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Comparison of Cumulative Corticosteroid Doses for Critically Ill Patients with COVID-19

Kritik Durumdaki COVID-19 Hastalarında Kümülatif Kortikosteroid Dozlarının Karşılaştırılması

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Abstract

Introduction: Dexamethasone is the first medication that improved survival in patients with Coronavirus disease-2019 (COVID-19); however, the effects of corticosteroids with different cumulative doses on disease outcome must be elucidated. Our study aimed to compare clinical features, hospital mortality, and secondary infections in patients with COVID-19 receiving different cumulative doses of systemic corticosteroids.

Materials and Methods: A retrospective, observational study was conducted on patients with COVID-19 admitted to intensive care unit between 21st March 2020 and 20th September 2020 to determine who did not receive systemic corticosteroids, who received low-to-moderate cumulative doses of corticosteroids as recommended by the RECOVERY trial [proposed 6 mg of dexamethasone (equivalent to 32 mg methylprednisolone)] for 10 days (total dose of ≤320 mg of methylprednisolone or equivalent doses of corticosteroids), and who received high cumulative doses of corticosteroids (total dose of >320 mg methylprednisolone equivalent).

Results: Among 134 patients, 35 (26%) did not receive systemic corticosteroids, 34 (25%) received low-to-moderate cumulative doses of corticosteroids, and 65 (49%) received high cumulative doses of corticosteroids. Secondary bacterial (31.4% vs. 41.2% and 63.1%, p=0.006) and opportunistic infections (2.9% vs. 5.9% and 21.5%, p=0.011) were more frequently observed in the low-to-moderate- and high-dose corticosteroid groups compared with those in the no corticosteroid group. Hospital mortality was 20% in patients who did not receive steroids and 29.4% and 46.2% in patients who received low-to-moderate and high doses of corticosteroids, respectively (p=0.012). High cumulative doses of systemic corticosteroids were found to be the independent determinant for hospital mortality [Odds ratio (OR): 6.302 (1.856-21.394); p=0.003] and secondary infection [OR: 3.334 (1.313-8.496); p=0.011].

Conclusion: Comparison among patients administered with and without systemic corticosteroids revealed that high cumulative doses may be associated with adverse events in critically ill patients with COVID-19.

Keywords: Dexamethasone, methylprednisolone, intensive care, coronavirus, SARS-CoV-2

Öz

Giriş: Deksametazon, Koronavirüs hastalığı-2019'da (COVID-19) sağkalımı iyileştirdiği gösterilen ilk ilaçtır. Bununla birlikte, farklı kümülatif dozlarda kortikosteroidlerin hastalık sonlanımı üzerindeki etkilerinin açıklığa kavuşturulması gerekmektedir. Çalışmamızın amacı, farklı kümülatif sistemik kortikosteroid dozlarına göre COVID-19 hastalarında klinik özellikleri, hastane mortalitesini ve sekonder enfeksiyonları karşılaştırmaktır.

Gereç ve Yöntem: Yoğun bakım ünitesine 21 Mart 2020 ile 20 Eylül 2020 tarihleri arasında kabul edilen COVID-19 hastaları, RECOVERY çalışmasına dayalı olarak [10 gün 6 mg deksametazon (32 mg metilprednizolona eşdeğer)] sistemik kortikosteroid almayan, düşük-orta kümülatif doz kortikosteroid alan (toplam doz ≤320 mg metilprednizolon veya eşdeğer dozlarda kortikosteroid) ve yüksek kümülatif doz kortikosteroid (toplam doz >320 mg metilprednizolon eşdeğeri) alan hastalar olacak şekilde retrospektif olarak gruplandırıldı.

Bulgular: Yüz otuz dört hastanın 35'i (%26) sistemik kortikosteroid almamış, 34'ü (%25) düşük-orta kümülatif doz kortikosteroid ve 65'i (%49) yüksek kümülatif doz kortikosteroid almıştır. Sekonder bakteriyel (%31,4'e karşı %41,2 ve %63,1, p=0,006) ve fırsatçı enfeksiyonlar (%2,9'a karşı %5,9

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ve %21,5, p=0,011) düşük-orta ve yüksek doz kortikosteroid gruplarında kortikosteroid uygulanmayan gruba kıyasla daha fazla görüldü. Hastane mortalitesi steroid almayan hastalarda %20 iken, düşük-orta ve yüksek doz kortikosteroid alan hastalarda sırasıyla %29,4 ve %46,2 idi (p=0,012). Yüksek kümülatif doz sistemik kortikosteroid, hastane mortalitesi [Odds oranı (OR): 6.302 (1,856-21,394); p=0,003] ve sekonder enfeksiyon [OR: 3,334 (1,313-8,496); p=0,011] için bağımsız belirleyiciydi.

Sonuç: Sistemik kortikosteroid kullanan ve kullanmayan hastaların karşılaştırılması sonucunda, kritik hastalığı olan COVID-19 hastalarında yüksek kümülatif doz advers olaylarla ilişkili olabilir.

Anahtar Kelimeler: Deksametazon, metilprednizolon, yoğun bakım, koronavirüs, SARS-CoV-2

Introduction

A novel coronavirus initially recognized in Wuhan, China in December 2019 causes Severe acute respiratory syndrome (SARS) named Coronavirus disease-2019 (COVID-19). COVID-19 was declared as a pandemic by World Health Organization on 11th March 2020[1]. The first case was reported on the same day in Turkey and admitted to our intensive care unit (ICU) on 21st March 2020.

