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Corticosteroid Use in Severe COVID-19 and Factors Associated with Secondary Infection and Mortality Among Patients Admitted to the Intensive Care Unit

Yoğun Bakım Ünitesinde Takip Edilen COVID-19 Hastalarında Kortikosteroid Kullanımının Sekonder Enfeksiyon Üzerine Etkisi

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Abstract

Objective: To assess the outcomes of corticosteroid usage in Coronavirus disease-2019 (COVID-19) patients treated in the intensive care unit (ICU) and determine factors associated with secondary infection and mortality.

Method: This retrospective analysis involved data from patients admitted to the ICU for COVID-19 treatment between April 1, 2020, and December 31, 2021. The medical records of 114 patients who received corticosteroids and the records of 94 patients who did not, were comprehensively reviewed, and information about demographic characteristics, clinical features, and laboratory results was recorded.

Results: The 28-day mortality rate was 52.9% (n=110), the overall mortality was 61.5% (n=128), and secondary infection occurred in 52.9% (n=110) of COVID-19 ICU patients. Steroid users had longer ICU stays (p=0.001), longer intubation periods (p<0.001), a higher need for positive inotropic therapy (p<0.001), and higher APACHE II scores (p=0.014). Overall mortality was higher in steroid recipients (p=0.001), while 28-day mortality was similar (p=0.061). The frequency of secondary infections in COVID-19 ICU patients was significantly higher in the steroid group (p=0.003). Multivariable logistic regression analysis indicated that extended ICU stays [odds ratio (OR): 1.174] and prolonged intubation (OR: 1.317) were independently associated with secondary infections. Similarly, older age (OR: 1.079), need for renal replacement therapy (OR: 7.600), need for positive inotropic therapy (OR: 25.627), and high SOFA score (OR: 1.528) were independently associated with mortality.

Öz

Amaç: Yoğun bakım ünitesinde (YBÜ) tedavi gören Koronavirüs hastalığı-2019 (COVID-19) hastalarında kortikosteroid kullanımının sonuçlarını değerlendirmek ve ikincil enfeksiyon ve mortalite ile ilişkili faktörleri belirlemektir.

Yöntem: Bu retrospektif analiz, 1 Nisan 2020-31 Aralık 2021 tarihleri arasında COVID-19 tedavisi için kabul edilen hastaların verilerini içermektedir. Kortikosteroid alan 114 ve almayan 94 hastanın tıbbi kayıtları kapsamlı bir şekilde incelenerek demografik özellikleri, klinik özellikleri ve laboratuvar sonuçlarına ilişkin bilgiler kaydedildi.

Bulgular: Hastaların 28 günlük mortalite oranı %52,9 (n=110), genel mortalite %61,5 (n=128) ve sekonder enfeksiyon %52,9 (n=110) olarak gerçekleşti. Steroid kullananlarda yoğun bakımda kalış süresi (p=0,001) daha uzun, entübasyon süreleri (p<0,001) daha uzun, pozitif inotropik tedavi ihtiyacı daha yüksek (p<0,001) ve APACHE II skorları daha yüksekti (p=0,014). Genel mortalite steroid alanlarda daha yüksekti (p=0,001), 28 günlük mortalite ise benzerdi (p=0,061). COVID-19 yoğun bakım hastalarında sekonder enfeksiyon sıklığı steroid grubunda anlamlı olarak daha yüksekti (p=0,003). Çok değişkenli lojistik regresyon analizi, yoğun bakımda uzun süreli kalış süresinin [olasılık oranı (OO): 1,174] ve uzun süreli entübasyonun (OO: 1,317) ikincil enfeksiyonlarla bağımsız olarak ilişkili olduğunu gösterdi. Benzer şekilde ileri yaş (OO: 1,079), renal replasman tedavisi ihtiyacı (OO: 7,600), pozitif inotropik tedavi ihtiyacı (OR: 25,627) ve yüksek SOFA skoru (OO: 1,528) bağımsız olarak mortaliteyle ilişkiliydi.

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Abstract

Conclusion: According to the findings of the study, although corticosteroid use in severe COVID-19 cases does not appear to increase the risk of secondary infections or mortality, the decision to use corticosteroids should be made with careful consideration of the patient's clinical condition. Additionally, more comprehensive and in-depth studies on the use of corticosteroids in COVID-19 patients are needed.

Keywords: Anti-inflammatory agents, Coronavirus infections, COVID-19, COVID-19 drug treatment, dexamethasone, methylprednisolone

Öz

Sonuç: Çalışmanın bulgularına göre, şiddetli COVID-19 olgularında kortikosteroid kullanımı sekonder enfeksiyon veya mortalite riskini artırmıyor gibi görünse de, kortikosteroid kullanım kararı olgunun klinik durumuna göre titizlikle verilmelidir. Ayrıca, COVID-19 hastalarında kortikosteroid kullanımına dair daha geniş kapsamlı ve derinlemesine araştırmalara ihtiyaç duyulmaktadır.

Anahtar kelimeler: Anti-enflamatuar ajanlar, COVID-19, COVID-19 da kullanılan ilaç tedavileri, deksametazon, Koronavirüs enfeksiyonu, metilprednizolon

Introduction

The clinical presentation of Coronavirus disease-2019 (COVID-19) ranges from asymptomatic/mild respiratory disease to severe pneumonia, hypoxemic lung failure, multi-system organ dysfunction, and death (1). Studies performed early in the pandemic demonstrated that acute respiratory distress syndrome (ARDS) occurred in approximately 17-41% of cases (2,3), while cytokine release syndrome was also implicated in severe COVID-19 (4). Furthermore, postmortem data showed that patients who died due to COVID-19 had high levels of inflammatory cytokines, tissue necrosis and interstitial macrophage and monocyte infiltrations in the lung, heart and gastrointestinal mucosa (5). Even during the initial waves of the pandemic, these data showed the importance of alleviating extreme immune activity in COVID-19, which encouraged trials focusing on anti-inflammatory therapies (4). Various agents have been used for this purpose, including immunoglobulin, colchicine, janus kinase inhibitor inhibitors, interleukin (IL)-6 inhibitors, IL-1 inhibitors, anti-tumor necrosis factor-α agents, and corticosteroids (6).

