11 (28.2)	.261	
Non-invasive mechanical ventilation	19 (11.9)	8 (6.6)	11 (28.2)	.001	14.469 (3.437-60.908) <0.001
Tocilizumab	120 (75.0)	96 (79.3)	24 (61.5)	.034	
Low dose (<200 mg)	70 (43.8)	61 (50.4)	9 (23.1)	.003	0.244 (0.081-0.736) 0.012
High dose (≥200 mg)	50 (31.3)	35 (28.9)	15 (38.5)	.321	
Tocilizumab median dose (mg) (min-max)	160 (80-800)	100 (80-800)	200 (80-800)	.109	
Prognosis					
Secondary infection	33 (20.6)	15 (12.4)	18 (46.2)	<.001	
Bacterial infection	31 (19.4)	14 (11.6)	17 (43.6)	<.001	
Invasive fungal infection	8 (5.0)	3 (2.5)	5 (12.8)	.021	
Median day of hospitalisation (min-max)	15 (5-54)	15 (6-55)	17 (5-34)	.584	

2.3 | Statistical analysis

The collected information was processed using Statistical Package for Social Sciences (SPSS) for Windows (version by 22.0). Categorical variables are expressed as numbers and percentages, and Chi-square or Fisher's Exact Test analysis was used for comparisons. Shapiro-Wilks test and histogram analyses were performed to determine whether continuous variables show normal distribution. Non-parametric data: median (min-max), while the significance between groups was determined using Mann Whitney *U* test. Binary logistic regression was used to estimate odds ratios (ORs) and 95% confidence interval. In all analyses, $P < .05$ was considered statistically significant.

3 | RESULTS

A total of 160 patients treated for severe COVID-19 were included in the study. One hundred twenty received tocilizumab and standard therapy, and 40 were treated with standard therapy as a control group. The patients' median age was 53 (24-65) years, and 65.6% were male. Hypertension was the most common (33.1%) comorbid disease, and dyspnoea was the most common (65.0%) symptom. According to thorax CT, 75.6% of patients were in an early-acute phase, and 24.4% had intralobular lines or fibrosis. All patients used antiviral before TCZ or including the control group, three of them used hydroxychloroquine, and two used remdesivir. A total of 148 (92.5) patients were given steroids. Nineteen patients (11.9%) were supporting non-invasive mechanical ventilation, and 34 (21.3%) were with a high flow O_2 (Table 1).

Seventy patients were treated with a low dose (<200 mg), and 50 patients with high-dose (≥200 mg) TCZ. Forty patients were enrolled in the control group. Forty-one patients needed intubation following hyper-inflammation because of respiratory failure. Secondary infection was observed in 34 (20.8%) patients within 14 days.

3.1 | Risk factors of mortality

Thirty-nine patients (24.3%) died within 28 days after TCZ infusion. The differences between the patients who survived and did not survived are presented in Table 1. Non-survivors were statistically significantly older than survivors ($P = .002$). Interlobular lines and fibrosis were more common in the non-survivor group ($P = .009$) and they needed more non-invasive mechanical ventilation ($P = .001$) at the time they were included in the study. The rates of secondary infection, secondary bacterial infection and secondary fungal infection within 14 days after TCZ were higher in the non-survivor group ($P < .001$, $P < .001$ and $P = .021$, respectively) (Table 1).

In multivariate analysis, the older age (OR: 1.158, $P < .001$), higher APACHE II score (OR: 1.225, $P = .001$) and the necessity of non-invasive mechanical ventilation were considered as risk factors for mortality (OR: 14.469, $P < .001$). Low-dose tocilizumab was reduced mortality (OR: 0.244, $P = .012$).

Subgroup analysis results were similar among patients who did not support non-invasive mechanical ventilation (n = 141). Patients who died were more likely older (median 59.5 vs 51, $P = .003$), had secondary bacterial infections (50.0% vs 10.65%, $P < .001$) and fungal infections (1.8% vs 21.4%, $P = .001$). In multivariate analysis, the age (OR: 1.166, $P = .003$) and higher APACHE score (OR: 1.223, $P = .002$) was defined as a risk factor of mortality. Low-dose tocilizumab reduced mortality (OR: 0.133, $P = .006$).