The clinical features of COVID-19 range from asymptomatic carriage to Acute respiratory distress syndrome (ARDS) and multi-organ dysfunction. Initial studies revealed that in the first months of the pandemic, the ICU mortality ranged from 16% to 78% due to the lack of standardized medical approach and proven treatments[2]. Corticosteroids with the strongest immunomodulatory effect were chosen as the initial treatment to manage the hyperinflammatory phenotype with cytokine storm encountered in patients with COVID-19[3]. In June 2020, a randomized control trial (RCT) named Randomized Evaluation of COVID-19 Therapy (RECOVERY)[4] reported an improvement in 28th day mortality after the intravenous (IV) administration of 6 mg of dexamethasone for 10 days in patients with COVID-19 with oxygen requirement and mechanical ventilation (MV). Other types of corticosteroids were also studied, and methylprednisolone was found to be an alternative agent. High-dose regimens were also utilized. Although corticosteroid therapy under standard daily dose and duration has been commonly used after the RECOVERY trial, high-dose corticosteroids are preferred by physicians for any reason in critically ill patients with COVID-19 admitted to ICUs. However, previous studies on corticosteroids in respiratory failure and/or ARDS reported controversial results[3,5,6]. Corticosteroids have several adverse effects, such as increased risk of infections, delayed wound healing, and hyperglycemia, and are also an important risk factor for ICU-acquired weakness. Timing, type, dose and duration of corticosteroid administration are still a matter of debate in COVID-19 management. Data on the total administered dose of corticosteroids and its consequences are still lacking.

This study primarily aimed to compare the clinical features and outcomes of patients with COVID-19 who did not receive systemic corticosteroids, who received low-to-moderate cumulative doses of corticosteroids, and who received high cumulative doses of corticosteroids. Our secondary aim was to find out the main determinants of hospital mortality and secondary infection in critically ill patients with COVID-19.

Materials and Methods

Study Groups

This retrospective, observational study was conducted on critically ill patients with COVID-19 who were older than 18 years of age and admitted to the Internal Medicine ICU of a University Hospital in which 28 beds were dedicated for patients with COVID-19. Patients who had positive results for polymerase chain reaction or antibody test for COVID-19 admitted to the ICU between 21st March 2020 and 20th September 2020 were included. The administered corticosteroid doses during the treatment period were summed up, and the cut-off dose was accepted as a total dose of 320 mg of methylprednisolone equivalent dose in accordance with recommendation of the RECOVERY trial[4], i.e., 6 mg of dexamethasone (equivalent to 32 mg of methylprednisolone), for 10 days. The patients were separated into three groups according to their received dose of systemic corticosteroids: no corticosteroids, low-to-moderate doses of corticosteroids (total dose of ≤320 mg of methylprednisolone or equivalent doses of corticosteroids), and high doses of corticosteroids (total dose of >320 mg of methylprednisolone equivalent).

Patient Follow-up

After the publication of the RECOVERY trial, the use of 6 mg of dexamethasone for up to 10 days became the standard of care for hospitalized patients with COVID-19 who require oxygen therapy or invasive MV (IMV). The patients were treated following the national guideline, which was updated as needed. Decisions regarding other immune-modulatory treatments for patients who had a severe and refractory course were deliberated during the meetings of the multidisciplinary council composed of attending physicians from different specialties.

Variables

Comorbidities, Eastern Cooperative Oncology Group Performance Status, Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) on admission, and length of the time between symptom onset and admission to hospital and ICU were calculated. Related admission laboratory values and partial pressure of oxygen/fraction of inspired oxygen ratios (PaO_2/FiO_2) of all patients upon ICU admission were also noted. Applied respiratory and rescue therapies for ARDS and medications, such as antiviral drugs and immunomodulatory therapies, were recorded.

Definitions and Outcome Measures

Secondary bacterial infection was considered as a positive culture result with clinical symptoms and signs of infection 72 hours after ICU admission[7]. The presence of *Pneumocystis jiroveci, Cytomegalovirus, Aspergillus* species, and candidemia was accepted as opportunistic infections. Secondary bacterial and opportunistic infections were defined as secondary infections. The occurrence day of secondary infection, and the duration of IMV were recorded. The patients were categorized in terms of prolonged MV, which was defined as "prolonged weaning" (accepted as more than seven days of IMV duration) [8] and "prolonged IMV" (accepted as more than 21 days of IMV duration)[9]. The presence of septic shock and acute kidney injury (AKI) on admission and septic shock during ICU stay were noted. Confirmation for the diagnosis of septic shock and AKI were based on Sepsis-3 definitions[10] and AKI criteria from 2012 Kidney Disease Improving Global Outcome[11], respectively. In addition, the 28-day, ICU, and hospital mortalities and ICU and hospital length of stay (LOS) were studied. The outcome variables were hospital mortality and development of secondary infections.

Statistical Analysis

Results were presented as medians with 25th and 75th quartiles, counts (percentages), Odds ratios (OR) and 95% confidence intervals (CI). Comparisons were studied by Mann-Whitney U, chi-square or Fisher's Exact tests and Kruskal-Wallis with Bonferroni correction for post-hoc test wherever appropriate. For multivariate analysis, clinically relevant significant variables detected from univariate analysis were further entered into the binary logistic regression analysis by Backward LR method to determine the independent predictors of primary outcome. Numeric variables were categorized according to their median values. A p value of <0.05 was accepted as significant. In terms of Bonferroni correction, a p value of <0.017 was accepted as significant. All analyses were performed with Statistical Package for the Social Sciences 23 IBM® statistics program.