Corticosteroids, which exert broad anti-inflammatory effects, are potent immunomodulatory medications that alleviate hyperinflammation (7). Initially, the World Health Organization (WHO) and infectious disease authorities had recommended avoiding systemic corticosteroids in COVID-19 patients due to limited improvements in mortality and the fact that prior studies involving patients with severe Middle-East respiratory syndrome (MERS) had shown delayed RNA clearance with glucocorticoids (8,9). Today, WHO recommends corticosteroids in severe or critical COVID-19 patients, especially in COVID-19 cases requiring respiratory support (10,11). This shift in guidance emerged as a result of numerous studies and meta-analyses that shared clinical evidence for the benefits of corticotherapy in patients with severe COVID-19 (2,7,12,13). Nonetheless, for the beneficial use of corticosteroids, COVID-19 patients need to be well targeted because patients requiring low-flow oxygen do not appear to experience the same benefits as those receiving ventilation or high-flow oxygen support (14).

As the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus continues to mutate over time, the possible role of glucocorticoids in different virus mutations will remain a topic of interest [15). Reviewing evidence to offer insights into the efficacy and safety of corticosteroids in the evolving landscape of COVID-19 can provide valuable guidance for future clinical interventions. In this study, we aimed to investigate the relationship between corticosteroids and clinical outcomes in patients followed up in the intensive care unit (ICU) due to COVID-19.

Materials and Methods

The medical records of patients diagnosed with COVID-19 who were admitted to the ICU of our Anesthesia Department, between 1 April 2020 and 31 December 2021, were examined. Inclusion criteria were: Having at least one positive SARS-CoV-2 polymerase chain reaction test in nasopharyngeal or oropharyngeal swab samples; being followed up in the ICU; and being 18 years of age or older. Exclusion criteria were pregnancy, malignancy, immunodeficiency, chronic organ failure, being in the postoperative period, receiving immunosuppressive/anti-cytokine therapy, secondary infection before treatment, culture growth in the ICU, ICU stay of less than 48 hours, and age younger than 18 years. The study plan was approved by the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, Clinical Research Ethics Committee (date/number: February 2022/#2022/34).

The medical records of the patients were examined in detail, and information on demographic characteristics, clinical features, and laboratory results relative to patients with and without corticosteroid therapy in addition to standard

treatment were recorded. Baseline values of laboratory measurements (IL-6, D-dimer, ferritin, fibrinogen) were recorded and longitudinal samples were assessed to determine the lowest, highest, and average values for several inflammatory parameters [C-reactive protein (CRP), procalcitonin, complete blood count parameters]. The emergence of secondary infection and mortality (28-day mortality and total mortality) was recorded as outcomes of interest.

All patients included in the study received the standard care specified in the COVID-19 treatment guideline published by the Ministry of Health, and the COVID-19 anticytokine, anti-inflammatory treatment guideline. Favipiravir, as antiviral treatment, and low molecular weight heparin as deep vein thrombosis prophylaxis were administered to all patients without contraindications. Corticosteroid treatment was initiated in patients with ARDS whose clinical condition worsened and whose oxygen demand or acute phase reactants had increased. The standardized daily therapy was 300 mg methylprednisolone or 56.3 mg dexamethasone (equivalent to 1500 mg hydrocortisone). According to respiratory symptoms and peripheral partial oxygen saturation values, patients were given oxygen support with a face mask, reservoir mask, or high-flow nasal cannula. When these interventions were inadequate, patients received non-invasive or invasive mechanical ventilation support. Fluid therapy was administered according to the fluid status of the patient, and vasopressor support was initiated in patients who did not respond to fluid therapy. Blood, urine, tracheal aspirate, and, if necessary, wound site cultures were obtained when there were findings suggestive of secondary infection (new onset fever, leukocyte count of ≥12,000, procalcitonin value of ≥0.5). The results of these cultures were recorded, and the patients received empirical antibiotic therapy to cover detected or possible microorganisms.

APACHE II Score

The APACHE II score developed by Knaus et al. (16) is widely used to assess disease severity and mortality in patients hospitalized in intensive care units. A total score is calculated using the acute physiologic score, age, and parameters indicating chronic disease status. Although the theoretical maximum score is 71, it is rarely seen above 50. An increase in the total score indicates a negative change in health status and is associated with an increased risk of mortality (16).

Sequential Organ Failure Assessment (SOFA)

SOFA was developed by the European Society of Intensive Care Medicine in 1996 to assess the acute morbidity of critical illness by defining the degree of organ failure due to sepsis. A total score can be calculated by summing the scores given to six organ systems (respiratory, cardiovascular, central nervous system, renal, coagulation, and liver) ranging from 0 to 4. The total score can be up to 24, and mortality increases as the score increases (17).

Statistical Analysis

Two-tailed p-values of less than 0.05 were considered statistically significant. SPSS version 25.0 (IBM, Armonk, NY, USA) was used for statistical analysis. The Kolmogorov-Smirnov test was used to examine the conformity of the variables to normal distribution. Descriptive statistics were presented using median (25^{th}-75^{th} percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables. Due to non-normal distributions, continuous variables were analyzed with the Mann-Whitney U test. Categorical variables were analyzed with the Pearson chi-square test or Fisher's Exact test. Logistic regression analyses were performed to determine significant factors independently associated with secondary infection or mortality. Variables were analyzed using univariable logistic regression , and statistically significant variables were included in multivariable logistic regression.