Laboratory data of all patients are given in Table 2. Before TCZ infusion, C-reactive protein (CRP) and D-dimer values were higher in the non-survivor group ($P = .010$ and $P = .001$). According to the laboratory findings evaluated on the seventh day of study; leukocyte,

TABLE 2 Laboratory measures of survivor and non-survivor patients

	Before tocilizumab infusion			Seventh day after tocilizumab		
Laboratory measures- median (min-max) (Normal values)	Survivor (n = 96)	Non-survivor (n = 24)	*P*	Survivor (n = 96)	Non-survivor (n = 24)	*P*
White blood cell count, $\times 10^3/\mu L$ (4.5-10)	9.59 (1.05-28.52)	10.11 (1.60-23.22)	1.000	11.41 (2.78-32.69)	14.66 (4.47-27.96)	<.001
Lymphocyte count,$\times 10^3/\mu L$ (0.8-3.2)	0.83 (0.31-3.38)	0.79 (0.29-2.03)	.928	1.38 (0.33-3.50)	0.64 (0.16-4.27)	<.001
Creatinine mg/dL (0.70-1.20)	0.79 (0.27-10.0)	0.94 (0.20-2.93)	.066	0.76 (0.09-11)	1.09 (0.31-8.80)	.027
Aspartate aminotransferase, U/L (0-40)	39 (9-242)	45 (21-140)	.169	31 (11-511)	44 (14-108)	.008
Alanine aminotransferase, U/L (0-41)	33 (5-374)	31 (9-114)	1.000	58 (9-701)	35 (7-119)	<.001
Procalcitonin, μg/mL (<0.5)	0.13 (0.01-1.65)	0.18 (0.01-9.00)	.314	0.05 (0.01-18.00)	0.81 (0.01-52.00)	<.001
C-reactive protein, mg/dL (0-5)	105 (7.5-366)	150 (18-320)	.010	7 (0.60-134)	68 (3.50-399)	<.001
Ferritin, μg/L (30-400)	110 (33-6967)	1097 (60-4200)	.924	726 (100-2197)	1145 (92-3150)	<.001
D- dimer, μg/L (0-500)	2066 (150-11 560)	2066 (150-14 180)	.001	1558 (120-11 280)	7403 (1890-13 600)	<.001
Fibrinogen, mg/L (2000-4000)	7079 (2050-11 650)	7048 (4220-10 860)	.536	3925 (670-8860)	4718 (1000-8620)	<.001

serum aspartate aminotransferase (AST), CRP, procalcitonin, D-dimer and fibrinogen levels were higher, and lymphocyte parameters were lower in the non-survivor group ($P < .001$, $P = .008$, $P < .001$, $P = .001$, $P < .001$, $P = .007$ and $P < .001$, respectively) (Table 2).

3.2 | The outcome of low- vs high-dose TCZ

Older age, demographic data, symptoms at admission, APACHE II scores, corticosteroid or antiviral treatment and respiratory support before TCZ of the patients treated with low- or high-dose TCZ and control group were similar (Table 3). Within 14 days, secondary infections and secondary bacterial infections were higher in the high-dose TCZ group than the low-dose TCZ and control groups ($P < .001$ and $P < .001$, respectively). The mortality rate was lower in the low-dose group (12.9%) than in the high-dose (30%) and control group. The difference was statistically significant ($P = .008$). In paired comparisons, there was a significant difference between low-dose TCZ and high-dose TCZ groups with $P = .036$, low-dose TCZ and control groups with $P = .004$.

TABLE 3 Demographic and clinical characteristics of patients treated with low- or high-dose tocilizumab and control group