Results

Among the 204 patients in the ICU during the study period, 134 (66%) were followed up with confirmed diagnosis of COVID-19. Among the patients with confirmed diagnosis, 35 (26%) did not receive systemic corticosteroids, 34 (25%) received low-to-moderate doses of corticosteroids, and 65 (49%) received high doses of corticosteroid.

General characteristics, laboratory findings, treatment and outcomes of the critically ill patients with COVID-19 grouped according to their received corticosteroid doses are shown in Table 1. The 28-day, ICU, and hospital mortalities were significantly higher (35.4%, 49.2%, and 46.2%, respectively) in the high-dose corticosteroid group compared with those in the no corticosteroid group (8.6%, 14.3%, and 20%, respectively). Low median admission lymphocyte count and high Neutrophil lymphocyte ratio (NLR) and fibrinogen levels were found in the high-dose corticosteroid group. PaO_2/FiO_2 ratio in the high-dose corticosteroid group was 132, which was significantly lower than that in the no corticosteroid group. For respiratory therapy, the no corticosteroid group frequently utilized conventional oxygen therapy (62.9%) and both corticosteroid groups mostly used IMV (41.2% and 52.3%). IMV duration and presence of prolonged MV were statistically similar among the study groups. Prone position was used in 80% of patients in the high-dose corticosteroid group. Convalescent plasma was more frequently applied to the high-dose corticosteroid group (27.7%) than to the low-to-moderate-dose corticosteroid group (5.9). In terms of outcome evaluation, secondary infections were more frequently observed in the high-dose corticosteroid group than in the no corticosteroid group (66.1% and 34.3%, respectively). The high-dose corticosteroid groups had longer ICU (median 14 days) and hospital (median 22 days) LOS than the low-to-moderate-dose corticosteroid group (seven and 12 days, respectively).

The total methylprednisolone equivalent dose was 224 (168-316) mg in the low-to-moderate-dose corticosteroid group and 944 (542-1330) mg in the high-dose corticosteroid group. As shown in Table 2, the median daily methylprednisolone equivalent dose was 32 (32-32) mg in the patients who received only dexamethasone (n=36) and 54 (39-81) mg in the patients who only received methylprednisolone (n=23). Forty patients were administered with dexamethasone and methylprednisolone. The total methylprednisolone equivalent dose was 592 (413-1405) mg in the patients who received only methylprednisolone and 288 (213-352) mg in the patients who only received dexamethasone. Treatment durations were 9 (6-10) and 15 (7-20) days for dexamethasone and methylprednisolone, respectively. Worse outcomes were more frequently encountered in the patients who received only methylprednisolone than in the other patients (Table 2). Comparison results of patients with COVID-19 in terms of hospital mortality and secondary infections are displayed in Table 3.

Table 1. Comparison of clinical characteristics, laboratory findings, treatment, and outcomes of critically ill patients with Coronavirus disease-2019 according to corticosteroid dose

