ORIGINAL RESEARCH

Bagcilar Med Bull
DOI: 10.4274/BMB.galenos.2025.30602

Comparison of the Effects of Tocilizumab and High-dose Steroid Treatment on Treatment Response and Mortality in Hospitalized COVID-19 Pneumonia Patients with Cytokine Storm

Sitokin Fırtınası Gelişen Hastanede Yatan COVID-19 Pnömonisi Hastalarında Tosilizumab ile Yüksek Doz Steroid Tedavisinin Tedavi Yanıtı ve Mortaliteye Etkilerinin Karşılaştırılması

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Abstract

Objective: Cytokine storm associated with coronavirus disease-2019 (COVID-19) is a major contributor to COVID-19-related mortality. This study aimed to evaluate and compare the clinical and laboratory effects, as well as mortality outcomes, of high-dose steroid therapy versus tocilizumab treatment in patients experiencing this hyperinflammatory state.

Method: This retrospective, single-center cohort study analyzed the records of 200 patients who were hospitalized at University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital with COVID-19 pneumonia and diagnosed with a cytokine storm between February 1 and September 30, 2021. Eligibility criteria required that

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Amaç: Koronavirüs hastalığı-2019 (COVID-19) ile ilişkili sitokin fırtınası sendromu, hastalıkla ilişkili mortalitenin önemli bir nedenidir. Bu çalışmada; sitokin fırtınası gelişen hastalarda; yüksek doz steroidler ile tosilizumabın klinik ve laboratuvar sonuçlar ile mortalite üzerindeki etkilerini karşılaştırmayı amaçladık.

Yöntem: Bu retrospektif, tek merkezli kohort çalışma 1 Şubat 2021 ile 30 Eylül 2021 tarihleri arasında Sağlık Bilimleri Üniversitesi, Gazi Yaşargil Eğitim ve Araştırma Hastanesi'nde COVID-19 pnömonisi nedeniyle hastaneye yatırılan ve sitokin fırtınası tanısı konulan 200 hastanın verileri incelenerek gerçekleştirilmiştir. Çalışmaya dahil edilen hastaların sitokin fırtınası için yalnızca tosilizumab veya yalnızca yüksek doz

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Received: 27.07.2025 **Accepted:** 25.11.2025 **Epub:** 03.12.2025

Cite this article as: Alakuş ÖF, Solmaz İ, Kayan F, Uzundere O, Kaya S, Ozan M, et al. Comparison of the effects of tocilizumab and high-dose steroid treatment on treatment response and mortality in hospitalized COVID-19 pneumonia patients with cytokine storm. Bagcilar Med Bull. [Epub Ahead of Print]

Abstract

patients have been treated exclusively with tocilizumab or high-dose methylprednisolone for cytokine storm management. Each treatment group included 100 patients. Demographic characteristics, existing chronic conditions, symptom duration, and clinical and laboratory parameters at admission (prior to treatment) and 72 hours after treatment were assessed. Mortality outcomes were also analyzed using appropriate statistical methods.

Results: Of the 200 patients evaluated, 116 (58%) were male and 84 (42%) were female, with a mean age of 63.3±13.9 years. Comorbidities were present in 63.5% of patients and were more common in the steroid group (p=0.005); hypertension was the most prevalent comorbidity (49.5%). The mean interval from symptom onset to treatment was 9.8±2.9 days and was significantly longer in the tocilizumab group (p=0.001). Both treatments showed similar effects on C-reactive protein, D-dimer, and temperature. Steroids were more effective at improving oxygen saturation and reducing ferritin levels, while tocilizumab resulted in a greater increase in lymphocyte count (p<0.001). Mortality rates did not differ significantly (p=0.767).

Conclusion: Based on our comparison of immunomodulatory therapies for cytokine storm in the context of COVID-19, high-dose steroid treatment appears more favorable than tocilizumab when comparable efficacy is expected, primarily because of its greater cost-effectiveness and wider accessibility.

Keywords: COVID-19, cytokine storm, pulse steroid, tocilizumab

Öz

metilprednizolon almış olması şartı aranmıştır. Her tedavi grubunda toplam 100 hasta analiz edilmiştir. Demografik veriler, kronik komorbiditeler, semptomların süresi ve başvuru sırasındaki, ilaç uygulamasından önceki ve ilaç uygulamasından 72 saat sonraki klinik ve laboratuvar değerleri, istatistiksel analiz yöntemleri kullanılarak mortalite sonuçları ile birlikte değerlendirilmiştir.

Bulgular: Çalışmaya dahil edilen 200 hastanın 116'sı (%58) erkek, 84'ü (%42) kadındı ve ortalama yaşları 63,3±13,9 yıldı. Komorbid hastalık oranı %63,5 olup, steroid tedavisi alan grupta bu oran anlamlı şekilde daha yüksekti (p=0,005). En sık görülen eşlik eden hastalık hipertansiyondu (%49,5). Semptomların başlamasından tedaviye kadar geçen süre ortalama 9,8±2,9 gün olup, tosilizumab grubunda bu süre belirgin şekilde daha uzundu (p=0,001). Her iki grup da C-reaktif protein, D-dimer ve vücut sıcaklığı parametrelerinde benzer iyileşme gösterdi. Yüksek doz metilprednizolon tedavisi oksijen satürasyonunu artırmada ve ferritin düzeyini düşürmede daha etkili olurken, tosilizumab tedavisi lenfosit sayısını artırmada daha başarılı bulundu (p<0,001). Mortalite açısından ise gruplar arasında anlamlı fark izlenmedi (p=0,767).

