J Nephropharmacol. 2023; 12(2): e10577.

https://jnephropharmacology.com DOI: 10.34172/npj.2023.10577

Journal of Nephropharmacology

Effectiveness of corticosteroid therapy in patients with moderate to severe coronavirus disease 2019: a retrospective study

Sara Sadeghi[1], Marjan Mansourian[2], Sara Ebrahimi[3], Baran Kahid Basiri[4], Niloofar Nikgoftar[5], Soheila Jalali[2], Ramin Sami[6*]

[1]Medical Student, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of Epidemiology and Biostatics, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran
[3]Alzahra Research Institute, Alzahra University Hospital Isfahan University of Medical Sciences Isfahan, Iran
[4]General Practitioner, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[5]General Physician, Department of Family and Emergency Medicine, Faculty of Medicine, Isfahan University of Medical Science, Isfahan, Iran
[6]Department of Internal Medicine, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

ARTICLE INFO

Article Type:
Original

Article History:
Received: 19 December 2022
Accepted: 5 March 2023
Published online: 16 May 2023

Keywords:
COVID-19
Steroids
Corticosteroids
Mortality
Mechanical ventilation
Intubation

ABSTRACT

Introduction: Ne An acute respiratory infection started in Wuhan city of China in December 2019. The pathogen was discovered as a novel coronavirus from the Coronaviridae family and called the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). According to clinical symptoms and laboratory tests, coronavirus disease 2019 (COVID-19) patients are categorized as asymptomatic, mild, moderate, severe and critical state. Suggested therapies used in moderate to severe COVID-19 disease include corticosteroids, anticoagulation and antiviral drugs (e.g., remdesivir).

Objectives: We reviewed the clinical outcomes associated with corticosteroid treatment for COVID-19.

Patients and Methods: We planned a retrospective study with 859 patients diagnosed with SARS-CoV-2 infection who were under treatment at Khorshid hospital affiliated with Isfahan University of Medical Sciences, Isfahan, Iran (from February to May 2020).

Results: A total of 859 patients were included in this study. The mean age was 63.33±15.45 years of which 43.8% (n = 376) were women. We subcategorized corticosteroids by dose prescribed in smaller groups to show better results. The secondary outcome including the rate of intensive care units (ICUs) admission and death was less with corticosteroid prescription. This study showed, mortality and ICU admission were fewer in patients with ≥51 mg/d and ≥201 mg/d of methylprednisolone therapy, respectively.

Conclusion: Based on this study, corticosteroid treatment can reduce both the need for ICU admission and mortality in moderate to severe COVID-19 patients. However, clinical trials are needed to investigate the effect of corticosteroid therapy on the need to mechanically ventilate a patient

Implication for health policy/practice/research/medical education:
The effectiveness of corticosteroid treatment in reducing the hospitalization rate in the ICU and reducing the mortality of moderate to severe COVID-19 patients.

Please cite this paper as: Sadeghi S, Mansourian M, Ebrahimi S, Kahid Basiri B, Nikgoftar N, Jalali S, Sami R. Effectiveness of corticosteroid therapy in patients with moderate to severe coronavirus disease 2019: a retrospective study. J Nephropharmacol. 2023;12(2):e10577. DOI: 10.34172/npj.2023.10577.

Introduction

An acute respiratory infection started in Wuhan city of China in December 2019. The pathogen was discovered as a novel coronavirus from the Coronaviridae family and called the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (1). On February 11, 2020, the respiratory illness caused by this virus was termed coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) and on March 11, 2020, it was declared a pandemic (2). The first case was linked to a seafood market. Subsequently, the human-to-human transmission was recognized to be responsible for the

***Corresponding author**: Ramin Sami, Email: r.sami@med.mui.ac.ir

Original

community spread of COVID-19 (3). Transmission of SARS-CoV-2 occurs from individual to individual through respiratory aerosols and droplets (4).

Based on clinical symptoms and laboratory tests, COVID-19 patients are classified as 1) Asymptomatic; when a COVID-19 diagnostic test is positive, but clinical symptoms are not seen, 2) Mild; signs of the upper respiratory tract infection or gastrointestinal (GI) symptoms, 3) Moderate; pneumonia without hypoxemia and pulmonary lesions in imaging, 4) Severe; pneumonia with hypoxemia (O_2Sat <92%), 5) critical state; acute respiratory distress syndrome (ARDS), accompanied by encephalopathy, shock and coagulation defects, acute kidney injury, and also heart failure (5).

