# Dexamethasone Treatment in Patients With Severe COVID-19: A Propensity Score-Matched Study

**Mahnaz Montazeri[1], Marzieh Pazoki[2], Azar Hadadi[1], Melika Shafeghat[3], Abdolazim Veisizadeh[1], Mohammad Reza Khajavi[4], Farhad Najmeddin[5], Samira Kafan[2]**

*[1] Department of Infectious Diseases, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran*

*[2] Department of Pulmonary Medicine, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran*

*[3] Students' Scientific Research Center (SSRC), Tehran University of Medical Sciences, Tehran, Iran*

*[4] Department of Anesthesiology, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran*

*[5] Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran*

***Received: 06 Oct. 2021; Accepted: 22 Jun. 2022***

**Abstract-** During the coronavirus disease-2019 (COVID-19) pandemic, which was caused by the novel coronavirus, there is an ongoing controversy about the use of corticosteroids. This study aims to investigate the association between Dexamethasone treatment and clinical outcomes in patients with severe COVID-19. In this single-center retrospective cohort study, patients with COVID-19 were enrolled from February 16, 2020, to November 1, 2020. After performing propensity score matching with age, sex, and disease severity. The independent effect of Dexamethasone treatment on in-hospital mortality was evaluated by multivariate proportional hazards regression models. Of 1413 patients with COVID-19 diagnosis, 1172 patients entered the final analysis. 473(40.4%) patients received dexamethasone treatment with a median duration of 6.0[4.0-9.0] days. After matching and adjustment with possible confounders in the multivariate model, administration of dexamethasone significantly increased the survival in severe patients (hazard ratio: 0.25, 95 confidence intervals: 0.16-0.38, $P$<0.001), but there was no difference in non-severe patients ($P$:0.888). The administering of dexamethasone was associated with an increased in-hospital survival rate (HR: 0.25 [0.16-0.38]) in severe COVID-19 patients. The survival rate was more significant in severe patients with diabetes mellitus or hypertension after receiving dexamethasone treatment (HR:0.19). On the other hand, patients without severe disease did not benefit from dexamethasone administration.



*Acta Med Iran* 2022;60(7):413-417.

**Keywords:** Coronavirus disease 2019 (COVID-19); Dexamethasone; Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Corticosteroid; Mortality

## Introduction

During the coronavirus disease-2019 (COVID-19) pandemic, some studies have suggested and evaluated the therapeutic effects of systemic corticosteroids in patients infected with the novel coronavirus (SARS-CoV-2) (1-4). Most adverse outcomes of COVID-19, such as acute respiratory distress syndrome and diffuse alveolar damage, are associated with a hyperinflammatory response; for that reason, administration of corticosteroids may be helpful in the advanced stages of the disease due to its anti-inflammatory and immunosuppressive properties (5-7). There is an ongoing controversy about the use of corticosteroids, and there are different therapeutic protocols for patients with COVID-19 in different countries (8-10). The meta-analysis of trial studies so far by Sterne *et al*., (11) showed that dexamethasone has the greatest effect on increasing recovery and survival rate in patients with severe COVID-19 compared to Hydrocortisone and Methylprednisolone. Due to the lack of information about this subject, there is great debate about the optimal type

**Corresponding Author:** S. Kafan
Department of Pulmonary Medicine, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 9125841846, Fax: +98 2166348550, E-mail address: Kafan.samira@gmail.com

of corticosteroid, dose, timing, and duration of these medications' administration. This study aims to investigate the association between dexamethasone administration and clinical outcomes in patients with severe COVID-19.

## Materials and Methods

The protocol of this study followed the 2013 Helsinki declaration and was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1399.005).

We retrospectively reviewed 1413 patients with COVID-19 diagnosis who were admitted to the Sina Hospital affiliated with Tehran University of Medical Sciences from February 16, 2020, to November 1, 2020. Sina hospital is a major tertiary teaching hospital designated by the government as a primary referral center for COVID-19. A detailed algorithm of patient care and data registry for individuals presenting with respiratory symptoms to the Sina hospital emergency department has been published (12). According to the WHO interim guidance and the Iranian national committee of COVID-19, we included patients ≥18 years old with a) positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) test of the oropharyngeal swab or endotracheal samples or b) compatible chest computed tomography (CT) scan findings including ground-glass opacity alone or ground-glass opacity accompanied by consolidation, not fully explained by volume overload, lobar or lung collapse, or nodules along with the history compatible with COVID-19. We extracted demographics, laboratory, imaging, and clinical information using electronic medical records.