Sonuç: COVID-19 ile ilişkili sitokin fırtınası için immünomodülatör tedavileri karşılaştıran çalışmamız, maliyet etkin ve kolay erişilebilir olan yüksek doz steroid tedavisinin tosilizumaba tercih edilebileceğini düşündürmektedir.

Anahtar kelimeler: COVID-19, sitokin fırtınası, tosilizumab, yüksek doz steroid

Introduction

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), was first recognized in late 2019 and has since evolved into a global pandemic. By 2023, hundreds of millions of confirmed cases and millions of deaths had been reported worldwide, highlighting its profound impact on public health. Despite a declining incidence in some regions, the disease continues to exhibit a variable course across populations and remains a major concern because of its high transmissibility, including transmission from asymptomatic individuals and via multiple routes. These features have posed substantial challenges to prevention and management strategies and have underscored the importance of timely diagnosis and effective treatment approaches (1).

COVID-19 pneumonia typically progresses through two clinically distinct stages. The initial phase is dominated by viral replication, leading to direct tissue injury. In the subsequent phase, immune activation occurs as infected host cells trigger the recruitment of T lymphocytes, monocytes, and neutrophils, resulting in heightened cytokine release. In severe COVID-19 cases, this immune overactivation is mediated by cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-gamma, tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-1β, IL-6, IL-8, and IL-12. This exaggerated inflammatory process, termed a "cytokine storm", is characterized particularly by marked elevations of IL-6 and TNF-α in the systemic circulation (2).

As the clinical severity of COVID-19 increases, acute lung injury—which primarily affects the lungs, the principal target of the virus—can advance to acute respiratory distress syndrome (ARDS). The pathogenesis of ARDS is closely linked to cytokine storm activity, and ARDS remains the predominant cause of mortality in patients with COVID-19 (3). Autopsy studies from China have revealed that individuals who died of severe COVID-19 had markedly elevated levels of IL-1, IL-6, and TNF-α in tissue specimens (4).

Multiple studies involving patients with COVID-19 have repeatedly demonstrated notably elevated IL-6 levels (5,6). Prompt identification of cytokine storm and timely intervention have been linked to improved clinical outcomes in patients with COVID-19 (7).

While antiviral and monoclonal antibody-based treatments mainly act during the initial phase of the disease by suppressing viral replication, immunomodulatory

agents—such as glucocorticoids and tocilizumab—are used to control the cytokine-driven hyperinflammatory state. Glucocorticoids exert their immunomodulatory effects by downregulating the expression of inflammation-related genes, leading to reduced levels of cytokines such as IL-6, IL-1β, IL-17, IL-12, GM-CSF, and TNF. Additionally, they inhibit enzymes like cyclooxygenase-2, suppress prostaglandin biosynthesis, and decrease inducible nitric oxide synthase activity (8,9).

Management of cytokine storm aims to suppress pro-inflammatory mediators—especially IL-6—while promoting anti-inflammatory responses, including the activity of cytokines like IL-10 (10).

As clinical research on COVID-19 expanded and scientific findings increasingly demonstrated the benefits of glucocorticoid therapy, the World Health Organization endorsed their use in severe cases—especially in patients with ARDS, sepsis, or septic shock, and those needing mechanical ventilation or vasopressor support (11).

The RECOVERY Collaborative Group et al. (12) trial, which enrolled more than 6.000 participants, demonstrated that administration of 6 mg of dexamethasone daily for 10 days provided clinical benefit to patients with severe COVID-19. The results demonstrated that this therapy led to notable clinical improvement in critically ill patients when compared with the control group. Nonetheless, the same study emphasized that glucocorticoids did not provide significant benefit for individuals who did not need respiratory support (12).

Tocilizumab, an IL-6 receptor–targeting monoclonal antibody, is widely employed in the treatment of rheumatoid arthritis and various rheumatic disorders. Given the pivotal role of IL-6 in the development of cytokine storm and the association between elevated IL-6 levels and increased mortality in severe COVID-19 cases, tocilizumab was considered a promising therapeutic option for such patients. Consequently, the US Food and Drug Administration approved its use in hospitalized patients with COVID-19 pneumonia complicated by cytokine storm (13).

Moreover, a retrospective analysis of approximately 1.400 hospitalized patients with COVID-19 pneumonia revealed that tocilizumab therapy led to a notable reduction in both mechanical ventilation requirements and mortality rates (14).

This study aimed to compare the impact of high-dose steroid treatment—recognized for its low cost and wide availability—with that of tocilizumab, which is comparatively more expensive and less accessible, in hospitalized patients with severe COVID-19 pneumonia complicated by cytokine storm. The evaluation focused on clinical progression, laboratory markers, oxygenation status, and mortality outcomes.