	Control n = 40 (%)	Low dose (<200 mg) n = 70 (%)	High dose (≥200 mg) n = 50 (%)	*P*
Age -median (min-max)	53 (41-63)	51 (24-65)	53 (27-65)	.490
Male gender	21 (52.5)	46 (65.7)	38 (76.0)	.660
Comorbidities				
Diabetes mellitus	12 (30.0)	13 (18.6)	13 (26.0)	.361
Hypertension	18 (45.0)	20 (28.6)	15 (30.0)	.190
Coronary artery disease		3 (4.3)	11 (22.0)	.093
Chronic obstructive pulmonary disease	2 (5.0)	3 (4.3)	4 (3.3)	.684
Asthma	6 (15.0)	5 (7.1)	5 (10.0)	.418
Symptoms				
Dyspnoea	27 (67.5)	44 (62.9)	33 (66.0)	.872
Cough	31 (77.5)	42 (60.0)	30 (60.0)	.135
Myalgia	13 (32.5)	18 (25.7)	17 (34.0)	.573
Fever	12 (30.0)	21 (30.0)	21 (42.0)	.331
APACHE II	9.05 (±6.49)	9.07 (±3.68)	9.42 (±3.52)	.898
Treatments				
Corticosteroid	35 (87.5)	64 (91.4)	49 (98.0)	.154
Methylprednisolone	20 (50.0)	35 (50.0)	28 (56.0)	.780
Dexamethasone	16 (40.0)	28 (40.0)	21 (42.0)	.972
Antiviral treatment				
Hydroxychloroquine	1 (2.5)	2 (2.9)	—	.495
Favipiravir	39 (97.5)	70 (100)	50 (100)	.221
Remdesivir	1 (1.4)	1 (2.5)	—	.561
Respiratory support before tocilizumab				
High flow O_2	9 (22.5)	10 (14.3)	15 (30.0)	.113
Non-invasive mechanical ventilation	6 (15.0)	7 (10.0)	6 (12.0)	.737
Prognosis				
Median day of hospitalisation (min-max)	14.5 (5-49)	15.5 (6-36)	16 (6-52)	.402
Mortality 28th day	15 (37.5)	9 (12.9)	15 (30.0)	.008
Secondary infection after tocilizumab	4 (10.0)	7 (10.0)	22 (44.0)	.000
Bacterial infection	4 (10.0)	7 (10.0)	20 (40.)	.000
Invasive fungal infection	—	2 (2.9)	6 (12.0)	.019

3.3 | The outcome of early vs late initiation of TCZ

Ninety (75%) of case group patients with earlier onset of symptoms and ground-glass radiological infiltration in thorax CT received TCZ infusion compared with 30 patients with later symptoms and late findings and fibrotic bands thorax CT. The characteristics of patients who received tocilizumab in the early or late period are presented in Table 4. The patients who received TCZ later were significantly older ($P = .005$). Gender, comorbid diseases, symptoms, antiviral and supportive treatment were similar (Table 4). More intubation was needed in the late period group was on the seventh day after treatment (36.7% vs 15.6%) ($P = .02$). The mortality rate with secondary bacterial infections was statistically higher among patients with late initiation ($P = .035$ and $P = .032$, respectively).

TABLE 4 Demographic and clinical characteristics of patients treated with tocilizumab at early or late stage

	Early administration n = 90 (%)	Late administration n = 30 (%)	*P*
Age-Median (min-max)	51 (24-65)	58.5 (27-65)	.005
Male gender	60 (66.7)	24 (80.0)	.250
Comorbidities			
Diabetes mellitus	18 (20.0)	8 (26.7)	.373
Hypertension	29 (32.2)	6 (20.0)	.250
Coronary artery disease	9 (10.0)	5 (16.7)	.335
Chronic obstructive pulmonary disease	3 (3.3)	4 (13.3)	.065
Asthma	7 (7.8)	4 (13.3)	.464
Symptoms			
Dyspnoea	54 (60.0)	23 (76.7)	.125
Cough	55 (61.1)	17 (56.7)	.673
Myalgia	28 (31.1)	7 (23.3)	.492
Fever	32 (35.6)	10 (33.3)	.825
Corticosteroid	85 (94.4)	28 (93.3)	.822
Methylprednisolone	48 (54.5)	15 (50.0)	.678
Dexamethasone	36 (40.9)	13 (43.3)	.833
Antiviral treatment before tocilizumab			
Hydroxychloroquine	2 (2.0)	0 (0.0)	1.000
Favipiravir	90 (100)	30 (100)	1.000
Remdesivir	0 (0.0)	1 (3.3)	.254
Respiratory support before tocilizumab			
High flow O_2	18 (20.0)	7 (23.3)	.796
Non-invasive mechanical ventilation	9 (10.0)	4 (13.3)	.735
Tocilizumab median dose (mg) (min-max)	100 (80-800)	200 (80-600)	.276
Low dose (<200 mg)	56 (62.2)	14 (20.0)	.142
High dose (≥200 mg)	34 (37.8)	16 (53.3)	.142
Prognosis			
Intubation after tocilizumab	14 (15.6)	11 (36.7)	.020
Median day of hospitalisation (min-max)	15 (6-52)	17.5 (6-34)	.366
Mortality 28th day	14 (15.6)	10 (33.3)	.035
Secondary infection after tocilizumab	18 (20.0)	11 (36.7)	.065
Bacterial infection	16 (17.8)	11 (36.7)	.032
Invasive fungal infection	4 (4.4)	4 (13.3)	.106