We defined the severe disease based on having each of these criteria: respiratory rate≥30/min, oxygen saturation ≤93%, >50% lung involvement on imaging, respiratory failure, shock, or multiorgan damage. Dexamethasone treatment was defined as the use of 8 mg/day of intravenous dexamethasone ordered by the attending physician. Patients were divided into two groups, including the "dexamethasone group" and the "control group," based on dexamethasone administration during hospital admission.

Categorical variables are presented as numbers (percentage) and compared using the Chi-square test. Continuous variables were demonstrated as mean±standard deviation or median [interquartile range] and compared using a t-test. We performed proportional hazards regression (Cox regression) for our multivariable analysis. Variables with clinically significant or $P<0.05$ in the univariate analysis were considered as possible confounders and entered into the multivariable model. We used propensity score analysis to match the age, sex, and disease severity of the two groups. A 1:1 exact matching was performed using Thoemmes techniques (13).

## Results

In this study, 1413 patients with COVID-19 diagnoses were evaluated. We excluded 153 patients with other systemic corticosteroid treatments (including Methylprednisolone, Prednisolone, and Hydrocortisone) and 88 patients due to a lack of key information in their medical records; eventually, 1172 patients entered the final analysis. During this study, 771(65.8%) patients developed the severe disease, and 185(15.8%) patients deceased during the in-hospital course. Based on the patient's condition and hospital protocol at the time, 473(40.4%) patients received dexamethasone treatment, and 164(14.0%) patients were admitted to an intensive care unit (ICU) for more precise care and monitoring. The median duration of dexamethasone use in patients was 6.0 days, with an interquartile range of 4.0-9.0 days.

The baseline characteristics between the dexamethasone-treated group and the control group are presented in (Table 1). Patients in the dexamethasone group were significantly older, with a higher history of hypertension. In terms of vital signs, patients in the dexamethasone group had higher systolic blood pressure and lower oxygen saturation on admission. In-hospital mortality, severity, and ICU admission rates were significantly higher in the dexamethasone-treated group.

In order to minimize the effect of dexamethasone treatment selection bias and consider potential confounding factors, we used propensity score matching. After matching the two groups based on age, gender, and disease severity, patients with dexamethasone treatments (N=473) were compared with 339 patients in the control group (Table 1). Patients in the dexamethasone group were mostly male ($P$:0.049), with a significantly lower history of chronic kidney disease (CKD) and higher heart rate, higher systolic blood pressure, and lower oxygen saturation and temperature on admission. The need for mechanical ventilation was significantly lower in the dexamethasone group (57(12.1%) vs. 58(17.1%), $P$:0.041), but the in-hospital mortality and severity were similar between groups. The hospital length of stay of dexamethasone group patients was significantly longer in both original and matched samples.

**Table 1. Baseline characteristics between the dexamethasone group and control group in the original sample and in the propensity score-matched sample**