Older patients (≥65 years) are at higher risk of developing severe SARS-CoV-2 infection. For diagnosing COVID-19, high-resolution computed tomography and samples collected from respiratory specimens for amplification of the viral genetic material by polymerase chain reaction (PCR) are used with high sensitivity (6). Suggested therapies conducted in moderate to severe COVID-19 disease include corticosteroids, anticoagulation and antiviral drugs (e.g., remdesivir) (7).

Objectives

In this study, we focused on corticosteroids; since, they exert anti-inflammatory effects by suppressing the production of many cytokines (interlukin-1β, interlukin-6, tumor necrosis factor α). Indeed, the corticosteroid is an effective and common therapeutic strategy for several inflammatory lung pathologies (e.g., asthma). However, results from studies of other respiratory viruses failed to show a conclusive benefit with corticosteroids. Nevertheless, these studies were largely observational, suffered from low statistical power and were commonly administered to patients with severe disease, which makes it difficult to compare outcomes between groups (8). Corticosteroids have transformed clinical practice in COVID-19; while there is evidence showing considerable benefits in the administration of steroids by physicians (9). Here, we conducted a fairly large study to investigate the clinical outcomes associated with corticosteroid treatment of COVID-19.

Patients and Methods

Study design

After institutional ethics approval, we planned a retrospective study with 859 patients diagnosed with SARS-CoV-2 infection who were under treatment at Khorshid hospital affiliated with Isfahan University of Medical Sciences, Isfahan, Iran (February to May 2020). This is a referral center that admits patients with COVID-19. The diagnosis, admission and management of the patients were based on updated recommendations from CDC and WHO (9). Patients between the age of 18 to 70 admitted to the hospital with confirmed COVID-19 by PCR and chest CT markings suggesting pneumonia compatible with COVID-19 were included. Participants with critical state, congestive heart failure, chronic renal failure, cirrhosis, active cancer, pregnant and breastfeeding women, elevated liver enzyme more than five times the normal range or patients with unstable hemodynamics were excluded. If the patient died immediately the day after entering the study or was transferred to the intensive care unit (ICU) or those who dissented to continue cooperation during hospitalization, they were excluded; although, their initial information was used in the analysis. Eligible patients were examined according to a checklist. Clinical and para-clinical findings, progression of the disease and drug side effects were recorded.

We recorded the following data for this study: demographic features gender, age, body mass index (BMI), laboratory findings white blood cells (WBCs), lymphocytes (in percent), lactate dehydrogenase (LDH), creatinine, aspartate aminotransferase (AST), alanine transaminase (ALT), C-reactive protein (CRP), comorbidities cardiovascular disease (CVD), chronic respiratory disease, diabetes and hypertension (HTN) and asthma,

In addition, presentation characteristics were: duration of symptoms, oxygen saturation (O_2Sat), respiratory rate (RR), blood pressure (BP), pulse rate (PR), body temperature in °C and hospitalization duration, death status, ICU admission, intubation status, the dose of corticosteroid administrated in each patient (in milligram), days from symptom onset to corticosteroid prescribed and corticosteroids used in patients (dexamethasone, hydrocortisone, methylprednisolone, and prednisone). To show a better and tangible understanding, steroid conversion calculator was conducted to convert different types of corticosteroids to methylprednisolone (10); therefore, in this study, when we mention corticosteroids/steroids/methylprednisolone, the converted form of them is meant (Table 1).

The primary outcomes were the mean length of hospital stay, the trend in arterial O_2 saturation (O_2Sat), the severity of cough and dyspnea in the hospital, and two days after discharge between the two trial arms. The secondary outcome included the rate of ICU admission, the need for mechanical ventilation, and death.

Statistical analysis

SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA) was conducted for statistical analysis. Categorical variables were presented in terms of frequency and percentage, and continuous variables were demonstrated in terms of mean ± standard deviation (SD). Kolmogorov–Smirnov were conducted to evaluate normality. All of the variables were evaluated for the covariate. To compare continuous and categorical variables, we used a two-sample t-test and a chi-square test (or Fisher's exact test), respectively. Repeated measures analysis of variance (ANOVA) was employed for

Table 1. Relative potencies of systemic glucocorticoids

Corticosteroid	Activity	Relative potency	Equivalent dose (mg)
Dexamethasone	Long-acting	25	0.75
Prednisone	Intermediate-acting	4	5.0
Methylprednisolone	Intermediate-acting	5	4.0
Hydrocortisone	Short-acting	1	20.0

the sake of the comparison of O_2 sat, dyspnea and cough, for each group at different times. The value of $P \leq 0.05$ was considered statistically significant.