Results

A total of 208 COVID-19 patients treated in the ICU were included in this study. One hundred-fourteen (54.8%) had received steroid treatment and 94 (45.2%) had not received steroid treatment. Overall, 59.1% were male, 40.9% were female, and the median age was 68 (55-76) (range: 27-89) years. The 28-day mortality rate was 52.9% (n=110), the overall mortality was 61.5% (n=128), and the secondary infection rate was 52.9% (n=110). Length of ICU stay and intubation were 12 (2-57) days and 6 (0-57) days, respectively. Age (p=0.788) and sex distribution (p=0.653) were similar in the steroid and non-steroid groups. The frequency of comorbidities (p=0.029), especially neurological disease (p=0.020), was higher in the non-steroid group. The length of ICU stay (p=0.001), the length of intubation (p<0.001), and the frequency of needing positive inotropic therapy (p<0.001) were higher in steroid users. While the overall mortality rate was significantly higher in the steroid group (p=0.001), the groups were similar in terms of 28-day mortality rate (p=0.061). APACHE II score, was significantly higher in the steroid group (p=0.014), while there was no

difference in terms of SOFA score (p=0.968). There was no difference between the groups in terms of baseline values for CRP (0.393), procalcitonin (p=0.338), leukocyte count (p=0.965), neutrophil count (p=0.390), IL-6 (p=0.313), D-dimer (p=0.501), ferritin (p=0.071) and fibrinogen (p=0.096). Baseline lymphocyte (p=0.001) and monocyte counts (p<0.001) were lower in the steroid group (Table 1).

Table 1. Summary of demographics, outcomes and laboratory measurements with regard to steroid use

		Steroid use		
	All patients (n=208)	**No (n=94)**	**Yes (n=114)**	**p**
Age	68 (55-76)	67 (54-76)	68 (55-76)	0.788
Sex				
Male	123 (59.1%)	54 (57.5%)	69 (60.5%)	0.653
Female	85 (40.9%)	40 (42.5%)	45 (39.5%)	
Comorbidity (1)	164 (78.9%)	81 (86.2%)	83 (72.8%)	0.029
Cardiovascular diseases	118 (56.7%)	60 (63.8%)	58 (50.9%)	0.061
Endocrine disorders	75 (36.1%)	37 (39.4%)	38 (33.3%)	0.368
Respiratory diseases	44 (21.2%)	21 (22.3%)	23 (20.2%)	0.834
Organ failure	22 (10.6%)	13 (13.8%)	9 (7.9%)	0.247
Neurological diseases	32 (15.4%)	21 (22.3%)	11 (9.7%)	0.020
Others*	12 (5.7%)	4 (4.3%)	8 (7.0%)	0.581
Length of stay in ICU, days	12 (7-20)	10.5 (5-18)	13 (10-23)	0.001
Duration of intubation, days	6 (0-13.5)	2 (0-11)	9 (2-16)	<0.001
Renal replacement therapy need	51 (24.5%)	20 (21.3%)	31 (27.2%)	0.409
Positive inotropic therapy need	131 (63.0%)	46 (48.9%)	85 (74.6%)	<0.001
28-days mortality	110 (52.9%)	43 (45.7%)	67 (58.8%)	0.061
Overall mortality	128 (61.5%)	46 (48.9%)	82 (71.9%)	0.001
APACHE II score	21.5 (15.0-29.0)	19.0 (14.0-29.0)	24.5 (18.0-30.0)	0.014
SOFA score	5.0 (4.0-8.5)	5.5 (4.0-9.0)	5.0 (4.0-8.0)	0.968
CRP				
Baseline	138.0 (79.9-224.4)	129.3 (68.2-214.4)	140.2 (84.1-232.1)	0.393
Lowest	39.0 (17.2-86.4)	59.71 (23.9-139.9)	28.2 (14.2-51.9)	<0.001
Highest	241.8 (145.4-346.9)	233.8 (121.5-349.9)	248.4 (162.8-338.5)	0.294
Average	122.61 (76.6-191.9)	144.0 (78.9-211.2)	114.2 (74.2-161.9)	0.106
Procalcitonin				
Baseline	0.32 (0.14-1.00)	0.31 (0.16-0.97)	0.33 (0.12-1.02)	0.338
Lowest	0.14 (0.07-0.39)	0.19 (0.08-0.55)	0.10 (0.06-0.29)	0.014
Highest	3.13 (0.52-14.36)	2.42 (0.31-13.30)	4.53 (0.85-14.87)	0.302
Average	1.02 (0.22-3.67)	0.76 (0.20-4.50)	1.13 (0.24-3.25)	0.902
Leukocyte ($x10^3$)				
Baseline	9.5 (7.1-13.6)	9.3 (7.4-13.6)	9.8 (6.8-13.6)	0.965
Lowest	7.0 (5.2-9.0)	7.0 (5.1-9.2)	7.02 (5.4-9.0)	0.900
Highest	16.9 (11.6-24.4)	14.3 (10.2-21.7)	21.7 (13.7-26.7)	<0.001
Average	11.4 (8.8-15.3)	10.3 (7.9-13.7)	12.0 (9.7-16.0)	0.011
Neutrophil ($x10^3$)				
Baseline	8.1 (5.7-13.1)	8.0 (6.1-11.5)	8.7 (5.4-13.2)	0.390
Lowest	5.6 (3.7-7.6)	5.1 (3.2-7.9)	5.7 (4.5-7.5)	0.285
Highest	15.6 (10.3-22.4)	12.7 (8.5-19.6)	19.8 (13.2-23.63)	<0.001
Average	10.0 (7.1-14.1)	8.6 (5.7-12.6)	10.2 (7.9-14.8)	0.004