Materials and Methods

Design of the Study and Selection of Participants

The study retrospectively analyzed patients diagnosed with severe or critical COVID-19 pneumonia who were admitted to either the general wards or the intensive care unit (ICU) at University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital. The study period spanned from February to September 2021, focusing on cases complicated by cytokine storm. Only patients who underwent treatment with either tocilizumab or high-dose methylprednisolone—without any additional immunomodulatory drugs—were included. The study protocol was approved by the Institutional Review Board of University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital (approval no: 154; date: August 10, 2022), and, given the retrospective design, the requirement for informed consent was waived.

Patient information was obtained retrospectively via the hospital's information management system. Patient characteristics, including age, sex, and chronic conditions present before hospitalization, were systematically recorded. The clinical progression of each patient was assessed from medical records, including the duration of symptoms before hospital admission, the time from symptom onset to the initiation of either tocilizumab or high-dose steroid treatment, the length of oxygen support prior to treatment, the type of hospital unit where the patient received care (ward or ICU), and the number of hospitalization days in each setting. Clinical and laboratory data collected included oxygen saturation, body temperature, C-reactive protein (CRP), lymphocyte count, D-dimer, ferritin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST), measured at admission, before treatment, and 72 hours after treatment. The primary outcome of the study was all-cause in-hospital mortality, while secondary outcomes were clinical and laboratory changes assessed 72 hours after initiation of immunomodulatory therapy.

A retrospective analysis of laboratory data from hospitalized COVID-19 patients in the inpatient ward and the ICU

showed that daily evaluations included CRP, complete blood count, D-dimer, ferritin, ALT, AST, bilirubin, and arterial blood gas measurements. In addition, daily chest X-rays were performed. The diagnosis of cytokine storm was based on trends in these laboratory parameters over time, deterioration on chest imaging, and clinical decline.

The criteria used to define cytokine storm included the following:

• Persistent high-grade fever

• Markedly elevated and progressively rising CRP levels (at least 10 times the upper normal limit)

• Continuously increasing ferritin concentrations (exceeding 400 µg/L)

• Rising D-dimer values over time

• Onset of lymphopenia, neutrophilia, and thrombocytopenia

• Abnormal liver function indicators, including ALT, AST, and LDH.

Due to variability in individual patient presentations and fluctuations in laboratory results relative to standard reference ranges, the core diagnostic criteria in this study were defined as: daily increases in ferritin, D-dimer, CRP, ALT, and AST levels; lymphocyte depletion; persistent fever; decline in oxygen saturation; and clinical and radiological progression to ARDS. This diagnostic approach aligns with the COVID-19 guideline issued by the Ministry of Health of the Republic of Turkey, which specifically addresses anticytokine and anti-inflammatory treatment strategies and coagulopathy management.

The reference ranges for the laboratory parameters examined in this study were based on the hospital's laboratory standards:

• Lymphocyte count: 1000-4800/µL

• CRP: <5 mg/L

• Ferritin: 30-400 µg/L

• Reference range for D-dimer: 0-243 ng/L

• ALT normal range: 0-41 U/L

• AST normal range: 0-40 U/L.

Treatment Protocols

Patients were categorized into two treatment groups:

High-dose steroid group: patients received intravenous methylprednisolone at a daily dose of 250 mg for three days, after which the treatment was tapered stepwise and definitively discontinued on day 25 (Figure 1).

Tocilizumab group: Patients received a fixed 400-mg dose of tocilizumab administered intravenously over 1 hour, followed by a second identical dose 12 hours later, for a total dose of 800 mg.

In this study, the terms pulse steroid therapy and high-dose steroid therapy were used interchangeably.

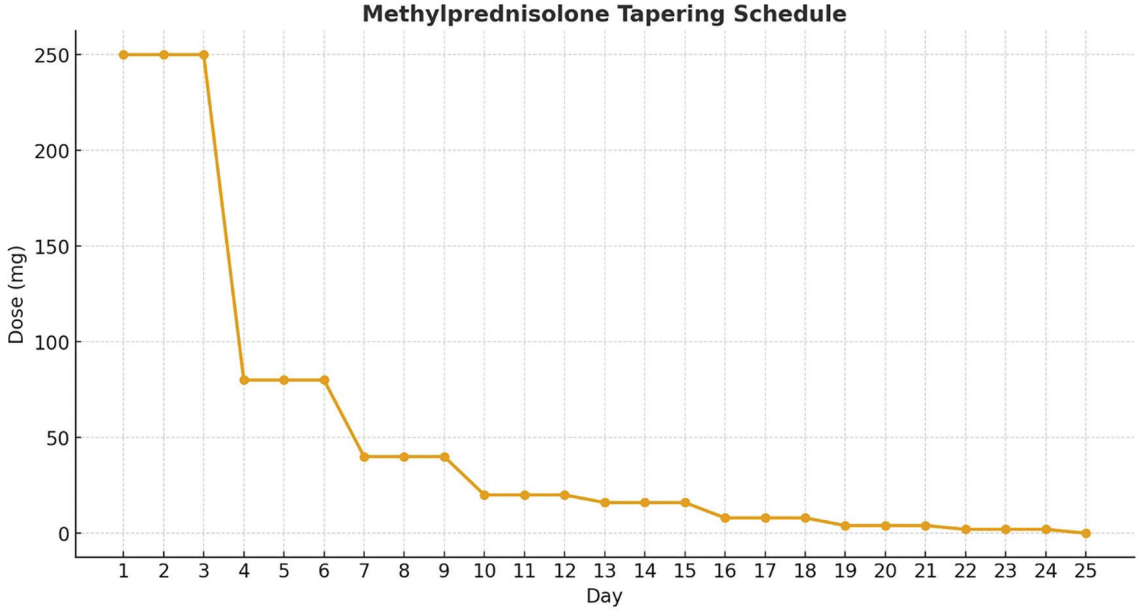

Figure 1. Methylprednisonole dose tapering schedule

Inclusion Criteria

• Individuals who were at least 18 years old at the time of diagnosis

• COVID-19 pneumonia cases complicated by cytokine storm, admitted either to the general inpatient service or the intensive care unit)