Results

A total of 859 patients were included in this study. The mean age was 63.33 ± 15.45 years and 43.8% (n=376) of patients were women. The mean prescribed methylprednisolone dose was 138.76 ± 140.97 mg/d. The mean time from symptom onset to corticosteroid prescription was 15.44 ± 8.86 days. A total of 188 (21.9%) patients had cardiovascular disease (CVD). Chronic respiratory disease was seen in 109 (12.7%) patients. Diabetes, hypertension (HTN), and asthma were seen in 276 (32.13%), 383 (44.64%), and 27 (3.16%) patients, respectively. The mean duration of symptoms was 8.06 ± 6.01 days. About O_2Sat, a total mean of 80.65 ± 10.33 percent was recorded. Mean systolic and diastolic blood pressure was 132.04 ± 40.36 and 80.94 ± 39.27 mm Hg, respectively. The mean hospitalization duration was 8.75 ± 6.31 days. The mortality rate in this study was 13.7% (Table 2).

Data recorded from patients' medical records were compared in groups of patients with and without ICU admission, mechanical ventilation and mortality. Age,

Table 2. Descriptive characteristics of patients in total and with and without mortality

Patients' characteristics	Total	Death status		*P*
		No (n=741)	Yes (n=118)	
Age, years	63.33 (15.45)	62.21 (15.14)	70.43 (15.54)	**<0.01**
Female, No. (%)	376 (43.77%)	329 (44.40%)	47 (39.83%)	0.37
Body mass index, kg/m^2	27.55 (5.71)	27.64 (5.66)	26.22 (6.29)	0.15
Time to drug methylprednisolone, days	1.12 (1.75)	1.08 (1.75)	1.42 (1.63)	0.09
Symptom to steroid, days	15.44 (8.86)	15.15 (8.58)	17.49 (10.48)	0.07
Laboratory findings				
LDH (IU/L)	780.38 (783.40)	742.09 (683.95)	1016.02 (1211.41)	0.08
WBC (×1000/µL)	7451.13 (10679.52)	7137.50 (11228.26)	9474.44 (5670.83)	**0.03**
Lymphocyte (×1000/µL)	16.69 (9.39)	17.41 (9.32)	12.06 (8.51)	**<0.01**
CR (mg/dl)	1.37 (1.08)	1.29 (1.02)	1.87 (1.35)	**<0.01**
ALT (IU/L)	45.62 (146.81)	41.27 (100.11)	72.88 (306.05)	0.28
AST (IU/L)	58.28 (154.11)	55.41 (148.04)	76.65 (188.07)	0.18
Comorbidities, N (%)				
CVD, yes	188 (21.89%)	161 (21.73%)	27 (22.88%)	0.81
Chronic respiratory disease, yes	109 (12.73%)	87 (11.77%)	22 (18.80%)	**0.05**
Diabetes, yes	276 (32.13%)	232 (31.31%)	44 (37.29%)	0.20
HTN, yes	383 (44.64%)	322 (43.51%)	61 (51.69%)	0.11
Asthma, yes	27 (3.16%)	24 (3.25%)	3 (2.59%)	0.99
Presentation characteristics				
Duration of symptoms, days	8.06 (6.01)	8.13 (5.97)	7.56 (6.35)	0.39
O_2Sat %	80.65 (10.33)	81.98 (8.38)	72.31 (16.01)	**<0.01**
RR median (IQR)	25.12 (7.82)	24.92 (7.80)	26.37 (7.92)	0.06
BP0-systolic, mm Hg	132.04 (40.36)	132.67 (42.11)	128.06 (26.78)	0.25
BP0-diastolic, mm Hg	80.94 (39.27)	80.93 (34.43)	81.03 (61.85)	0.98
PR mean (SD)	93.10 (17.25)	93.37 (16.36)	97.97 (21.70)	**0.03**
T, °C	37.56 (1.02)	37.58 (1.00)	37.46 (1.16)	0.30
Hospitalization duration (day)	8.75 (6.31)	8.47 (5.87)	10.47 (8.43)	**0.01**
CRP (mg/L)	66.92 (56.27)	67.58 (57.04)	62.51 (50.85)	0.42

Data are presented as mean (SD – standard deviation) for continuous and frequency (percentage) for categorical data, P≤0.05 is statistically significant
LDH, Lactate dehydrogenase; CR, Creatinine; ALT, Alanine transaminase; AST, Aspartate transaminase; CVD, Cardiovascular disease; HTN, Hypertension; RR, Respiratory rate; BP, Blood pressure; PR, Pulse rate; T, Temperature; CRP; C-reactive protein.