Table 1. Continued

		Steroid use		
	All patients (n=208)	**No (n=94)**	**Yes (n=114)**	**p**
Lymphocyte (x10³)				
Baseline	0.70 (0.60-1.15)	0.95 (0.60-1.40)	0.70 (0.60-0.90)	0.001
Lowest	0.40 (0.30-0.65)	0.60 (0.40-0.90)	0.30 (0.30-0.50)	<0.001
Highest	1.80 (1.10-2.90)	1.65 (1.10-2.40)	1.90 (1.10-2.90)	0.182
Average	1.07 (0.65-1.28)	1.09 (0.73-1.61)	1.02 (0.60-1.07)	0.001
Monocyte (x10³)				
Baseline	0.38 (0.27-0.63)	0.48 (0.34-0.78)	0.34 (0.25-0.48)	<0.001
Lowest	0.25 (0.16-0.39)	0.33 (0.21-0.50)	0.21 (0.13-0.29)	<0.001
Highest	0.91 (0.66-1.35)	0.91 (0.57-1.29)	0.90 (0.67-1.35)	0.474
Average	0.59 (0.40-0.74)	0.65 (0.43-0.82)	0.57 (0.38-0.70)	0.059
LDH, baseline	473.5 (328-651.5)	383 (295-560)	531 (366-695)	<0.001
IL-6, baseline	96.5 (44.3-235.6)	84.0 (43.3-207.2)	97.5 (48.1-275.6)	0.313
D-dimer, baseline	1.9 (1.0-4.3)	2.1 (1.0-4.6)	1.8 (1.0-3.9)	0.501
Ferritin, baseline	650.4 (318.8-1302.0)	540.8 (234.9-1224.0)	732.95 (362.9-1370.0)	0.071
Fibrinogen, baseline	580.5 (442-729)	519 (426-681)	589 (479-738)	0.096

Descriptive statistics were presented by using median (25th-75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables. (1) Patients may have more than one of the followings.
*Others: Rheumatologic disease, Behçet's disease, psychiatric disease, Down syndrome, multiple myeloma, prostate hyperplasia, ICU: Intensive care unit, IL: Interleukin, LDH: Lactate dehydrogenase, CRP: C-reactive protein, SOFA: Sequential Organ Failure Assessment

The frequency of secondary infection was significantly higher in the steroid group (p=0.003). There was no difference between the groups in terms of blood culture positivity (p=0.169), but urine culture positivity (p=0.035) and *Klebsiella pneumoniae* in urine culture (p=0.001) were more common in steroid recipients. The frequency of tracheal culture positivity (p=0.001) and *Klebsiella pneumoniae* presence in tracheal cultures (p<0.001) was significantly higher in steroid recipients (Table 2).

Multivariable logistic regression revealed that longer stay in the ICU [odds ratio (OR): 1.174, 95% confidence interval (CI): 1.070-1.287, p=0.001] and longer intubation duration (OR: 1.317, 95% CI: 1.150-1.509, p<0.001) were independently associated with secondary infection likelihood. In the univariate analysis, corticosteroid use was found to be associated with an increased risk of secondary infections, while in the multivariate analysis, no significant relationship was observed between corticosteroid use and the risk of secondary infections (OR: 0.828, 95% CI: 0.329-2.084, p=0.689) (Table 3).

Multivariable logistic regression revealed that higher age (OR: 1.079, 95% CI: 1.027-1.134, p=0.003), need for renal replacement therapy (OR: 7.600, 95% CI: 1.380-41.843, p=0.020), need for positive inotropic therapy (OR: 25.627, 95% CI: 6.261-104.902, p<0.001), and high SOFA score (OR: 1.528, 95% CI: 1.098-2.125, p=0.012) were independently associated with mortality likelihood. While corticosteroid use was found to increase mortality in the univariate analysis, it was not identified as one of the factors influencing mortality in the multivariate analysis (OR: 2.005, 95% CI: 0.579-6.944, p=0.272) (Table 4).

Discussion

The COVID-19 pandemic has placed an unforeseen burden on the global health system, requiring the world to react quickly to find different solutions, both for preventive and therapeutic purposes. One of the agents used for this purpose is a corticosteroid, which has strong anti-inflammatory properties (18). Systemic glucocorticoids are not routinely indicated in COVID-19, and their use is limited to cases with severe complications such as ARDS or the so-called "cytokine storm" (19). In this study, we examined a group of patients who were admitted for severe COVID-19 and received steroids (or not) based on available guidelines. We also investigated factors associated with mortality and secondary infections. Our data showed that steroid recipients had longer ICU stay and intubation periods, as well as higher APACHE II scores and increased inflammatory parameters. Notably, steroid recipients also had higher frequencies of positivity for urine and tracheal cultures - largely as a result of increased *Klebsiella*

Table 2. Summary of secondary infection and culture results with regard to steroid use