	All patients (n=134)	No CS (n=35)	Low-moderate dose CS (n=34)	High-dose CS (n=65)	p	*p
Age, years	66 [55-75]	61 [54-78]	64 [55-73]	68 [59-74]	0.761	
Age >65 years old, n (%)	70 (52.2)	17 (48.6)	15 (44.1)	38 (58.5)	0.351	
Male sex, n (%)	90 (67.2)	25 (71.4)	16 (47.1)*	49 (75.4)*	**0.014**	**0.005**
BMI, kg/m^2	26.4 [23.4-29.4]	24.7 [21.8-28.1]*	27.7 [24.7-31.0]*	26.1 [24.0-29.5]	**0.031**	**0.010**
Comorbidities, n (%)						
Hypertension	72 (53.7)	18 (51.4)	14 (41.2)	40 (61.5)	0.148	
Diabetes mellitus	48 (35.8)	9 (25.7)	14 (41.2)	25 (38.5)	0.337	
Cardiac disease	42 (31.3)	6 (17.1)	10 (29.4)	26 (40)	0.061	
Chronic lung disease	24 (17.9)	2 (5.7)	7 (20.6)	15 (23.1)	0.087	
Malignancy	22 (16.4)	2 (5.7)	8 (23.5)	12 (18.5)	0.112	
Chronic kidney disease	11 (8.2)	3 (8.6)	2 (5.9)	6 (9.2)	0.843	
Chronic liver disease	6 (4.5)	1 (2.9)	4 (11.8)	1 (1.5)	0.056	
Smoking, n (%)	32 (24)	5 (25.7)	6 (17.6)	17 (26.2)	0.614	
ECOG	1 [0-2]	1 [0-3]	2 [1-3]*	1 [0-2]*	**0.020**	**0.005**
APACHE II score	15 [12-20]	15 [12-19]	16 [12-23]	16 [11-20]	0.762	
SOFA score						
Admission day	4 [3-6]	3 [2-5]	4 [3-7]	4 [3-6]	0.096	
Symptom to hospital, days	5 [2-8]	4 [1-7]	7 [3-10]	4 [2-8]	**0.040**	
Symptom to ICU, days	8 [4-11]	6 [3-10]	9 [6-13]	8 [4-11]	0.059	
Laboratory values on admission						
Lymphocyte, $\times10^3$/mm^3	0.8 [0.5-1.1]	0.9 [0.6-1.5]*	0.8 [0.5-1.1]	0.6 [0.4-1.1]*	0.054	
NLR	7.7 [3.9-14.0]	5.2 [2.3-10.3]*	5.7 [3.8-10.1]	8.8 [4.8-20.0]*	**0.004**	**0.015**
D-dimer, mg/L	1.1 [0.6-3.0]	1.2 [0.7-3.7]	1.1 [0.8-1.9]	1.1 [0.6-3.6]	0.718	**0.003**
Fibrinogen, mg/dl	469 [384-632]	406 [323-481]*	502 [406-644]	524 [431-634]*	**0.034**	
Ferritin, mcg/L	462 [188-896]	421 [181-1071]	478 [134-896]	470 [218-842]	0.826	**0.013**
CRP, mg/dL	8.3 [4.4-15.9]	7.7 [2.6-13.0]	10.2 [6.6-16.5]	9.7 [4.6-17.5]	0.112	
Procalcitonin, ng/mL	0.15 [0.07-0.35]	0.08 [0.04-0.28]	0.19 [0.07-0.80]	0.18 [0.08-0.42]	0.058	
Lactate, mmol/L	1.4 [1.0-2.1]	1.2 [0.7-2.0]	1.4 [1.1-2.0]	1.4 [1.0-2.2]	0.174	
PaO_2/FiO_2 on admission	159 [117-225]	216 [142-273]*	159 [122-221]	132 [109-192]*	**0.003**	**0.001**
Categories					0.058	
<100, n (%)	23 (17.2)	4 (11.4)	4 (11.8)	15 (23.1)		
100-200, n (%)	67 (50.0)	12 (34.3)	20 (58.8)	35 (53.8)		
200-300, n (%)	29 (21.6)	13 (37.1)	6 (17.6)	10 (15.4)		
>300, n (%)	15 (11.2)	6 (17.1)	4 (11.8)	5 (7.7)		
Respiratory support, n (%)					**<0.001**	
Conventional oxygen	43 (32.1)	22 (62.9)	13 (38.2)	8 (12.3)		
HFNO	4 (3.0)	1 (2.9)	1 (2.9)	2 (3.1)		
HFNO+NIMV	31 (23.1)	4 (11.4)	6 (17.6)	21 (32.3)		
IMV	56 (41.8)	8 (22.9)*	14 (41.2)	34 (52.3)*		
IMV duration, days	9 [3-23]	8 [3-32]	4 [2-8]	11 [5-27]	0.118	
Prolonged weaning (>7 days), n (%)	33 (58.9)	4 (11.4)	5 (14.7)	24 (36.9)	0.080	
Prolonged IMV (>21 days), n (%)	16 (28.5)	2 (5.7)	2 (5.8)	12 (18.5)	0.346	
Prone position, n (%)	84 (62.7)	12 (34.3)*	20 (58.8)	52 (80.0)*	**<0.001**	**<0.001**
Medications						

Table 1. Continued

	All patients (n=134)	No CS (n=35)	Low-moderate dose CS (n=34)	High-dose CS (n=65)	p	*p
Antiviral agents						
Favipiravir	120 (89.6)	27 (77.1)	32 (94.1)	61 (93.8)	**0.020**	
Hydroxychloroquine	33 (24.6)	17 (48.6)*	8 (23.5)	8 (12.3)*	**<0.001**	**<0.001**
Azithromycin	32 (23.9)	18 (51.4)*	5 (14.7)	9 (13.8)*	**<0.001**	**<0.001**
Oseltamivir	21 (15.7)	15 (42.9)*	4 (11.8)	2 (3.1)*	**<0.001**	**<0.001**
Others	8 (6.0)	5 (14.3)*	2 (5.9)	1 (1.5)*	**0.037**	**0.010**
Convalescent plasma, n (%)	24 (17.9)	4 (11.4)	2 (5.9)*	18 (27.7)*	**0.014**	**0.010**
IVIG, n (%)	9 (6.7)	3 (8.6)	1 (2.9)	5 (7.7)	0.587	
Tocilizumab, n (%)	5 (3.7)	1 (2.9)	0 (0.0)	4 (6.2)	0.293	
Outcome						
Secondary infection, n (%)**	69 (51.5)	12 (34.3)*	14 (41.2)	43 (66.1)*	**0.004**	**0.002**
Secondary infection day	6 [4-10]	5 [4-6]	5 [3-6]	7 [4-10]	0.056	
Septic shock, n (%)						
Admission	21 (15.7)	5 (14.3)	6 (17.6)	10 (15.4)	0.925	
Follow-up	48 (35.8)	6 (17.1)*	11 (32.4)	31 (47.7)*	**0.009**	**0.003**
AKI, n (%)	45 (33.6)	8 (22.9)	10 (29.4)	27 (41.5)	0.141	
RRT, n (%)	14 (10.4)	2 (5.7)	3 (8.8)	9 (13.8)	0.420	
28th days mortality, n (%)	35 (26.1)	3 (8.6)*	9 (26.5)	23 (35.4)*	**0.014**	**0.004**
ICU mortality, n (%)	48 (35.8)	5 (14.3)*	11 (32.4)	32 (49.2)*	**0.002**	**0.001**
Hospital mortality, n (%)	50 (37.3)	7 (20)*	10 (29.4)	30 (46.2)*	**0.012**	**0.004**
ICU LOS, days	12 [5-18]	8 [4-12]	7 [3-16]*	14 [8-24]*	**<0.001**	**0.001**
Hospital LOS*, days	19 [13-31]	21 [13-34]	12 [8-27]*	22 [16-32]*	**0.004**	**0.001**

Continuous variables were indicated as median (interquartile range).