• Patients identified as having severe or critical COVID-19, based on the classification criteria established by the National Institutes of Health

• Patients who received either tocilizumab or high-dose methylprednisolone for treatment.

Exclusion Criteria

• Patients younger than 18 years of age at the time of diagnosis

• Individuals identified as pregnant during hospital admission or the course of hospitalization

• Subjects with pre-existing diagnoses of solid organ malignancies or hematologic cancers

• Patients who refused treatment and did not provide informed consent for tocilizumab or high-dose methylprednisolone therapy.

Statistical Analysis

Statistical analysis was performed using SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables were presented as numbers (n) and percentages (%). Categorical comparisons were made using the chi-square test or Fisher's exact test where appropriate. The normality of distribution for continuous variables was assessed through the Kolmogorov-Smirnov test. For variables with a normal distribution, comparisons were made using the Student's t-test, whereas the Mann-Whitney U test was used for non-normally distributed variables. A p-value below 0.05 was considered statistically significant.

Results

Of the 200 patients evaluated in this study, 116 (58%) were male and 84 (42%) were female. In the tocilizumab group, 69 patients (69%) were male and 31 patients (31%) were female, whereas in the high-dose steroid group, 47 patients (47%) were male and 53 patients (53%) were female. The average age of all patients was 63.25±13.9 years. The mean age was 61.8±12.8 years in the tocilizumab group and 64.6±14.7 years in the steroid group.

Upon initial hospital admission, 124 patients (62%) were placed in the inpatient ward, while 76 patients (38%) were admitted directly to the ICU. Some patients who were first monitored in the inpatient ward required transfer to the ICU due to clinical worsening. Conversely, patients who completed their treatment in the ICU and showed signs of recovery were later managed in the inpatient ward until hospital discharge. A comprehensive overview of the patients' demographic data is provided in Table 1.

Compared with the tocilizumab group, the high-dose steroid group had a significantly shorter interval between symptom onset and treatment initiation (8.5±2.4 days vs. 11.1±2.9 days; p<0.05). Likewise, patients in the high-dose steroid group received oxygen therapy for a significantly shorter period prior to treatment initiation than those in the tocilizumab group (2.3±1.5 days vs. 3.5±2.8 days; p=0.006).

Table 1. Demographic details and admission-time clinical features of the cohort

Characteristic	All patients (n=200)	Tocilizumab (n=100)	Pulse steroid (n=100)	p-value
Age (years)	63.25±13.9	61.8±12.8	64.6±14.7	0.09
Duration of symptoms prior to treatment initiation (days)	9.8±2.9	11.1±2.9	8.5±2.4	<0.001
Duration of oxygen support before treatment initiation (days)	2.9±2.3	3.5±2.8	2.3±1.5	0.006
Duration of symptoms before hospital admission (days)	6.4±2.4	6.6±2.6	6.1±2.2	0.156
Hospitalization unit (n, %)				0.08
- General ward	124 (62%)	56 (56%)	68 (68%)	
- Intensive care unit	76 (38%)	44 (44%)	32 (32%)	
Gender (n, %)				0.002
- Female	84 (42%)	31 (31%)	53 (53%)	
- Male	116 (58%)	69 (69%)	47 (47%)	

However, no statistically significant differences were found between the groups regarding age, duration of symptoms prior to hospital admission, or the initial site of hospitalization (inpatient ward versus ICU) (p>0.05) (Table 1).

When comorbidity status was assessed, 127 patients (63.5%) were found to have at least one chronic condition, whereas 73 patients (36.5%) had none. Comparison of the treatment groups showed that comorbidities occurred more frequently in the high-dose steroid group than in the tocilizumab group (p=0.005). Detailed information on the distribution of comorbidities for each group is provided in Table 2.

A comparative overview of the patients' clinical and laboratory findings at the time of admission for both groups is shown in Table 3.

Table 4 provides a comparative overview of clinical and laboratory measurements for the two treatment groups prior to commencement of therapy.

Table 5 compares the clinical and laboratory data of patients in both groups, measured at the 72nd hour after treatment administration.

Comparison of lengths of stay in inpatient and intensive care units revealed no statistically significant difference between the tocilizumab and pulse steroid groups (p>0.05).

Evaluation of patient groups regarding oxygen delivery methods revealed that nasal oxygen was more commonly used in the tocilizumab group, whereas the high-dose steroid group more frequently required oxygen via a reservoir mask (p<0.001) (Table 6).

As presented in Table 7, the statistical analysis showed no significant difference in mortality between the tocilizumab and pulse-steroid groups (p>0.05).