Table 3. Descriptive characteristics of patients with and without ICU admission

Patients characteristics	ICU admission		*P*
	No (n = 643)	Yes (n = 216)	
Age, years	63.54 (15.36)	62.71 (15.72)	0.49
Female, No. (%)	298 (46.35%)	78 (36.11%)	**<0.01**
Body mass index, kg/m^2	27.42 (5.37)	27.99 (6.70)	0.32
Time to drug methylprednisolone, days	0.98 (1.65)	1.45 (1.89)	**<0.01**
Symptom to steroid, days	13.49 (6.81)	20.07 (11.18)	**<0.01**
Laboratory findings			
LDH (IU/L)	680.59 (267.60)	1045.96 (1403.81)	**<0.01**
WBC (x1000/µL)	7143.71 (11547.84)	8364.67 (7479.07)	0.15
Lymphocyte (×1000/µL)	17.78 (9.28)	13.46 (8.98)	**<0.01**
CR (mg/dl)	1.31 (0.93)	1.55 (1.44)	**0.03**
ALT (IU/L)	37.77 (49.84)	68.62 (277.42)	0.11
AST (IU/L)	50.29 (56.45)	81.96 (290.17)	0.12
Comorbidities, N (%)			
CVD, yes	145 (22.55%)	43 (19.91%)	0.45
Chronic respiratory disease, yes	73 (11.39%)	36 (16.74%)	**0.04**
Diabetes, yes	209 (32.50%)	67 (31.02%)	0.74
HTN, yes	298 (46.35%)	85 (39.53%)	0.10
Asthma, yes	20 (3.13%)	7 (3.27%)	0.99
Presentation characteristics			
Duration of symptoms, days	8.02 (5.65)	8.18 (7.02)	0.75
O_2Sat%	82.86 (8.02)	74.09 (13.26)	**<0.01**
RR median (IQR)	24.56 (7.45)	26.80 (8.65)	**<0.01**
BP0-systolic, mm Hg	132.58 (44.88)	130.42 (22.06)	0.50
BP0-diastolic, mm Hg	80.83 (36.69)	81.26 (46.23)	0.89
PR mean (SD)	92.94 (16.86)	97.18 (18.02)	**<0.01**
T, °C	37.57 (1.00)	37.54 (1.09)	0.64
Hospitalization duration (day)	6.93 (4.00)	14.18 (8.47)	**<0.01**
CRP (mg/L)	67.58 (56.83)	64.85 (54.57)	0.58

Data are presented as mean (SD – standard deviation) for continuous and frequency (percentage) for categorical data, P≤0.05 is statistically significant
LDH, Lactate dehydrogenase; CR, Creatinine; ALT, Alanine transaminase; AST, Aspartate transaminase; CVD, Cardiovascular disease; HTN, Hypertension; RR, Respiratory rate; BP, Blood pressure; PR, Pulse rate; T, Temperature; CRP; C-reactive protein.

WBC, lymphocytes, creatinine, chronic respiratory disease, O_2Sat, PR and hospitalization duration were different between with and without mortality groups. About ICU admission, gender, days of which patients have taken methylprednisolone, days from onset of symptoms to corticosteroid prescription, lactate dehydrogenase (LDH), creatinine, lymphocyte, chronic respiratory disease, O_2Sat, RR, PR, and hospitalization duration were different. Comparison of patients with and without mechanical intubation, showed a difference in age, time from symptoms onset and steroid prescription, lymphocytes, creatinine, O_2Sat, pulse rate, respiratory rate, and hospitalization duration. Of all these variables, fewer lymphocytes and O_2Sat, higher respiratory rate and creatinine and longer hospitalization were common in patients who experienced death, ICU admission, and mechanical ventilation (Tables 2-4).

We subcategorized corticosteroids by dose prescribed in smaller groups to show better results. The secondary outcome including the rate of ICU admission and death were less with corticosteroid prescription. Our results showed that mortality and ICU admission were fewer in patients with ≥51 mg/d and ≥201 mg/d of methylprednisolone, respectively (Tables 5 and 6).

Discussion

We conducted a relatively large retrospective study that examined the effectiveness of corticosteroids for COVID-19. Corticosteroid therapy decreased the need for ICU admission and mortality in COVID-19 patients. Our study suggests that corticosteroid treatment can enhance the results in patients with moderate to severe COVID-19. Well-known mechanisms of action combined with the extensive accessibility of corticosteroids make them a suitable treatment for various pathologies, including COVID-19 pneumonia.