*p value represents statistical significance for binary comparison of groups and in p value indicated statistical significance for all groups.

**Secondary infection means combination of secondary bacterial infections and opportunistic infections.

CS: Corticosteroid, BMI: Body mass index, ECOG: Eastern Cooperative Oncology Group, APACHE: Acute physiology and chronic health evaluation, SOFA: Sequential organ failure assessment, ICU: Intensive care unit, NLR: Neutrophil lymphocyte ratio, CRP: C-reactive protein, PaO_2/FiO_2: Partial pressure of oxygen/Fraction of inspired oxygen, HFNO: High flow nasal oxygen, NIMV: Non-invasive mechanical ventilation, IMV: Invasive mechanical ventilation, IVIG: Intravenous immunoglobulin, AKI: Acute kidney injury, RRT: Renal replacement therapy, LOS: Length of stay

Table 2. General characteristics of corticosteroid treatment

	Only dexamethasone (n=36)	Only methylprednisolone (n=23)	Both (n=40)
Median daily dose as methylprednisolone equivalent, mg	32 [32-32]	54 [39-81]	65 [40-88]
Total dose, mg	288 [213-352]	592 [413-1405]	994 [617-1341]
Symptom to start of treatment, days	9 [7-12]	6 [4-9]	10 [7-12]
Treatment duration, days	9 [6-10]	15 [7-20]	17 [12-23]
Outcomes			
Secondary infection, n (%)	16 (44.4)	16 (69.6)	25 (62.5)
28th days mortality, n (%)	8 (22.2)	9 (39.1)	15 (37.5)
ICU mortality, n (%)	10 (27.8)	12 (52.2)	21 (52.5)
Hospital mortality, n (%)	10 (27.8)	12 (52.2)	21 (52.5)

Continuous variables were indicated as median (interquartile range).

ICU: Intensive care unit

Table 3. Comparison of patients with Coronavirus disease-2019 in terms of hospital mortality and secondary infections

	Survivors (n=84)	Non-survivors (n=50)	p	Secondary infection No (n=65)	Secondary infection Yes (n=69)	p
Age (years)	62 [54-72]	71 [61-81]	**<0.001**	62 [52-72]	70 [60-77]	**0.007**
Age >65 years old, n (%)	35 (41.7)	35 (70)	**0.001**	27 (41.5)	43 (62.3)	**0.016**
Male sex, n (%)	54 (64.3)	36 (72)	0.358	40 (61.5)	50 (72.5)	0.178
BMI, kg/m²	27.2 [24.0-30.3)	24.0 [22.4-29.1]	**0.009**	27.0 [23.4-29.3]	26.0 [23.4-29.7]	0.612
Comorbidities, n (%)						
Hypertension	40 (47.6)	32 (64.0)	0.066	25 (38.5)	47 (68.1)	**0.001**
Diabetes mellitus	30 (35.7)	18 (36.0)	0.973	23 (35.4)	25 (36.2)	0.919
Cardiac disease	21 (25.0)	21 (42.0)	**0.040**	14 (21.5)	28 (40.6)	**0.018**
Chronic lung disease	16 (19.0)	8 (16.0)	0.656	11 (16.9)	13 (18.8)	0.772
Malignancy	7 (8.3)	15 (30.0)	**0.001**	6 (9.2)	16 (23.2)	**0.029**
Chronic kidney disease	9 (10.7)	2 (4.0)	0.171	5 (7.7)	6 (8.7)	0.833
Chronic liver disease	0 (0)	6 (12.0)	**0.001**	4 (6.2)	2 (2.9)	0.431
Smoking, n (%)	16 (19.0)	16 (32.0)	0.089	14 (21.5)	18 (26.1)	0.537
ECOG	1 [0-2]	2 [1-3]	**<0.001**	1 [0-2]	2 [0-3]	**0.043**
APACHE II score	14 [11-17]	19 [16-24]	**<0.001**	14 [11-17]	17 [13-23]	**0.006**
Admission SOFA score	3 [2-4]	6 [4-7]	**<0.001**	3 [2-5]	4 [3-7]	**0.001**
Symptom to hospital, days	6 [3-9]	3 [1-4]	**<0.001**	6 [2-8]	4 [2-7]	0.159
Symptom to ICU, days	9 [6-11]	5 [3-10]	**0.006**	8 [5-10]	7 [4-12]	0.657
Laboratory values on admission						
Lymphocyte, $\times10^3/mm^3$	0.8 [0.5-1.1]	0.7 [0.4-1.1]	0.287	0.9 [0.6-1.2]	0.6 [0.4-1.0]	**0.028**
NLR	7.5 [3.8-10.4]	10.0 [4.5-20.0]	**0.025**	6.0 [4.0-9.8]	8.8 [4.0-17.0]	**0.047**
D-dimer, mg/L	1.0 [0.6-1.8]	1.7 [0.8-5.5]	**0.008**	1.0 [0.6-1.7]	1.5 [0.7-4.6]	**0.021**
Fibrinogen, mg/dL	495 [415-640]	441 [350-557]	**0.020**	479 [406-635]	446 [374-595]	0.195
Ferritin, mcg/L	436 [179-798]	602 [203-1229]	0.116	371 [151-821]	480 [248-921]	0.103
CRP, mg/dL	8.8 [4.4-15.6]	8.2 [4.5-16.2]	0.901	8.6 [6.1-15.8]	8.3 [4.1-15.8]	0.648
Procalcitonin, ng/mL	0.12 [0.06-0.25]	0.28 [0.09-0.80]	**0.003**	0.12 [0.06-0.27]	0.20 [0.08-0.70]	**0.027**
Lactate, mmol/L	1.4 [0.9-2.0]	1.5 [1.1-2.5]	0.064	1.4 [1.0-2.1]	1.3 [1.0-1.8]	0.585
PaO_2/FiO_2 on admission	165 [125-234]	142 [108-200]	**0.048**	169 [125-240]	142 [110-211]	0.071
Categories			0.137			0.326
<100, n (%)	11 (13.1)	12 (24.0)	0.105	9 (13.8)	14 (20.3)	0.323
100-200, n (%)	40 (47.6)	27 (54.0)	0.475	30 (46.2)	37 (53.6)	0.387
200-300, n (%)	21 (25.0)	8 (16.0)	0.221	18 (27.7)	11 (15.9)	0.099
>300, n (%)	12 (14.3)	3 (6.0)	0.141	8 (12.3)	7 (10.1)	0.691
Respiratory support, n (%)			**<0.001**			**<0.001**
Conventional oxygen	39 (46.4)	4 (8.0)		32 (49.2)	11 (15.9)	
HFNO	3 (3.6)	1 (2.0)		1 (1.5)	3 (4.3)	
HFNO+NIMV	28 (33.3)	3 (6.0)		20 (30.8)	11 (15.9)	
IMV	14 (16.7)	42 (84.0)		12 (18.5)	44 (63.8)	
IMV duration, days	8 [4-16]	9 [3-23]	0.710	3 [2-8]	10 [4-27]	**0.031**
Prolonged weaning (>7 days), n (%)	7 (8.3)	26 (52.0)	0.604	4 (6.1)	29 (42.0)	0.094
Prolonged IMV (>21 days), n (%)	3 (3.5)	13 (26.0)	0.734	1 (1.5)	15 (21.7)	0.146
Prone position, n (%)	51 (60.7)	33 (66.0)	0.541	40 (61.5)	44 (63.8)	0.790
Medications						