		Steroid use		
	All patients (n=208)	**No (n=94)**	**Yes (n=114)**	**p**
Secondary infection	110 (52.9%)	39 (41.5%)	71 (62.3%)	0.003
Blood culture positivity (1)	62 (29.8%)	23 (24.5%)	39 (34.2%)	0.169
Acinetobacter baumannii	13 (6.3%)	5 (5.3%)	8 (7.0%)	0.829
Klebsiella pneumoniae	30 (14.4%)	9 (9.6%)	21 (18.4%)	0.108
Corynebacterium spp.	3 (1.4%)	1 (1.1%)	2 (1.8%)	1.000
Candida spp.	21 (10.1%)	9 (9.6%)	12 (10.5%)	1.000
Pseudomonas aeruginosa	1 (0.5%)	0 (0.0%)	1 (0.9%)	1.000
Escherichia coli	3 (1.4%)	0 (0.0%)	3 (2.6%)	0.253
Enterococcus spp.	4 (1.9%)	2 (2.1%)	2 (1.8%)	1.000
Staphylococcus spp.	8 (3.9%)	3 (3.2%)	5 (4.4%)	0.732
Enterobacter spp.	1 (0.5%)	1 (1.1%)	0 (0.0%)	0.452
Others*	1 (0.5%)	1 (1.1%)	0 (0.0%)	0.452
Urine culture positivity (1)	63 (30.3%)	21 (22.3%)	42 (36.8%)	0.035
Acinetobacter baumannii	3 (1.4%)	1 (1.1%)	2 (1.8%)	1.000
Klebsiella pneumoniae	19 (9.1%)	1 (1.1%)	18 (15.8%)	0.001
Corynebacterium spp.	1 (0.5%)	1 (1.1%)	0 (0.0%)	0.452
Candida spp.	26 (12.5%)	8 (8.5%)	18 (15.8%)	0.171
Pseudomonas aeruginosa	1 (0.5%)	1 (1.1%)	0 (0.0%)	0.452
Escherichia coli	8 (3.9%)	4 (4.3%)	4 (3.5%)	1.000
Enterococcus spp.	7 (3.4%)	5 (5.3%)	2 (1.8%)	0.248
Staphylococcus spp.	2 (1.0%)	1 (1.1%)	1 (0.9%)	1.000
Enterobacter spp.	4 (1.9%)	1 (1.1%)	3 (2.6%)	0.628
Others	1 (0.5%)	0 (0.0%)	1 (0.9%)	1.000
Tracheal aspirate culture (1)	74 (35.6%)	22 (23.4%)	52 (45.6%)	0.001
Acinetobacter baumannii	19 (9.1%)	8 (8.5%)	11 (9.7%)	0.967
Klebsiella pneumoniae	36 (17.3%)	6 (6.4%)	30 (26.3%)	<0.001
Corynebacterium spp.	5 (2.4%)	4 (4.3%)	1 (0.9%)	0.178
Candida spp.	23 (11.1%)	6 (6.4%)	17 (14.9%)	0.084
Pseudomonas aeruginosa	3 (1.4%)	1 (1.1%)	2 (1.8%)	1.000
Escherichia coli	4 (1.9%)	1 (1.1%)	3 (2.6%)	0.628
Enterococcus spp.	1 (0.5%)	1 (1.1%)	0 (0.0%)	0.452
Staphylococcus spp.	5 (2.4%)	2 (2.1%)	3 (2.6%)	1.000
Enterobacter spp.	1 (0.5%)	0 (0.0%)	1 (0.9%)	1.000
Others	4 (1.9%)	0 (0.0%)	4 (3.5%)	0.128

Descriptive statistics were presented using frequency (percentage) for categorical variables. (1) Culture positivity counts are based on culture specimens and are calculated separately; thus, total numbers exceed patient counts.
*Others: Proteus mirabilis, moellerella wisconsensis, stenotrophomonas maltophilia, blastoschizomyces capitatus, gemella haemolysans, stenotrophomonas maltophilia

pneumoniae prevalence. Finally, the multivariate analyses revealed that steroid use was not independently associated with the development of secondary infections or mortality.

A meta-analysis of 20,197 patients reported that findings from both observational studies and randomized controlled trials confirmed the beneficial effect of corticosteroids on reducing the need for mechanical ventilation (12). Despite the presence of several large studies and meta-analyses on the topic, there are various studies with notable outcomes and notable findings. Tomazini et al. (20) reported that there was no difference in the duration of mechanical ventilation at 28 days with dexamethasone use among COVID-19 patients with moderate/severe ARDS. Sarkar et al. (21) reported that systemic steroid treatment was not effective in reducing the length of hospital stay. In a study

Table 3. Odds ratios for secondary infection, logistic regression analysis results

	Univariable		Multivariable	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.012 (0.993-1.032)	0.209		
Sex, Female	1.276 (0.732-2.225)	0.389		
Any comorbidity	1.158 (0.595-2.254)	0.666		
Cardiovascular diseases	1.226 (0.708-2.125)	0.467		
Endocrine disorders	0.870 (0.494-1.534)	0.630		
Respiratory diseases	0.685 (0.351-1.337)	0.268		
Organ failure	0.879 (0.363-2.127)	0.775		
Neurological diseases	0.872 (0.411-1.853)	0.722		
Other comorbidity	1.264 (0.388-4.119)	0.697		
Length of stay in ICU, days	1.245 (1.167-1.329)	<0.001	1.174 (1.070-1.287)	0.001
Duration of intubation, days	1.416 (1.291-1.552)	<0.001	1.317 (1.150-1.509)	<0.001
Renal replacement therapy need	2.692 (1.365-5.308)	0.004	1.360 (0.444-4.161)	0.590
Positive inotropic therapy need	10.907 (5.515-21.574)	<0.001	1.644 (0.558-4.839)	0.367
Steroid use	2.329 (1.332-4.070)	0.003	0.828 (0.329-2.084)	0.689
APACHE II score	1.005 (0.980-1.032)	0.682		
SOFA score	1.125 (1.030-1.229)	0.009	1.025 (0.872-1.205)	0.765
CRP, baseline	1.005 (1.002-1.008)	0.001	1.002 (0.997-1.007)	0.445
Procalcitonin, baseline	1.012 (0.982-1.043)	0.431		
Leukocyte ($x10^3$), baseline	0.991 (0.947-1.036)	0.685		
Neutrophil ($x10^3$), baseline	1.006 (0.959-1.055)	0.805		
Lymphocyte ($x10^3$), baseline	0.783 (0.488-1.256)	0.310		
Monocyte ($x10^3$), baseline	0.690 (0.336-1.415)	0.311		
LDH, baseline	1.000 (0.999-1.001)	0.655		
IL-6, baseline	1.000 (1.000-1.000)	0.362		
D-dimer, baseline	1.023 (0.990-1.058)	0.176		
Ferritin, baseline	1.000 (1.000-1.000)	0.727		
Fibrinogen, baseline	1.000 (0.999-1.001)	0.587		
Nagelkerke R^2	-		0.699	