| Characteristic† | | Original sample | | | Matched sample | | |
|---|---|---|---|---|---|---|---|
| | | Dexamethasone group (N=473) | Control group (N=699) | *P** | Dexamethasone group (N=473) | Control group (N=339) | *P** |
| **Demographics** | | | | | | | |
| **Age** | | 60.27±16.08 | 57.77±16.70 | 0.011 | 60.27±16.08 | 60.11±15.57 | 0.887 |
| **Sex** | **Female** | 194(41.0%) | 253(36.2%) | 0.096 | 194(41.0%) | 116(34.2%) | 0.049 |
| | **Male** | 279(59.0%) | 446(63.8%) | | 279(59.0%) | 223(65.8%) | |
| **BMI (kg/m$^2$)** | | 27.57±4.54 | 27.37±4.69 | 0.568 | 27.57±4.54 | 27.52±4.72 | 0.898 |
| **Comorbidities** | **Diabetes Mellitus** | 138(29.2%) | 195(27.9%) | 0.634 | 138(29.2%) | 111(32.7%) | 0.277 |
| | **Hypertension** | 235(49.7%) | 277(39.6%) | 0.001 | 235(49.7%) | 154(45.4%) | 0.231 |
| | **Cardiac disease** | 112(23.7%) | 162(23.2%) | 0.842 | 112(23.7%) | 86(25.4%) | 0.580 |
| | **Cerebrovascular disease** | 20(4.2%) | 27(3.9%) | 0.754 | 20(4.2%) | 15(4.4%) | 0.892 |
| | **Chronic lung disease** | 24(5.1%) | 36(5.2%) | 0.954 | 24(5.1%) | 18(5.3%) | 0.881 |
| | **Chronic kidney disease** | 15(3.2%) | 30(4.3%) | 0.327 | 15(3.2%) | 21(6.2%) | 0.039 |
| | **Malignancy** | 19(4.0%) | 30(4.3%) | 0.818 | 19(4.0%) | 14(4.1%) | 0.936 |
| **Vital signs** | **Heart rate (beat/min)** | 92.56±14.87 | 89.66±30.19 | 0.058 | 92.56±14.87 | 88.36±17.91 | <0.001 |
| | **Systolic blood pressure (mmHg)** | 128.65±20.75 | 124.56±20.87 | 0.002 | 128.65±20.75 | 124.14±21.32 | 0.005 |
| | **Diastolic blood pressure (mmHg)** | 77.53±13.83 | 75.95±12.11 | 0.058 | 77.53±13.83 | 75.65±12.49 | 0.062 |
| | **$O_2$ saturation (%)** | 87.17±8.31 | 91.26±6.98 | <0.001 | 87.17±8.31 | 89.71±8.10 | <0.001 |
| | **Temperature (ºC)** | 37.17±0.88 | 37.22±0.86 | 0.399 | 37.17±0.88 | 37.27±0.90 | 0.147 |
| **Medications** | **Remdesivir** | 97(20.5%) | 9(1.3%) | <0.001 | 97(20.5%) | 6(1.8%) | <0.001 |
| **Clinical outcomes** | **Hospital length of stay (days)** | 6.0[4.0-10.0] | 3.0[1.0-6.0] | <0.001 | 6.0[4.0-10.0] | 4.0[2.0-6.0] | <0.001 |
| | **Severity** | 359(75.9%) | 412(58.9%) | <0.001 | 359(75.9%) | 247(72.9%) | 0.327 |
| | **ICU admission** | 85(18.0%) | 79(11.3%) | 0.001 | 85(18.0%) | 59(17.4%) | 0.835 |
| | **Mechanical ventilation** | 57(12.1%) | 66(9.4%) | 0.153 | 57(12.1%) | 58(17.1%) | 0.041 |
| | **In-hospital mortality** | 92(19.5%) | 93(13.3%) | 0.005 | 92(19.5%) | 69(20.4%) | 0.750 |

BMI: body mass index, ICU: intensive care unit
† Data are presented as mean ± standard deviation, number (%), or median [interquartile range]
* Statistically significant *P* are bolded

**Table 2. Association of dexamethasone treatment with in-hospital mortality of patients with COVID-19 in Cox Regression modeling after propensity score matching**

| | | Model 1† | | | | Model 2 ‡ | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | | *P** | HR | 95% CI | | *P** |
| | | | Lower | Higher | | | Lower | Higher | |
| **All patients** | **Severe patients** | 0.31 | 0.21 | 0.44 | <0.001 | 0.25 | 0.16 | 0.38 | <0.001 |
| | **Non-severe patients** | 1.18 | 0.31 | 4.54 | 0.812 | 1.15 | 0.16 | 8.43 | 0.888 |
| **Severe diabetic patients** | | 0.23 | 0.13 | 0.41 | <0.001 | 0.19 | 0.10 | 0.39 | <0.001 |
| **Severe hypertensive patients** | | 0.27 | 0.17 | 0.43 | <0.001 | 0.19 | 0.11 | 0.35 | <0.001 |