Table 3. Continued

	Survivors (n=84)	Non-survivors (n=50)	p	Secondary infection No (n=65)	Secondary infection Yes (n=69)	p
Antiviral agents						
Favipiravir	72 (85.7)	48 (96.0)	0.060	54 (83.1)	66 (95.7)	**0.017**
Hydroxychloroquine	23 (27.4)	10 (20.0)	0.337	18 (27.7)	15 (21.7)	0.424
Azithromycin	20 (23.8)	12 (24.0)	0.980	17 (26.2)	15 (21.7)	0.549
Oseltamivir	15 (17.9)	6 (12.0)	0.367	13 (20.0)	8 (11.6)	0.181
Others	7 (8.3)	1 (2.0)	0.135	8 (12.3)	0 (0)	**0.003**
Convalescent plasma, n (%)	15 (17.9)	9 (18.0)	0.983	11 (16.9)	13 (18.8)	0.772
IVIG, n (%)	4 (4.8)	5 (10.0)	0.293	4 (6.2)	5 (7.2)	1.000
Tocilizumab, n (%)	4 (4.8)	1 (2.0)	0.650	2 (3.1)	3 (4.3)	1.000
Outcome						
Secondary infection, n (%)	29 (34.5)	40 (80.0)	**<0.001**	0 (0)	69 (100)	NA
Secondary infection day	7 [4-9]	6 [4-10]	0.878	-	6 [4-10]	NA
Septic shock, n (%)						
Admission	5 (6.0)	16 (32.0)	**<0.001**	5 (7.7)	16 (23.2)	**0.014**
Follow-up	12 (14.3)	36 (72.0)	**<0.001**	9 (13.8)	39 (56.5)	**<0.001**
AKI, n (%)	13 (15.5)	32 (64.0)	**<0.001**	13 (20.0)	32 (46.4)	**0.001**
RRT, n (%)	2 (2.4)	12 (24.0)	**<0.001**	3 (4.6)	11 (15.9)	**0.032**
28th days mortality	0 (0)	35 (70.0)	**<0.001**	10 (15.4)	25 (36.2)	**0.006**
ICU mortality	0 (0)	48 (96.0)	**<0.001**	10 (15.4)	38 (55.1)	**<0.001**
Hospital mortality	0 (0)	50 (100)	**<0.001**	10 (15.4)	40 (58.0)	**<0.001**
ICU LOS, days	9 [5-16]	14 [7-25]	**0.043**	8 [4-13]	14 [8-27]	**<0.001**
Hospital LOS, days	19 [13-30]	21 [13-32]	0.798	16 [10-23]	26 [16-38]	**<0.001**

Continuous variables were indicated as median (interquartile range).

Text in bold in p value indicated statistical significance.