We detected a low-rate of mortality in our study (13.7%) in comparison with similar previous studies (11). Early

Table 4. Descriptive characteristics of patients with and without mechanical ventilation

Patients characteristics	Intubation Status		*P*
	No (n = 790)	Yes (n = 69)	
Age, years	63.03 (15.35)	66.84 (16.28)	0.04
Female, No. (%)	353 (44.69%)	23 (33.33%)	0.08
Body mass index, kg/m^2	27.64 (5.74)	26.07 (4.94)	0.14
Time to drug methylprednisolone, days	1.11 (1.75)	1.30 (1.59)	0.41
Symptom to steroid, days	14.98 (8.49)	20.31 (11.10)	**<0.01**
Laboratory findings			
LDH (IU/L)	771.50 (813.62)	867.56 (368.77)	0.44
WBC (x1000/µL)	7386.61 (10991.30)	8209.70 (5883.26)	0.55
Lymphocyte (×1000/µL)	17.06 (9.36)	12.34 (8.64)	**<0.01**
CR (mg/dl)	1.33 (1.06)	1.86 (1.27)	**<0.01**
ALT (IU/L)	46.25 (152.70)	38.45 (37.01)	0.68
AST (IU/L)	58.52 (159.94)	55.55 (50.33)	0.88
Comorbidities, N (%)			
CVD, yes	173 (21.90%)	15 (21.74%)	0.99
Chronic respiratory disease, yes	100 (12.69%)	9 (13.24%)	0.85
Diabetes, yes	250 (31.65%)	26 (37.68%)	0.34
HTN, yes	350 (44.36%)	33 (47.83%)	0.61
Asthma, yes	26 (3.30%)	1 (1.49%)	0.71
Presentation characteristics			
Duration of symptoms, days	8.14 (6.06)	7.02 (5.34)	0.17
O_2Sat%	81.54 (9.08)	70.57 (16.66)	**<0.01**
RR median (IQR)	24.90 (7.72)	7.62 (8.60)	**0.01**
BP0-systolic, mm Hg	132.21 (41.37)	130.01 (26.27)	0.66
BP0-diastolic, mm Hg	81.27 (40.58)	77.20 (18.65)	0.41
PR mean (SD)	93.44 (16.78)	100.53 (20.97)	**<0.01**
T, °C	37.58 (1.00)	37.33 (1.24)	0.10
Hospitalization duration (day)	8.28 (5.73)	14.14 (9.51)	**<0.01**
CRP (mg/L)	66.37 (56.07)	73.67 (58.80)	0.364

Data are presented as mean (SD – standard deviation) for continuous and frequency (percentage) for categorical data, P≤0.05 is statistically significant
LDH, Lactate dehydrogenase; CR, Creatinine; ALT, Alanine transaminase; AST, Aspartate transaminase; CVD, Cardiovascular disease; HTN, Hypertension; RR, Respiratory rate; BP, Blood pressure; PR, Pulse rate; T, Temperature; CRP; C-reactive protein.

in the pandemic, studies showed that overall mortality rates for admitted patients reached 20%; however, in those with ICU admission, mortality approximated 40% (11). As the pandemic has progressed, mortality rates of patients with severe COVID-19 have improved from 42% to 20% (12). In this study, corticosteroid therapy reduced mortality in patients with moderate to severe COVID-19 disease. A previous trial conducted by Group et al showed corticosteroid therapy causes lesser mortality rates (29.3% versus 41.4%) in moderate to severe COVID-19 patients (13). They carried out this study in 2021 and investigated dexamethasone therapy in hospitalized patients with COVID-19. Recently, Tang et al planned a multi-center, single-blind, randomized control trial to study the administration of corticosteroids in patients with COVID-19 pneumonia. This study showed a lower mortality with corticosteroid therapy in their study patients (14). A recent systematic review and meta-analysis by Hong et al, indicated that, compared with no glucocorticoids therapy, methylprednisolone in the treatment of COVID-19 patients is associated with reduced mortality without increasing the risk of secondary infections. In their study, patients with severe COVID-19 were more likely to benefit from methylprednisolone treatment (15). Taken together, these data indicated that corticosteroid treatment does provide a mortality benefit in COVID-19 patients that experience moderate to severe symptoms.