† Model 1: Unadjusted Cox regression analysis
‡ Model 2: Multivariate Cox regression analysis, adjusted with: age, history of diabetes mellitus, hypertension, cardiac disease, cerebrovascular disease, chronic kidney disease, malignancy, admission heart rate, oxygen saturation, and use of Remdesivir
* Statistically significant *P* are bolded

In univariate regression analysis, age, history of diabetes mellitus, hypertension, cardiac disease, cerebrovascular disease, CKD, malignancy, admission heart rate, oxygen saturation, use of Remdesivir, and disease severity were significantly associated with in-hospital mortality and were considered as confounders in the multivariate analysis. In multivariant Cox regression in the matched sample, after adjustment with possible confounders (Table 2), administration of dexamethasone significantly increased the survival in severe patients (hazard ratio (HR): 0.25, 95 confidence intervals (CI): 0.16-0.38, *P*<0.001), but there was no difference in non-severe patients (HR: 1.15, 95% CI: 0.16-8.43, *P*:0.888) (Figure 1). We repeated this analysis in severe patients with diabetes mellitus and hypertension separately (Table 2), and dexamethasone treatment was associated with higher survival in subgroups compared to all patients (HR: 0.19 vs. 0.25, *P*<0.001).

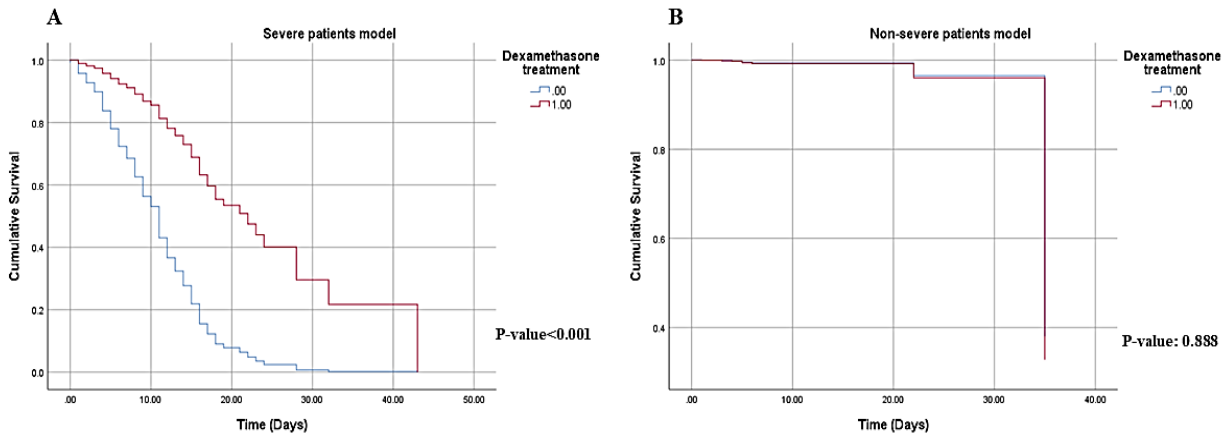


**Figure 1.** Cumulative survival of patients based on dexamethasone treatment in the (A) severe patients' model and (B) non-severe patients' model

## Discussion

In this cohort study, we found that administering 8 mg/day of intravenous dexamethasone with a median duration of 6.0 [4.0-9.0] days was associated with an increased in-hospital survival rate (HR:0.25 [0.16-0.38]) in severe COVID-19 patients. The survival rate was more significant in severe patients with diabetes mellitus or hypertension after receiving dexamethasone treatment (HR:0.19). On the other hand, patients without severe disease did not benefit from dexamethasone administration.

The RECOVERY trial study is the only clinical trial investigating dexamethasone administration (6 mg/day) in both severe and non-severe patients (1). They showed that the use of dexamethasone decreased the 28-day mortality only among patients who were receiving either invasive mechanical ventilation or oxygen support. The two other clinical trials (2,11) evaluated the use of dexamethasone (20 mg/day) only in patients with invasive mechanical ventilation, and there was no difference in mortality between the two groups. Our findings support the RECOVERY trial results. Patients with hypoxemia (oxygen saturation≤93%) or severe manifestation of COVID-19 had significantly lower in-hospital mortality after administration of dexamethasone (8 mg/day). Also, we found no association between the use of dexamethasone and mortality in non-severe patients, which is similar to other studies (1,9). Besides, some studies have found that early, low-dose, and short-term use of corticosteroids in mild or moderate cases can increase viral shedding, risk of severe disease, and length of hospital stay (14,15). Different results in studies can be due to different timing, dose, and duration of dexamethasone treatment in these studies; in addition, different ethnic groups and populations must be considered.