BMI: Body mass index, ECOG: Eastern Cooperative Oncology Group, APACHE: Acute physiology and chronic health evaluation, SOFA: Sequential organ failure assessment, ICU: Intensive care unit, NLR: Neutrophil lymphocyte ratio, CRP: C-reactive protein, PaO_2/FiO_2: Partial pressure of oxygen/fraction of inspired oxygen, HFNO: High flow nasal oxygen, NA: Not-applicable, NIMV: Non-invasive mechanical ventilation, IMV: Invasive mechanical ventilation, IVIG: Intravenous immunoglobulin, AKI: Acute kidney injury, RRT: Renal replacement therapy, LOS: Length of stay

Multivariate analyses were performed by Backward LR method with corticosteroid dose groups, age above 65 years, malignancy, cardiac disease, hypertension, symptom to ICU admission <8 days, admission SOFA score ≥4, and APACHE II score ≥15 as clinically relevant parameters. The results showed that high-dose corticosteroid use, APACHE II score ≥15, symptom to ICU admission <8 days, and history of malignancy were found to be independent variables for predicting hospital mortality. In addition, high-dose corticosteroid use, presence of hypertension, and admission SOFA score ≥4 were independent factors associated with secondary infections during COVID-19 (Table 4).

Discussion

This study revealed that a total systemic corticosteroid use of more than 320 mg of methylprednisolone equivalent dose might be associated with undesirable consequences in critically ill patients with COVID-19 in the medical ICU of a tertiary university hospital. High-dose corticosteroid use was found to be an independent risk factor for hospital mortality and secondary infections during COVID-19 course. Dexamethasone is one of the medications with scientifically proven efficacy for COVID-19[4]. Corticosteroids have failed in other coronavirus infections, such as SARS and Middle East respiratory syndrome, and other respiratory viral infections, such as influenza[12,13]. Possible reasons for this failure in large studies included inadequate randomization, heterogeneity in clinical status, and disease severity[5].

Timing, type, dosing, and duration of corticosteroids are important factors for its usage[14]. The RECOVERY trial from the United Kingdom proved that a 10-day regimen of 6 mg of dexamethasone reduces 28-day mortality by one-third in the IMV group and one-fifth in the oxygen-treated group among hospitalized patients with COVID-19[4]. A multicenter

Table 4. Factors associated with hospital mortality and secondary infection in logistic regression analysis

	Hospital mortality		Secondary infection	
Parameters	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Corticosteroid (reference no corticosteroid use)				
Low-moderate dose	1.948 (0.480-7.901)	0.351	1.242 (0.420-3.668)	0.696
High-dose	6.302 (1.856-21.394)	**0.003**	3.334 (1.313-8.496)	**0.011**
Malignancy	3.450 (1.059-11.240)	**0.040**	2.811 (0.910-8.680)	0.072
Hypertension	NA	NA	3.393 (1.556-7.396)	**0.002**
Symptom to ICU admission <8 days	3.848 (1.452-10.201)	**0.007**	NA	NA
Admission SOFA score ≥4	2.291 (0.889-5.901)	0.086	2.526 (1.128-5.654)	**0.024**
APACHE II score ≥15	6.017 (2.188-16.549)	**0.001**	NA	NA

OR: Odds ratio, CI: Confidence interval, NA: Not-applicable, ICU: Intensive care unit, SOFA: Sequential organ failure assessment, APACHE II: Acute Physiology and Chronic Health Evaluation II

RCT named as COVID STEROD 2 trial compared 12 mg of daily dexamethasone with 6 mg dose and found no statistical significance in days of living without life support at 28 days among patients with COVID-19 with severe hypoxemia[15]. However, secondary Bayesian analysis of the same trial revealed the benefits with low probabilities of harm for dexamethasone at 12 mg versus 6 mg daily in patients with COVID-19 and severe hypoxemia on all outcomes up to 90 days[16]. Another RCT on dexamethasone from Brazil reported that ventilator-free days during the first 28 days, which was defined as being alive and free from MV, was improved from four days to 6.6 days without any mortality benefit and adverse events, such as secondary bacterial infections; the dexamethasone regimen was 20 mg for five days, followed by 10 mg for five days or until ICU discharge, whichever comes first[17]. In general, viral proliferation reaches its peak in the 2nd week in other coronavirus infections; however, this peak occurs in the first seven days for patients with COVID-19[18,19]. In the RECOVERY trial, patients were administered with dexamethasone after the first seven days of infection. Therefore, the start time of corticosteroid regimen could be more appropriate in studies of COVID-19 compared with that in studies of other coronavirus infections.

Methylprednisolone was initially studied in a single-blind RCT for hospitalized patients with severe COVID-19 at the early pulmonary phase. A comparison was performed between 250 mg/day IV methylprednisolone treatment as a three-day regimen (n=34) and standard care (n=28) and revealed a decrease in hospital mortality in favor of methylprednisolone[20]. In another RCT, 0.5 mg/kg IV methylprednisolone twice a day for five days failed to decrease 28-day mortality, except in the subgroup of patients above 60 years old[5]. Physicians' preference for methylprednisolone can be attributed to the successful results attained with short-term methylprednisolone usage in previous studies of ARDS and other community-acquired pneumonias. In a recent triple blinded RCT[21], the effectiveness of methylprednisolone (2 mg/kg/day) was investigated as an intervention group against dexamethasone (6 mg/day) as a standard of care group in 86 hospitalized patients with COVID-19. The methylprednisolone group showed a reduction in hospital LOS, need of MV, and improved clinical status at 5th and 10th days. Furthermore, the desired results could not be achieved with hydrocortisones, which are known to have the lowest immunosuppressive effect[22,23].