OR: Odds ratio, CI: Confidence interval, ICU: Intensive care unit, IL: Interleukin, LDH: Lactate dehydrogenase, CRP: C-reactive protein, SOFA: Sequential Organ Failure Assessment

conducted by Emgin et al. (22) with COVID-19 patients in the ICU, the length of stay was reported to be longer in patients who received dexamethasone treatment. In the present study, ICU stay, intubation duration, need for positive inotropic therapy, and APACHE-II score were higher in steroid-treated patients. These relationships are not surprising as the present study included patients who had severe COVID-19 (admitted to the ICU) and steroid recipients were those who required advanced treatment due to their clinical and laboratory prognosis.

Secondary bacteremia is an important complication that can lead to a poor prognosis in COVID-19 patients and requires an appropriate treatment strategy, especially for patients with concomitant predisposing factors. Given that steroids can frequently obscure infection indicators by reducing body temperature and levels of acute phase proteins like CRP, it is essential to be cautious about potential secondary infections and conduct thorough assessments when employing steroid treatment for COVID-19 (23). Contrary to the results of a previous study evaluating the follow-up of MERS coronavirus infection in the ICU (8), no increased risk of bacterial infection or delayed viral clearance was reported when using corticosteroids in managing COVID-19 patients requiring oxygen support (7,19). Corticosteroids are reported to be important options in criticallyill COVID-19 patients, particularly since they have been suggested to have no impact on secondary infection (24). Similarly, Abelenda-Alonso et al.

Table 4. Odds ratios for mortality, logistic regression analysis results

	Univariable		Multivariable	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.050 (1.027-1.073)	<0.001	1.079 (1.027-1.134)	0.003
Sex, female	1.153 (0.652-2.040)	0.624		
Any comorbidity	2.056 (1.049-4.031)	0.036	0.713 (0.138-3.675)	0.686
Cardiovascular diseases	1.322 (0.753-2.322)	0.331		
Endocrine disorders	0.987 (0.552-1.765)	0.964		
Respiratory diseases	0.779 (0.397-1.531)	0.469		
Organ failure	0.892 (0.363-2.193)	0.803		
Neurological diseases	1.728 (0.755-3.953)	0.195		
Other comorbidity	1.267 (0.369-4.352)	0.707		
Length of stay in ICU, days	1.024 (0.995-1.054)	0.107		
Duration of intubation, days	1.219 (1.144-1.298)	<0.001	1.041 (0.965-1.122)	0.302
Renal replacement therapy need	3.853 (1.756-8.451)	0.001	7.600 (1.380-41.843)	0.020
Positive inotropic therapy need	35.385 (16.009-78.209)	<0.001	25.627 (6.261-104.902)	<0.001
Steroid use	2.674 (1.505-4.751)	0.001	2.005 (0.579-6.944)	0.272
Seconder infection	7.105 (3.775-13.372)	<0.001	0.977 (0.220-4.336)	0.976
APACHE II score	1.075 (1.039-1.113)	<0.001	1.016 (0.949-1.087)	0.656
SOFA score	1.526 (1.315-1.771)	<0.001	1.528 (1.098-2.125)	0.012
CRP, baseline	1.007 (1.003-1.010)	<0.001	1.004 (0.998-1.011)	0.193
Procalcitonin, baseline	0.974 (0.931-1.019)	0.255		
Leukocyte ($x10^3$), baseline	1.008 (0.962-1.056)	0.735		
Neutrophil ($x10^3$), baseline	1.018 (0.968-1.070)	0.490		
Lymphocyte ($x10^3$), baseline	0.983 (0.817-1.183)	0.860		
Monocyte ($x10^3$), baseline	0.362 (0.166-0.790)	0.011	0.402 (0.060-2.710)	0.349
LDH, baseline	1.003 (1.001-1.004)	<0.001	1.000 (0.998-1.002)	0.988
IL-6, baseline	1.000 (1.000-1.000)	0.618		
D-dimer, baseline	1.041 (0.998-1.086)	0.063		
Ferritin, baseline	1.000 (1.000-1.000)	0.707		
Fibrinogen, baseline	1.003 (1.001-1.004)	0.001	1.002 (0.999-1.006)	0.232
Nagelkerke R^2	-		0.775	

OR: Odds ratio, CI: Confidence interval, ICU: Intensive care unit, IL: Interleukin, LDH: Lactate dehydrogenase, CRP: C-reactive protein, SOFA: Sequential Organ Failure Assessment