Our study suggests that corticosteroid therapy provides conditions that fewer patients require ICU admission. Angus et al, conducted a study in 2020 which recruited 614 adult patients with COVID-19 to investigate the corticosteroid effect on admission to an ICU for respiratory or cardiovascular organ support at 121 sites in eight countries (16). They concluded that among patients with severe COVID-19, treatment with hydrocortisone, compared with no hydrocortisone administration, resulted in improvement in organ support-free days. In

Table 5. Comparison of corticosteroids prescribed per day in different outcome groups

Dose per day (mg)	Total	Death status		Intubation status		ICU admission	
		Yes	No	Yes	No	Yes	No
1-50	69	7 (10.1)	62 (89.9)	5 (7.2)	64 (92.8)	20 (29.0)	49 (71.0)
51-100	275	24 (8.7)	251 (91.3)	12 (4.4)	263 (95.6)	53 (19.3)	222 (80.7)
101-150	74	10 (13.5)	64 (86.5)	8 (10.8)	66 (89.2)	28 (37.8)	46 (62.2)
151-200	49	14 (28.6)	35 (71.4)	12 (24.5)	37 (75.5)	30 (61.2)	19 (38.8)
≥201	121	26 (21.5)	95 (78.5)	22 (18.2)	99 (81.8)	54 (44.6)	67 (55.4)
P value		**<0.01**		**< 0.01**		**< 0.01**	

Data are presented as frequency and %, $P \leq 0.05$ is statistically significant.

Table 6. Estimated hazard risk and 95% confidence interval (HRs and 95% CIs) by Cox proportional hazards regression models for different outcomes

	Model 1*		Model 2*		Model 3*	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Intubation status						
Methylprednisolone 1-50 mg	1.135 (0.337-3.826)	0.84	1.101 (0.315-3.849)	0.88	1.129 (0.321-3.972)	0.85
Methylprednisolone 51-100 mg	1.157 (0.468-2.863)	0.75	1.148 (0.463-2.843)	0.76	1.156 (0.466-2.868)	0.75
Methylprednisolone 101-150 mg	0.934 (0.338-2.579)	0.89	0.765 (0.264-2.219)	0.62	0.826 (0.273-2.499)	0.73
Methylprednisolone 151-200 mg	1.061 (0.426-2.638)	0.89	0.796 (0.295-2.148)	0.65	0.813 (0.300-2.200)	0.68
Methylprednisolone ≥201mg	1.089 (0.4782.480)	0.83	0.838 (0.334-2.102)	0.71	0.849 (0.339-2.127)	0.73
Mortality						
Methylprednisolone 1-50 mg	0.824 (0.319-2.130)	0.70	0.871 (0.332-2.281)	0.78	0.931 (0.353-2.455)	0.88
Methylprednisolone 51-100 mg	0.468 (0.259-0.847)	**0.01**	0.466 (0.257-0.847)	**<0.01**	0.498 (0.271-0.916)	**0.02**
Methylprednisolone 101-150 mg	0.348 (0.171-0.710)	**<0.01**	0.354 (0.173-0.723)	**<0.01**	0.302 (0.141-0.645)	**<0.01**
Methylprednisolone 151-200 mg	0.376 (0.197-0.717)	**<0.01**	0.396 (0.205-0.768)	**<0.01**	0.404 (0.208-0.787)	**<0.01**
Methylprednisolone ≥201mg	0.483 (0.284-0.820)	**<0.01**	0.468 (0.272-0.805)	**<0.01**	0.463 (0.268-0.800)	**<0.01**
ICU admissions						
Methylprednisolone 1-50 mg	0.792 (0.437-1.437)	0.44	0.736 (0.400-1.354)	0.32	0.736 (0.400-1.354)	0.32
Methylprednisolone 51-100 mg	0.758 (0.473-1.212)	0.25	0.746 (0.466-1.194)	0.22	0.749 (0.467-1.199)	0.23
Methylprednisolone 101-150 mg	0.689 (0.406-1.170)	0.17	0.656 (0.385-1.116)	0.12	0.649 (0.380-1.107)	0.11
Methylprednisolone 151-200 mg	0.764 (0.455-1.284)	0.31	0.714 (0.423-1.204)	0.21	0.713 (0.422-1.203)	0.20
Methylprednisolone ≥201mg	0.518 (0.324-0.829)	**<0.01**	0.513 (0.318-0.829)	**<0.01**	0.512 (0.317-0.827)	**<0.01**

Data are shown as hazard risks (HRs) with 95% confidence intervals, $P \leq 0.05$ is statistically significant.
* Model 1; unadjusted, Model 2: adjusted by age and gender, model 3; adjusted by age, gender, and comorbidity diseases; The analysis was conducted following adjusting by age, gender and comorbidities to be more precise in reporting data.