Other retrospective studies with large number of patients have also been conducted in this field. One studied high-dose (≥250 mg/day) and standard-dose (≤1.5 mg/kg/day) methylprednisolone and found that high-dose methylprednisolone statistically significantly increased mortality (OR: 2.46, 95% CI: 1.59-3.81; p<0.01) and MV requirement (OR: 2.35, 95% CI: 1.49-4.20; p<0.01)[6]. The poor outcome for high-dose corticosteroids could be due to the serious adverse events and accompanying or additive infections. This result may be interpreted as the evolving intention of immunomodulation to immunosuppression[5]. In our study, the 28-day, ICU, and hospital mortalities were higher and secondary infections were more frequently encountered in the patients who received corticosteroids compared with those in the patients who did not. By contrast, PaO_2/FiO_2 ratio was lower and IMV and prone position were more frequent in the patients administered with systemic corticosteroids compared with those who were not. This finding illuminated that corticosteroids were used in severe cases in our cohort. However, in the multivariate analysis, high-dose corticosteroid use was found to be an independent predictor of hospital mortality (OR: 6.302, 95% CI: 1.856-21.394; p=0.003) and secondary infection (OR: 3.334, 95% CI: 1.313-8.496; p=0.011). In another retrospective trial on 60-day mortality among patients with COVID-19, reduced risk of death (OR: 0.42, 95% CI: 0.21-0.85; p=0.02) and unhampered viral clearance were achieved with a maximum median dose of 80 mg/day (40-80) equivalent methylprednisolone for a median of 7 days (4-12) treatment duration[14]. Although the total cut-off dose of 320 mg of methylprednisolone equivalent is quite lower than that in the aforementioned work, the outcomes were worse in the current study.

In general, adverse events and complications during ICU stay are the main factors of poor outcome and have also been studied for COVID-19[24]. The presence of developing bacterial infections during the course of viral infections has been frequently reported and found to be associated with increased morbidity and mortality[25]. A multicenter prospective cohort study reported dexamethasone as a risk factor for ICU-required respiratory tract infections in patients with severe COVID-19[26]. Furthermore, opportunistic infections are also another poor prognostic factor during critical COVID-19[27]. In our recent study, we showed invasive aspergillosis in one-fifth of critically ill patients with COVID-19[28]. In another work, dexamethasone was found as a risk factor for COVID-19-associated pulmonary aspergillosis in ICU patients[29]. A retrospective multicenter study showed that early use of methylprednisolone in the ICU (≤3 days after ICU admission) was associated with increased 90-day mortality[30]. In our cohort, the median symptom day to ICU admission was 8 (4-11), and the median symptom day to the commencement of corticosteroid treatment was 8 (6-11) days for the patients who received dexamethasone and 10 (6-13) days for the patients who received methylprednisolone. Owing to the immunosuppressive effect of corticosteroids and its use in patients with COVID-19 receiving oxygen therapy even before ICU admission, corticosteroids may lead to the delayed onset of secondary infections even after a long period of time. This effect may not be reflected in the 28-day outcome. Therefore, long-term follow-up is crucial.

Patients with COVID-19 with increased disease severity and other chronic medical conditions have an increased risk of progressively worsening consequences[31]. In our cohort, APACHE II and SOFA scores of ≥15 and ≥4, respectively, and presence of malignancy were found to be three independent determinants of hospital mortality. Furthermore, the time between the onset of the first symptom and admission to the hospital and ICU in patients with COVID-19 provides important information to predict clinical progression. A study revealed poor ICU and 28-day mortality in patients who had symptom onset to ICU admission shorter than seven days[32]. This situation was explained by the aggressive and early presentation of multiple organ failure. Similarly, the duration of admission to the ICU from the onset of the first symptom was shorter in the group who passed away during hospital stay compared with the other groups. Therefore, symptom to ICU admission less than 8 days was an independent predictor for hospital mortality.

Study Limitations

In this study, the retrospective design with a limited patient number prevents the generalization of the results. Some other complications associated with corticosteroid use, such as hyperglycemia and critical illness myopathy, were not recorded. The lack of mortality benefit even with low-to-moderate doses of systemic corticosteroids, which is contrary to the findings of the RECOVERY trial and other RCTs, may be attributed to the insufficient power. Although the use of high cumulative doses of corticosteroids was found to be an independent risk factor for hospital mortality and secondary infections in logistic regression analysis, the results seem to be biased because of serious heterogeneity among the study groups in terms of demographics, disease severity, and utilized medications in the patients who received high cumulative doses corticosteroids. However, the unfavorable effect of high-dose corticosteroids on critically ill patients with COVID-19 is worthy of further consideration.

Conclusion

This single center retrospective study in a medical ICU of a tertiary university hospital demonstrated a reversed association between cumulative corticosteroid dose and outcome in critically ill patients with COVID-19. Long-term follow-up results of prospective studies and RCTs on large numbers of patients regarding type, timing, dose and duration of corticosteroid use for patients with COVID-19 should be documented.

Ethics

Ethics Committee Approval: Hacettepe University Non-Interventional Clinical Researches Ethics Board approved the study (reference number: GO 20/1012, date: 03.11.2020) and the approval of Ministry of Health was received.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.H., G.T., M.Y., İ.T.G., E.O.E., A.T., Concept: B.H., A.T., Design: B.H., A.T., Data Collection or Processing: B.H., G.T., M.Y., İ.T.G., E.O.E., A.T., Analysis or Interpretation: B.H., G.T., M.Y., İ.T.G., E.O.E., A.T., Literature Search: B.H., G.T., A.T., Writing: B.H., G.T., A.T.

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