(25) reported that there was no association between steroid use and the development of nosocomial bloodstream infections in patients with severe COVID-19 pneumonia. In a study evaluating the outcomes of COVID-19 patients admitted to the ICU in two different hospitals, it was reported that immunosuppressive treatments such as steroids and tocilizumab were not associated with an increased risk of bacteremia. In addition, it was reported that those who developed bacteremia among COVID-19 patients in the ICU had a higher SOFA score, were intubated more frequently and for longer durations, stayed in the ICU longer, and had higher mortality (26). In the present study, although the prevalence of secondary infection was found to be higher in steroid recipients compared to non-recipients, in multivariable analysis, we found that this increase in secondary infection was independently associated with longer ICU stay and longer intubation. There was no independent relationship between steroid use and the risk of secondary infection. Our results are consistent with the information in the literature. However, this does not change the fact that the decision to use corticosteroids should be made cautiously to prevent the risk of secondary infections. This is because there are also studies in the literature reporting opposite results.In a study evaluating COVID-19 patients admitted to an ICU, dexamethasone treatment was associated with a threefold

increase in the risk of pulmonary aspergillosis (27). In a retrospective study, it was reported that steroid treatment increased the risk of non-respiratory nosocomial bacterial infections, while male sex, advanced age, and ICU need were found to be risk factors for bacteremia (23). Of note, both studies centered around specific pathogens (23,27) which may explain the differences in results. In addition, prophylactic antimicrobial treatment protocols can vary from institution to institution, and it is possible that other factors contributed to these conflicting findings, including drug access, management guidelines, and antibiotic resistance patterns.

In COVID-19, corticosteroids (dexamethasone, hydrocortisone or methylprednisolone) have been reported to increase the chances of survival (7). The RECOVERY study was the first to evaluate the effect of dexamethasone treatment on mortality in COVID-19 patients who required oxygen therapy or mechanical ventilation. The authors reported that 28-day mortality was lower with dexamethasone (6 mg once daily for up to 10 days) in patients who received invasive mechanical ventilation or oxygen support; but no difference was found in patients without respiratory support (2). In a prospective meta-analysis by the WHO Rapid Evidence Assessment for COVID-19 Treatments Working Group, evaluating data from 12 countries from February 26, 2020 to June 9, 2020, it was reported that systemic corticosteroids were associated with lower 28-day all-cause mortality in patients with critical COVID-19 compared to usual care or placebo (13). In another retrospective study of COVID-19 patients in the ICU, corticosteroid administration was found to significantly reduce the likelihood of 28-day mortality (24). A recent meta-analysis evaluating the results of fifteen randomized controlled trials reported that in patients with severe and critical COVID-19, glucocorticoid therapy reduced the risk of all-cause mortality compared to conventional therapy, but no difference was found in those with mild disease (15). In another meta-analysis, mortality was shown to be significantly reduced with the use of corticosteroids (12). In the present study, mortality was higher in severe COVID-19 cases with steroid use in univariate analyses. However, in the multivariable model, this significance disappeared, and the use of steroids in treatment was not one of the factors independently affecting the risk of mortality. Factors identified included higher age, higher SOFA score, need for positive inotropic drugs, and need for renal replacement therapy. There are other studies reporting similar results. In a meta-analysis evaluating the efficacy and safety of steroids in COVID-19 (with data from randomized controlled trials and cohorts), there was no association between systemic glucocorticoid use and mortality in COVID-19 patients (21). Tomazini et al. (20) reported no difference in 28-day mortality among recipients and non-recipients of dexamethasone therapy after being diagnosed with moderate or severe ARDS. In contrast, a previous meta-analysis reported that overall mortality increased with the use of glucocorticoids in hospitalized patients who did not need respiratory support (28). Despite varying levels of evidence and partially conflicting results, it is evident that corticosteroids should not be used in COVID-19 cases that do not require respiratory support, but this therapy must be considered in patients requiring respiratory support. In patients requiring respiratory support, particularly those with advanced age, renal replacement therapy, positive inotropic therapy, and high SOFA scores, the decision to use corticosteroids should be made with caution. The variables included in the model used for the analyses may have influenced the results obtained in the study. Additionally, differences in the type, dose, and duration of corticosteroid protocols may further explain the heterogeneity in the reported evidence.When reviewing the existing literature regarding the use of steroids in COVID-19 cases, it is clear that physicians must exercise caution when making decisions about steroid utilization. The primary determining factor for initiating corticosteroid therapy in COVID-19 appears to be the requirement for respiratory support and overall clinical condition. Nonetheless, the decision for corticosteroid treatment should not be solely based on the severity of disease, but should also include consideration of the benefits and risks on a case-by-case basis (19). Although corticosteroids are currently widely used in the treatment of severe COVID-19 patients on respiratory support, many aspects of their use, such as the preferred agent, optimal dose and duration of treatment, are yet to be clarified (7). In addition, we believe that it is important to continuously update the information on this issue. It should be noted that the use of steroids in this population may have negative effects on both mortality and secondary infections.To better prepare for future outbreaks and reduce mortality among COVID-19 patients, a global effort is essential to develop novel treatments targeting both the clinical aspects of COVID-19 and the hyperinflammatory response triggered by the infection.

Study Limitations

This study has notable limitations, including its retrospective and single-center design, which restricts the generalization of results. A significant constraint is the absence of specific

data regarding the decision to administer steroids to COVID-19 ICU patients. The variation in clinical severity between patient groups may have influenced the findings. Additionally, the study did not investigate different types, doses, or durations of corticosteroid treatment. The study also did not consider various SARS-CoV-2 variants. Despite these limitations, the data provide valuable insights into corticosteroid use in treating severe COVID-19 cases.

Conclusion

Our results demonstrated that while corticosteroid use in critically ill COVID-19 patients was associated with increased mortality and secondary infections in univariate analyses, this association was not confirmed in multivariate analyses. The primary independent factors contributing to an increased risk of secondary infections were identified as prolonged ICU stay and extended duration of intubation. Furthermore, advanced age, the need for renal replacement therapy, the requirement for positive inotropic support, and a high SOFA score were determined to be independent predictors of increased mortality. In this context, it can be concluded that decisions regarding the use of corticosteroids in severe COVID-19 cases should be made with careful consideration of the individual clinical condition of each patient. To assess whether the effects of corticosteroid use are influenced by SARS-CoV-2 variants or other factors, broader and more comprehensive prospective studies involving various viral variants are needed.