another study by Kim et al, the Republic of Korea found that anti-inflammatory agents, including corticosteroids, were associated with improved outcomes of hospitalized COVID-19 patients, including the rate of ICU admission (17). Hong et al, showed a significant reduction in ICU admission in patients with corticosteroid treatment (15). Hamed et al, reported in their randomized study that patients with severe COVID-19 pneumonia administrated with methylprednisolone were associated with reduced 45-day mortality and lower ICU admission (18). Concerning the WHO recommendations on corticosteroid therapy (19), our study also showed the advantages of corticosteroid treatment in patients with COVID-19 pneumonia.

Similar to our study, the mechanical ventilation in the trial by Corral-Gudino et al did not show a benefit with corticosteroid treatment (20). The study was a multi-centric trial of severe COVID-19 patients, who were assigned to standard of care or standard of care plus intravenous methylprednisolone. However, several trials observed a significant reduction in the incidence of mechanical ventilation in the methylprednisolone group (21). A successful study on mechanical ventilation using methylprednisolone for treatment of severe COVID-19 was showed in a systematic review and meta-analysis by Liu et al (22). However, further studies are needed for an exact and definite conclusion about the mechanical ventilation outcome.

Numerous studies have been published for glucocorticoid treating in patients with COVID-19 that could not show

its benefit in the outcome of patients (23). We believe that those assessments were not precise, as the number of genes influences by various glucocorticoid drugs is not the same and the clinical impacts may be varied (19). Furthermore, in some studies the interventions were not restricted to corticosteroid treatment. These studies, also included other treatments like tocilizumab, in relation to the control measure (23). Such results may interfere with the therapeutic effects of methylprednisolone. These studies included a relatively limited outcome and had small sample size (only mortality). Therefore, the results obtained on this basis different from our study, are inconclusive and unstable.

The main strength of our study was that we could include an appropriate number of patients. There was a limitation for our study as it was a retrospective study limited by the inaccuracy and quality of data reporting. Glucocorticoids can exert their anti-inflammatory effects through non-genetic and genetic pathways; reduced inflammatory response may result in the easier relief of symptoms, faster recovery of lung injury and lower risk of mortality and ICU admission (24). This conclusion is proved by our findings. It is believed that the mortality benefit of corticosteroids observed in this study comprehensively reflect the usual enhancement in these clinical results.

Conclusion

Based on our retrospective study, corticosteroid treatment can reduce both the need for ICU admission and mortality in moderate to severe COVID-19 patients. Clinical trials are needed to investigate the effect of corticosteroid therapy on the need to mechanically ventilate a patient.

Limitations of the study

The limitations of this research are that it is not a clinical trial study and the sample size is small.

Acknowledgements

The authors wish to thank all participants for their contributions to our study. Furthermore, we would like to thank Research Administration of Isfahan University of Medical Sciences.

Authors' contribution

Conceptualization: RS and SS.
Methodology: RS and MM.
Validation: RS and MM.
Formal analysis: MM and SG.
Investigation: RS, SS, BK and SE.
Resources: RS.
Data curation: SS and NN.
Writing-original draft preparation: SS, BK, SE and NN.
Writing-review and editing: RS, MM, SS and BK.
Visualization: RS.
Supervision: RS.
Project administration: RS and MM.
Funding acquisition: RS

Availability of data and materials

All the questionnaires, and the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

The authors declare that they have no competing interests.

Consent to participate

Information about the aim of the study, confidentiality of the data, and voluntariness of participation in and withdrawal from the study was provided to participants and they were asked to sign the informed consent form of the study.

Consent for publication

We declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Isfahan University of Medical Sciences approved this study (Ethical code #IR.MUI.MED.REC.1399.597). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

The authors did not receive any financial support for this study.