Table 2. Evaluation of patients based on comorbidities

Characteristic	All patients (n=200)	Tocilizumab (n=100)	Pulse steroid (n=100)	p-value
Comorbidity (n, %)	127 (63.5%)	54 (54%)	73 (73%)	0.005
- Absent	73 (36.5%)	46 (46%)	27 (27%)	
Hypertension (n, %)	99 (49.5%)	34 (34%)	65 (65%)	<0.001
- Absent	101 (50.5%)	66 (66%)	35 (35%)	
Chronic obstructive pulmonary disease (n, %)	15 (7.5%)	6 (6%)	9 (9%)	0.421
- Absent	185 (92.5%)	94 (94%)	91 (91%)	
Coronary artery disease (n, %)	42 (21%)	17 (17%)	25 (25%)	0.165
- Absent	158 (79%)	83 (83%)	75 (75%)	
Asthma (n, %)	9 (4.5%)	4 (4%)	5 (5%)	0.733
- Absent	191 (95.5%)	96 (96%)	95 (95%)	
Diabetes mellitus (n, %)	63 (31.5%)	24 (24%)	39 (39%)	0.022
- Absent	137 (68.5%)	76 (76%)	61 (61%)	
Chronic kidney disease (n, %)	18 (9%)	5 (5%)	13 (13%)	0.048
- Absent	182 (91%)	95 (95%)	87 (87%)	
Cerebrovascular disease (n, %)	2 (1%)	0	2 (2%)	0.155
- Absent	198 (99%)	100	98 (98%)	
Congestive heart failure (n, %)	12 (6%)	1 (1%)	11 (11%)	0.003
- Absent	188 (94%)	99 (99%)	89 (89%)	

Table 3. Initial clinical signs and laboratory values at hospital entry

Characteristic	All patients (n=200)	Tocilizumab (n=100)	Pulse steroid (n=100)	p-value
SpO_2 (%)	88.6±6.45	87±7.9	90.2±3.9	0.002
Body temperature (°C)	36.5±0.86	36.9±1	36.1±0.3	<0.001
Lymphocyte count (/mm^3)	988.5±604.9	1049.9±661.4	927.1±538.8	0.028
C-reactive protein (mg/L)	121.5±64.7	113.4±65.4	129.7±63.2	0.026
D-dimer (ng/mL)	1465.9±313.2	1113.7±3104.4	1818±3137	<0.001
Ferritin (ng/mL)	914.9±654.8	954.6±744	875.3±552.3	0.811
Alanine aminotransferase (U/L)	41.4±33.1	44.1±37.4	38.7±28.1	0.587
Aspartate aminotransferase (U/L)	54.3±33.5	58.8±90.1	49.8±32	0.973

Table 4. Clinical and laboratory characteristics of patients before drug administration

Characteristic	All patients (n=200)	Tocilizumab (n=100)	Pulse steroid (n=100)	p-value
SpO_2 (%)	86.2±6.8	82.9±7.2	89.4±4.5	<0.001
Body temperature (°C)	36.7±0.86	37.9±3.76	36.9±3.37	<0.001
Lymphocyte count (/mm^3)	785.5±385.3	859.6±346.8	711.4±408.7	<0.001
C-reactive protein (mg/L)	149.8±66.6	149.4±73.7	150.1±59.1	0.464
D-dimer (ng/mL)	2949.9±475.5	2928.9±5269.4	2971±4205	0.114
Ferritin (ng/mL)	1249.4±731.3	1384.7±793.3	1114.06±639.3	0.005
Alanine aminotransferase (U/L)	47.8±38.6	51.9±45.7	43.6±29.4	0.397
Aspartate aminotransferase (U/L)	49.3±36.7	52.6±43.2	46.01±28.7	0.439

Table 5. Clinical parameters and lab results 72 hours post-treatment initiation

Characteristic	All patients (n=200)	Tocilizumab (n=100)	Pulse steroid (n=100)	p-value
SpO_2 (%)	88.8±6.8	86.08±7.27	91.3±5.4	<0.001
Body temperature (°C)	36.1±0.35	36.1±0.32	36.09±0.38	0.188
Lymphocyte count (/mm^3)	957.8±575.03	1136.1±584	786.9±513.03	<0.001
C-reactive protein (mg/L)	40.6±25.5	35.5±43.8	45.5±46.8	0.111
D-dimer (ng/mL)	3869.9±678.07	4694.3±8327.8	3079.5±4771	0.024
Ferritin (ng/mL)	1040.5±624.1	1210.1±661.6	877.8±541.05	<0.001
Alanine aminotransferase (U/L)	72.8±35.5	75.03±116	70.8±202	0.052
Aspartate aminotransferase (U/L)	71.5±33.2	77.7±150.5	65.6±292.1	<0.001

Table 6. Types of oxygen support administered to patients

Oxygen support type	All patients (n=200)	Tocilizumab (n=100)	Pulse steroid (n=100)	p-value
Nasal oxygen	75 (37.5%)	51 (51%)	24 (24%)	<0.001
Reservoir mask	64 (32%)	15 (15%)	49 (49%)	
High-flow nasal cannula	6 (3%)	4 (4%)	2 (2%)	
Continuous positive airway pressure	41 (20.5%)	22 (22%)	19 (19%)	
Mechanical ventilation	14 (7%)	8 (8%)	6 (6%)	

Table 7. Comparison of mortality between groups

Mortality outcome	All patients (n=200)	Tocilizumab (n=100)	Pulse steroid (n=100)	p-value
Present	70 (35%)	36 (36%)	34 (34%)	0.767
Absent	130 (65%)	64 (64%)	66 (66%)	

Discussion

A review of existing literature on immunomodulatory treatments in COVID-19 patients reveals that, although numerous studies address this topic, direct comparisons between high-dose steroid therapy and tocilizumab remain limited.