Ethics

Ethics Committee Approval: The study plan was approved by the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, Clinical Research Ethics Committee (date/number: February 2022/#2022/34).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: P.K., E.K., A.S.Ş., Concept: A.S.Ş., Design: A.S.Ş., Data Collection or Processing: P.K., Analysis or Interpretation: P.K., A.S.Ş., Literature Search: P.K., Writing: P.K., E.K., A.S.Ş.

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References

1. Huang X, Wei F, Hu L, Wen L, Chen K. Epidemiology and clinical characteristics of COVID-19. Arch Iran Med. 2020;23(4):268-271.
2. 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.
3. Villar J, Confalonieri M, Pastores SM, Meduri GU. Rationale for prolonged corticosteroid treatment in the acute respiratory distress syndrome caused by coronavirus disease 2019. Crit Care Explor. 2020;2(4):e0111.
4. Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J Autoimmun. 2020;111:102452.
5. Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, et al. [A pathological report of three COVID-19 cases by minimal invasive autopsies]. Zhonghua Bing Li Xue Za Zhi. 2020;49(5):411-417. Chinese.
6. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol. 2020;39(7):2085-2094.
7. Annane D. Corticosteroids for COVID-19. J Intensive Med. 2021;1(1):14-25.
8. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. Am J Respir Crit Care Med. 2018;197(6):757-767.
9. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020;368(6490):473-474.
10. World Health Organization, Coronavirus disease (COVID-19): Corticosteroids, including dexamethasone. Available from: https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-covid-19-dexamethasone#:~:text=Patients%20with%20severe%20or%20critical%20COVID%2D19%20should%20be%20given,critical%20COVID%2D19%20receive%20corticosteroids., access date: 11.10.2023.
11. Salton F, Confalonieri P, Meduri GU, Mondini L, Trotta L, Barbieri M, et al. Theory and practice of glucocorticoids in COVID-19: Getting to the heart of the matter-a critical review and viewpoints. Pharmaceuticals (Basel). 2023;16(7):924.
12. van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. Crit Care. 2020;24(1):696.
13. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group; Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis. JAMA. 2020;324(13):1330-1341.
14. Tortajada C, Colomer E, Andreu-Ballester JC, Esparcia A, Oltra C, Flores J. Corticosteroids for COVID-19 patients requiring oxygen support? Yes, but not for everyone: Effect of corticosteroids on mortality and intensive care unit admission in patients with COVID-19 according to patients' oxygen requirements. J Med Virol. 2021;93(3):1817-1823.
15. Qiao W, Meng L, Zhang Y, Li D, Chen J, Wang J, et al. Safety and efficacy of glucocorticoids in the treatment of COVID-19: A meta-analysis of randomized control trials. Expert Rev Respir Med. 2023;17(1):81-96.

16. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818-829.

17. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707-710.

18. Bahsoun A, Fakih Y, Zareef R, Bitar F, Arabi M. Corticosteroids in COVID-19: pros and cons. Front Med (Lausanne). 2023;10:1202504.

19. Bruscoli S, Puzzovio PG, Zaimi M, Tiligada K, Levi-Schaffer F, Riccardi C. Glucocorticoids and COVID-19. Pharmacol Res. 2022;185:106511.

20. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: The CoDEX randomized clinical trial. JAMA. 2020;324(13):1307-1316.

21. Sarkar S, Khanna P, Soni KD. Are the steroids a blanket solution for COVID-19? A systematic review and meta-analysis. J Med Virol. 2021;93(3):1538-1547.

22. Emgin O, Rollas K, Saritas A, Ersan G, Senoglu N. Dexamethasone in critically ill patients admitted to intensive care unit with COVID-19 pneumonia. The Egyptian Journal of Critical Care Medicine. 2023;10(2):35-40.

23. Nakagawara K, Kamata H, Chubachi S, Namkoong H, Tanaka H, et al. Diagnostic significance of secondary bacteremia in patients with COVID-19. J Infect Chemother. 2023;29(4):422-426.

24. Ritter LA, Britton N, Heil EL, Teeter WA, Murthi SB, Chow JH, et al. The impact of corticosteroids on secondary infection and mortality in critically ill COVID-19 patients. J Intensive Care Med. 2021;36(10):1201-1208.

25. Abelenda-Alonso G, Rombauts A, Gudiol C, Oriol I, Simonetti A, Coloma A, et al. Immunomodulatory therapy, risk factors and outcomes of hospital-acquired bloodstream infection in patients with severe COVID-19 pneumonia: A Spanish case–control matched multicentre study (BACTCOVID). Clinical Microbiology and Infection, 2021;27(11): 1685-1692.

26. Bonazzetti C, Rinaldi M, Giacomelli A, Colombo R, Ottolina D, Rimoldi SG, et al.. Risk factors associated with bacteremia in COVID-19 patients admitted to intensive care unit: a retrospective multicenter cohort study. Infection. 2023;51(1):129-136.

27. Leistner R, Schroeter L, Adam T, Poddubnyy D, Stegemann M, Siegmund B, et al. Corticosteroids as risk factor for COVID-19-associated pulmonary aspergillosis in intensive care patients. Crit Care. 2022;26(1):30.

28. Covello RD, Pasin L, Fresilli S, Tóth K, Damiani C, Hajjar LA, et al. Meta-analysis of glucocorticoids for Covid-19 patients not receiving oxygen. NEJM Evid. 2023;2(5):EVIDoa2200283.