References

1. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol. 2020;215:108427. doi: 10.1016/j.clim.2020.108427.
2. Phelan AL, Katz R, Gostin LO. The Novel Coronavirus Originating in Wuhan, China: Challenges for Global Health Governance. JAMA. 2020;323:709-710. doi: 10.1001/jama.2020.1097.
3. Bogoch II, Watts A, Thomas-Bachli A, Huber C, Kraemer MUG, Khan K. Pneumonia of unknown aetiology in Wuhan, China: potential for international spread via commercial air travel. J Travel Med. 2020;27:taaa008. doi: 10.1093/jtm/taaa008.
4. Cascella M, Rajnik M, Aleem A. Features, Evaluation, and Treatment of Coronavirus (COVID-19) [Updated 2022 Oct 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/.
5. WHO. Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19). Geneva: WHO; 2020.
6. Ochani R, Asad A, Yasmin F, Shaikh S, Khalid H, Batra

S, et al. COVID-19 pandemic: from origins to outcomes. A comprehensive review of viral pathogenesis, clinical manifestations, diagnostic evaluation, and management. Infez Med. 2021;29:20-36.
7. Kollias A, Kyriakoulis KG, Dimakakos E, Poulakou G, Stergiou GS, Syrigos K. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. Br J Haematol. 2020;189:846-847. doi: 10.1111/bjh.16727.
8. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020;395:473-475. doi: 10.1016/S0140-6736(20)30317-2.
9. Pan Y, Zhang D, Yang P, Poon LLM, Wang Q. Viral load of SARS-CoV-2 in clinical samples. Lancet Infect Dis. 2020;20:411-412. doi: 10.1016/S1473-3099(20)30113-4.
10. Zoorob RJ, Cender D. A different look at corticosteroids. Am Fam Physician. 1998;58:443-50.
11. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;324:782-793. doi: 10.1001/jama.2020.12839.
12. Dennis JM, McGovern AP, Vollmer SJ, Mateen BA. Improving survival of critical care patients with coronavirus disease 2019 in england: a national cohort study, March to June 2020. Crit Care Med. 2021;49:209-214. doi: 10.1097/CCM.0000000000004747.
13. RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021;384:693-704. doi: 10.1056/NEJMoa2021436.
14. Tang X, Feng YM, Ni JX, Zhang JY, Liu LM, Hu K, et al. Early Use of Corticosteroid May Prolong SARS-CoV-2 Shedding in Non-Intensive Care Unit Patients with COVID-19 Pneumonia: A Multicenter, Single-Blind, Randomized Control Trial. Respiration. 2021;100:116-126. doi: 10.1159/000512063.
15. Hong S, Wang H, Zhang Z, Qiao L. The roles of methylprednisolone treatment in patients with COVID-19: A systematic review and meta-analysis. Steroids. 2022;183:109022. doi: 10.1016/j.steroids.2022.109022.
16. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA. 2020;324:1317-1329. doi: 10.1001/jama.2020.17022.
17. Kim MS, An MH, Kim WJ, Hwang TH. Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis. PLoS Med. 2020;17:e1003501. doi: 10.1371/journal.pmed.1003501.
18. Hamed DM, Belhoul KM, Al Maazmi NA, Ghayoor F, Moin M, Al Suwaidi M, et al. Intravenous methylprednisolone with or without tocilizumab in patients with severe COVID-19 pneumonia requiring oxygen support: A prospective comparison. J Infect Public Health. 2021;14:985-989. doi: 10.1016/j.jiph.2021.06.003.
19. World Health Organization. Corticosteroids for COVID-19. https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1. Accessed 9 November 2020.
20. Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, Gómez-Barquero J, Abadía-Otero J, García-Ibarbia C, et al; GLUCOCOVID investigators. Methylprednisolone in adults hospitalized with COVID-19 pneumonia : An open-label randomized trial (GLUCOCOVID). Wien Klin Wochenschr. 2021;133:303-311. doi: 10.1007/s00508-020-01805-8.
21. Cusacovich I, Aparisi Á, Marcos M, Ybarra-Falcón C, Iglesias-Echevarria C, Lopez-Veloso M, et al. Corticosteroid Pulses for Hospitalized Patients with COVID-19: Effects on Mortality. Mediators Inflamm. 2021;2021:6637227. doi: 10.1155/2021/6637227.
22. Liu J, Zheng X, Huang Y, Shan H, Huang J. Successful use of methylprednisolone for treating severe COVID-19. J Allergy Clin Immunol. 2020;146:325-327. doi: 10.1016/j.jaci.2020.05.021.
23. Cano EJ, Fonseca Fuentes X, Corsini Campioli C, O'Horo JC, Abu Saleh O, Odeyemi Y, et al. Impact of Corticosteroids in Coronavirus Disease 2019 Outcomes: Systematic Review and Meta-analysis. Chest. 2021;159:1019-1040. doi: 10.1016/j.chest.2020.10.054.
24. Spies CM, Strehl C, van der Goes MC, Bijlsma JW, Buttgereit F. Glucocorticoids. Best Pract Res Clin Rheumatol. 2011;25:891-900. doi: 10.1016/j.berh.2011.11.002.