For instance, Kumar et al. (15) conducted a study similar in design to ours, involving 336 patients with severe COVID-19 in which they compared tocilizumab with pulse-steroid treatment. In their cohort, 72.9% were male and 27.1% were female, with a reported mean age of 57.4±13.6 years. Likewise, Mikulska et al. (16) evaluated 215 patients with COVID-19 pneumonia to compare the therapeutic efficacy of tocilizumab and steroids, reporting that 67.4% of participants were male and that the mean age was 67.9 years.

In our analysis, the average patient age was 63.25±13.9 years, with a gender distribution of 58% male and 42% female. Mikulska et al. (16) reported no statistically significant

difference in age or sex distribution between treatment groups. In contrast, Kumar et al. (15) found a notably higher proportion of male patients in the tocilizumab arm (p=0.016), while age distribution remained statistically comparable between groups (p>0.05). A similar pattern was observed in our study: There was a significantly greater male predominance in the tocilizumab group (p=0.002), although no significant difference was detected with regard to age (p>0.05).

The findings of these studies indicate that both middle and older age groups are key risk factors linked to the progression of severe COVID-19, the onset of cytokine storm, and the need for immunomodulatory treatment. In Kumar et al.'s (15) research, diabetes mellitus emerged as the most prevalent comorbidity, while Mikulska et al. (16) reported hypertension as the leading chronic condition. Furthermore, in the latter study, 78.1% of patients were found to have at least one underlying disease (15,16).

In our cohort, 63.5% of the patients had at least one chronic condition, with hypertension being the most prevalent, affecting 49.5% of cases. When the comorbidity distribution was analyzed across groups, a significantly higher rate of chronic illnesses was observed in the pulse steroid group (p=0.005). Comparable studies have also identified chronic disease as a contributing factor to severe COVID-19 progression and an increased need for immunomodulatory intervention. Nevertheless, a meta-analysis indicated that the presence of comorbidities did not affect the therapeutic efficacy of either tocilizumab or steroids in managing cytokine storm (17).

In the study conducted by Kumar et al. (15), the duration of symptoms before hospital admission 5.53±4.69 days in the pulse steroid group and 5.04±2.55 days in the tocilizumab group, with no statistically significant difference between groups (p>0.05). Likewise, Mikulska et al. (16) reported the duration as 7.2±4.7 days for the pulse steroid group and 7.7±3.5 days for the tocilizumab group, with no statistically significant difference (p>0.05).

In our study, the mean duration of symptoms prior to hospital admission was 6.6±2.6 days in the pulse-steroid group and 6.1±2.2 days in the tocilizumab group, which aligns with the averages reported in previous studies. In line with the existing literature, the difference between the two groups was not statistically significant (p>0.05).

In our cohort, the average interval from symptom onset to the initiation of therapy was 9.8±2.9 days overall, with 11.1±2.9 days observed in the tocilizumab group and 8.5±2.4 days in the pulse steroid group. This observation is consistent with the literature, which notes that hyperinflammatory complications—such as admission to intensive care, cytokine storm, ARDS, the need for mechanical ventilation, and multi-organ dysfunction—typically emerge during the second week of illness (18).

In our study, oxygen saturation, body temperature, CRP, lymphocyte count, ferritin, D-dimer, ALT, and AST levels were evaluated at three time points: At hospital admission, immediately before treatment initiation, and 72 hours after drug administration. Comparison of measurements taken just prior to treatment with those at initial admission revealed an increase in CRP, D-dimer, and ferritin levels, along with elevated body temperature and reduced oxygen saturation and lymphocyte counts, findings that are consistent with the typical course of a cytokine storm.

Comparison of the two treatments' effects on clinical and laboratory markers at 72 hours post-administration showed that body temperature tended to decrease more in the tocilizumab group than in the pulse-steroid group, although the difference was not statistically significant. In contrast, the tocilizumab group showed a significantly greater increase in lymphocyte count (p<0.001). This finding aligns with the established immunosuppressive action of steroids, which are known to lower lymphocyte levels. Moreover, considering that IL-6 functions as an endogenous pyrogen, its inhibition is expected to reduce fever more effectively.

In addition, both treatment groups exhibited comparable reductions in CRP levels. However, ferritin—a key acute-phase reactant—demonstrated a more substantial decline in patients receiving pulse steroid therapy. Since D-dimer typically shows a slower downward trend, its levels continued to decrease in both groups even 72 hours after treatment.

It is widely recognized that mortality in COVID-19 correlates directly with the severity of ARDS. In patients with severe or critical disease, reported mortality rates vary substantially—from 12% up to 78%—depending on healthcare infrastructure and the circulating SARS-CoV-2 variant. Mortality rates generally range from 25% to 50%. Outcomes are often poorer in regions with limited medical resources, whereas lower mortality rates have been documented in areas with robust healthcare systems (18).