4 | DISCUSSION

In this study, we retrospectively evaluated the effect of different doses of TCZ on survival in patients with severe COVID-19 pneumonia. We observed that low-dose TCZ treatment when administered with low-dose and early-stage COVID-19 reduced mortality compared with those who did not receive TCZ or those who received high-dose TCZ. Also, secondary bacterial and opportunistic fungal infections were less common in the low-dose group. The most important prognostic factors affecting mortality in patients included in our study were older age, higher APACHE II and the need for non-invasive mechanical ventilation.

It is known that cytokine levels correlate with the disease severity of COVID-19.[16-18] Based on this point, TCZ treatment, which is used and effective through IL-6 blockade, has different results in the literature and its efficacy remains controversial. In a meta-analysis, seven studies were evaluated and reported that TCZ treatment did not reduce mortality in the treatment of severe COVID-19.[19] On the other hand, Rossi et al showed that early and low-dose TCZ treatment reduced mortality compared with standard therapy in COVID-19-related respiratory failure patients.[12] In our study, the mortality rate was lower in the low-dose group than in the high-dose and control group.

Secondary infections are the most important safety concerns in treatment with TCZ. In the study by Quartuccio et al, bacterial superinfection was observed in 17 of 42 patients treated with TCZ, but none in the control group.[20] Somers et al reported that two times more superinfections were reported in patients treated with TCZ than in the control group. (54% vs 26%, $P < .001$).[21] In the study by Kimmig et al, more secondary bacterial 2.76 (95% CI, 1.11-7.20; $P = .0295$) infections were observed in patients who received TCZ compared with the control group. Also, invasive fungal infection was reported in three patients in the TCZ group. Accordingly, more deaths were reported in the TCZ group.[9] In our cases, the secondary infection rate did not significantly result in the multi analysis but was lower in the low-dose TCZ group than in the high-dose TCZ group and control. Besides, the secondary infection rate was very high in the non-survivor group. The IL-6 level measured in patients with cytokine storm because of COVID-19 was shown to be lower than in patients with sepsis.[22,23] Therefore, the use of high doses of TCZ might result in more immunosuppression than targeted. In this case, high doses of TCZ will inevitably cause secondary infections.

Older age, dyspnoea or respiratory distress, increased WBC, CRP and procalcitonin and low lymphocyte levels were previously determined to risk factors for poor prognosis.[24-26] Consistent with the literature, in our study, older age and the need for non-invasive mechanical ventilation were defined as risk factors for mortality. Leukocytosis, CRP and procalcitonin were increased in non-survivor patients, and lymphocytes were decreased. Patients in the non-survivor group had higher C-reactive protein (CRP) and D-dimer values before TCZ infusion.

The most important limitation was that the IL-6 level was not measured. Based on previous studies, treatment was determined based on the idea that IL-6 levels were lower than sepsis. In addition, in the early initiation group, 56 patients were treated with low-dose TCZ, 34 patients were high-dose TCZ; in the late initiation group, 14 patients were low-dose treatment and 16 patients were high-dose treatment. In our study, when we divided patients into subgroups, the number of patients was relatively low. Another important limitation was that some clinical data, such as vasopressor dose or fluid-electrolyte balance, were not available because of the retrospective study. Further multicentre and randomised trials are needed to confirm the efficacy and safety of early administration of a low dose of TCZ in larger populations.

5 | CONCLUSION

Early (within the first seven days of symptoms onset) and low-dose TCZ appear to contribute to recovery in severe COVID-19 pneumonia patients. At this point, the rational use of TCZ is essential. Older age and the need for non-invasive mechanical ventilation are factors affecting mortality. There was a lower secondary infection with low-dose TCZ.

ETHICS

This research was approved by the local ethics committee (Date: 01.10.2020, Number: 171).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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