A wide range of pharmacological agents and therapeutic strategies has been investigated to reduce mortality among patients with COVID-19. In this context, numerous studies have assessed the impact of both tocilizumab and high-

dose corticosteroids on mortality, particularly compared with standard treatment protocols.

A randomized controlled trial involving 66 non-intubated patients with severe COVID-19 compared high-dose methylprednisolone to standard treatment. The study reported a mortality rate of 5.9% in the methylprednisolone group versus 42.9% in the standard care group, indicating a statistically significant survival benefit in those receiving steroid therapy (19). Conversely, some other investigations have found no meaningful difference in mortality outcomes between corticosteroid-treated patients and those managed with standard care protocols (20).

Regarding the use of tocilizumab in COVID-19 treatment, Klopfenstein et al. (21) reported a mortality rate of 25% among patients receiving tocilizumab, significantly lower than the 48% observed in the standard care group (p=0.006). Furthermore, the study reported that patients treated with tocilizumab had lower rates of admission to intensive care units (21).

In comparative studies assessing the effectiveness of tocilizumab versus pulse steroid therapy, Kumar et al. (15) reported mortality rates of 36% in the tocilizumab group and 34% in the high-dose steroid group. The difference between the two treatments was not statistically significant (p>0.05) (15), indicating similar efficacy profiles.

Likewise, Mikulska et al. (16) reported mortality rates of 20.7% in the tocilizumab group, 20% in the pulse steroid group, and 12.5% in the group receiving both therapies. Their multivariate analysis, which accounted for key risk factors, showed no statistically significant differences in mortality outcomes among the three groups. The relatively lower mortality observed in this study compared to other reports may be attributed to the early initiation of immunomodulatory therapy—within three days of hospitalization—and the inclusion of only non-intubated patients (16).

In a study conducted in Turkey, Aslan et al. (22) divided ICU patients into three treatment arms: pulse steroid, tocilizumab, and combination therapy. Although no statistically significant differences in mortality was detected among the groups, the reported mortality rates remained high: 55% in the pulse steroids group, 60% in the tocilizumab group, and 50% in the combined treatment group (22).

Kılıç Erol et al. (23) evaluated 208 critically ill COVID-19 patients admitted to the ICU, of whom 114 received corticosteroids and 94 did not. In their analysis, overall mortality was higher among patients treated with steroids; however, after adjusting for independent predictors such as age, SOFA score, renal replacement therapy, and inotropic support, corticosteroid use was not identified as an independent determinant of mortality (23).

In contrast, our study of 200 patients with cytokine storm demonstrated that high-dose methylprednisolone and tocilizumab provided comparable efficacy, with no significant difference in mortality outcomes between the two treatment groups. These findings collectively suggested that, although crude analyses associated corticosteroid use with worse outcomes in severe COVID-19, after adjustment for confounding factors, corticosteroids did not independently increase mortality and may have represented a viable alternative to IL-6 blockade in the setting of cytokine storm.

In our study population, which consisted of patients with cytokine storm treated with either tocilizumab or pulse steroid therapy, the overall mortality rate was 35%. Specifically, mortality was 36% in the tocilizumab group and 34% in the pulse steroid group, and statistical analysis revealed no significant difference in mortality between the two treatment arms (p>0.05). These results were consistent with the findings reported by Kumar et al. (15).

Study Limitations

It is important to recognize certain limitations of this research. Most notably, the retrospective design, single-center cohort methodology, and limited sample size constrain the extent to which these results can be generalized. Another limitation was the lack of detailed documentation regarding additional treatments administered to patients beyond immunomodulatory agents.

Furthermore, the absence of measurements of cytokine levels, particularly IL-6, in laboratory evaluations posed a limitation. An additional limitation was the exclusion of patients who received combination therapy with tocilizumab and high-dose steroids for cytokine storm, which precluded direct comparison between monotherapy and combination therapy.

Furthermore, patients with severe and critical COVID-19 experiencing a cytokine storm who received only standard care were not included as a control group, meaning that the treatment groups were not compared with a standard-care group, which represents an additional limitation of the study.

Finally, potential confounders such as circulating viral variants, vaccination rates, and temporal changes in clinical management during the study period (February-September 2021) could have influenced the outcomes and should be considered when interpreting the results.

Conclusion

Early identification of a cytokine storm and timely initiation of immunomodulatory therapy can lead to favorable treatment outcomes. Such treatment modalities are essential to control the excessive inflammatory response observed in COVID-19 patients with a cytokine storm. In our comparative analysis of high-dose methylprednisolone and tocilizumab, both agents demonstrated comparable efficacy in reducing inflammatory markers and showed similar mortality outcomes.

Based on our findings, high-dose methylprednisolone, due to its lower cost and accessibility, may serve as a viable alternative to tocilizumab in the treatment of COVID-19-related cytokine storm.

Ethics

Ethics Committee Approval: The Ethics Commission of University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital authorized the study and waived the necessity for informed consent (approval no: 154; date: August 10, 2022). The present study was conducted in accordance with the provisions of the Declaration of Helsinki (2013).

Informed Consent: Given the retrospective design, the requirement for informed consent was waived.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.F.A., O.U., M.O., C.D., Concept: Ö.F.A., İ.S., O.U., S.K., Ş.K., Design: Ö.F.A., F.K., Ş.K., Data Collection or Processing: Ö.F.A., F.K., O.U., M.O., Ş.K., Analysis or Interpretation: Ö.F.A., İ.S., F.K., M.O., C.D., Literature Search: Ö.F.A., İ.S., O.U., S.K., Ş.K., C.D., Writing: Ö.F.A., C.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Gönenç Ortaköylü M, Akbaba Bağcı B, Tural Onur S, Özen T, Tokgöz Akyıl F, Akalın Karaca ES. Impact of nosocomial COVID-19 infection among hospitalized patients with respiratory diseases. Bagcilar Med Bull. 2023;8(4):341-348.
2. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm; what we know so far. Front Immunol. 2020;11:1446.
3. Shimizu M. Clinical features of cytokine storm syndrome. In: Cron RQ, Behrens EM, editors. Cytokine storm syndrome [Internet]. Cham: Springer; 2019. p. 31-41. [cited 2022 Nov 25]. Available from:https://link.springer.com/chapter/10.1007/978-3-030-22094-5_3
4. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846-848. Erratum in: Intensive Care Med. 2020;46(6):1294-1297.
5. Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, von Bergwelt-Baildon M, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol. 2020;146(1):128-136.e4.
6. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-1062. Erratum in: Lancet. 2020;395(10229):1038. Erratum in: Lancet. 2020;395(10229):1038.
7. Republic of Turkey, Ministry of Health. COVID-19 (SARS-CoV-2 infection) anti-cytokine–anti-inflammatory treatments, coagulopathy management: Scientific Advisory Board Report. Ankara: Republic of Turkey, Ministry of Health; 2020.
8. Baschant U, Tuckermann J. The role of the glucocorticoid receptor in inflammation and immunity. J Steroid Biochem Mol Biol. 2010;120(2-3):69-75.
9. Ronchetti S, Migliorati G, Bruscoli S, Riccardi C. Defining the role of glucocorticoids in inflammation. Clin Sci (Lond). 2018;132(14):1529-1543.
10. Bruscoli S, Puzzovio PG, Zaimi M, Tiligada K, Levi-Schaffer F, Riccardi C. Glucocorticoids and COVID-19. Pharmacol Res. 2022;185:106511.
11. Agarwal A, Hunt B, Stegemann M, Rochwerg B, Lamontagne F, Siemieniuk RA, et al. A living WHO guideline on drugs for COVID-19. BMJ. 2020;370:m3379. Update in: BMJ. 2020;371:m4475. Update in: BMJ. 2021;372:n860. Update in: BMJ. 2021;374:n1703. Update in: BMJ. 2021;374:n2219. Erratum in: BMJ. 2022;377:o1045.
12. RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693-704.
13. Roche. Doing now what patients need next [Internet]. [cited 2020 Nov 27]. Available from:https://www.roche.com/media/releases/med-cor-2020-03-19.htm.
14. Campochiaro C, Della-Torre E, Cavalli G, De Luca G, Ripa M, Boffini N, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. Eur J Intern Med. 2020;76:43-49.

15. Kumar V, Kashyap AK, Kaur S, John M, Sibia RS, Chopra V, et al. Comparison of tocilizumab and high-dose methylprednisolone pulse on outcomes in severe corona virus disease-2019: TAME-COVID, a retrospective multicentric study. Int J Appl Basic Med Res. 2021;11(4):263-269.

16. Mikulska M, Nicolini LA, Signori A, Di Biagio A, Sepulcri C, Russo C, et al. Tocilizumab and steroid treatment in patients with COVID-19 pneumonia. PLoS One. 2020;15(8):e0237831.

17. Lim PC, Wong KL, Rajah R, Chong MF, Chow TS, Subramaniam S, et al. Comparing the efficacy of tocilizumab with corticosteroid therapy in treating COVID-19 patients: a systematic review and meta-analysis. Daru. 2022;30(1):211-228.

18. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transplant. 2020;39(5):405-407.

19. Edalatifard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S, et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. Eur Respir J. 2020;56(6):2002808.

20. Fusina F, Albani F, Granato E, Meloni A, Rozzini R, Sabatini T, et al. Effect of corticosteroids on mortality in hospitalized COVID-19 patients not receiving invasive mechanical ventilation. Clin Pharmacol Ther. 2021;109(6):1660-1667.

21. Klopfenstein T, Zayet S, Lohse A, Balblanc JC, Badie J, Royer PY, et al. Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. Med Mal Infect. 2020;50(5):397-400.

22. Aslan M, Sabaz MS, Yilmaz R, Aşar S, Şeker YT, Hergünsel GO. Effect of pulsed corticosteroids and tocilizumab on hyperinflammation in COVID-19 patients with acute respiratory distress syndrome. Journal of Acute Disease. 2021;10(5):195-201.

23. Kılıç Erol P, Kaya E, Şahin AS. Corticosteroid use in severe COVID-19 and factors associated with secondary infection and mortality among patients admitted to the intensive care unit. Bagcilar Med Bull. 2025;10(2):182-192.