The current report has several limitations. First, this is an observational study with potential biases, which indicates caution in extrapolating its results. Further randomized clinical trial studies are warranted. Second, this is a single-center study, and further multi-center studies on different ethnicities are necessary. Third, we could not define the symptom onset to admission duration time in our study, which can be an important factor in interpreting the results.

In summary, the use of dexamethasone (8 mg/day) in patients with severe COVID-19 was associated with a significantly lower mortality rate, especially in patients with diabetes or hypertension. Our results support the WHO recommendations not to use systemic corticosteroids for non-severe patients.

This study has been supported by the Tehran University of Medical Sciences (grant number: 99-1-101-47211 to HA). The funding source had no role in the study design, data collection, data analysis, data interpretation, writing of the manuscript, or decision of submission.

## Acknowledgments

We acknowledge all healthcare workers involved in the diagnosis and treatment of patients in Sina Hospital. We are indebted to the Research Development Center of Sina Hospital for its support. The authors are grateful to Mrs. Masoumeh Taleh and Mr. Saeed Hejrani for their help and to members of the COVID-19 Crisis Committee of the Sina Hospital for their help and consult.

## References

1. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med 2021;384:693-704.
2. 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;324:1307-16.
3. Bartoli A, Gabrielli F, Alicandro T, Nascimbeni F, Andreone P. COVID-19 treatment options: a difficult journey between failed attempts and experimental drugs. Intern Emerg Med 2021;16:281-308.
4. Soleimani A, Kazemian S, Karbalai Saleh S, Aminorroaya A, Shajari Z, Hadadi A, et al. Effects of Angiotensin Receptor Blockers (ARBs) on In-Hospital Outcomes of Patients With Hypertension and Confirmed or Clinically Suspected COVID-19. Am J Hypertens 2020;33:1102-11.
5. Ahmed MH, Hassan A. Dexamethasone for the Treatment of Coronavirus Disease (COVID-19): a Review. SN Compr Clin Med 2020;2:2637-46.
6. Ranjbar K, Moghadami M, Mirahmadizadeh A, Fallahi MJ, Khaloo V, Shahriarirad R, et al. Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: a triple-blinded randomized controlled trial. BMC Infect Dis 2021;21:337.
7. Lester M, Sahin A, Pasyar A. The use of dexamethasone in the treatment of COVID-19. Ann Med Surg (Lond) 2020;56:218-9.
8. Johnson RM, Vinetz JM. Dexamethasone in the management of covid -19. BMJ 2020;370:m2648.
9. Shuto H, Komiya K, Yamasue M, Uchida S, Ogura T, Mukae H, et al. A systematic review of corticosteroid treatment for noncritically ill patients with COVID-19. Sci Rep 2020;10:20935.
10. Pazoki M, Keykhaei M, Kafan S, Montazeri M, Mirabdolhagh Hazaveh M, Sotoodehnia M, et al. Risk indicators associated with in-hospital mortality and severity in patients with diabetes mellitus and confirmed or clinically suspected COVID-19. J Diabetes Metab Disord. 2021;20:59-69.
11. Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA 2020;324:1330-41.
12. Talebpour M, Hadadi A, Oraii A, Ashraf H. Rationale and Design of a Registry in a Referral and Educational Medical Center in Tehran, Iran: Sina Hospital Covid-19 Registry (SHCo-19R). Adv J Emerg Med 2020;4:e53.
13. Thoemmes F. Propensity score matching in SPSS. arXiv 2012:12016385.
14. Li Q, Li W, Jin Y, Xu W, Huang C, Li L, et al. Efficacy Evaluation of Early, Low-Dose, Short-Term Corticosteroids in Adults Hospitalized with Non-Severe COVID-19 Pneumonia: A Retrospective Cohort Study. Infect Dis Ther 2020;9:823-36.
15. Hu Z, Lv Y, Xu C, Sun W, Chen W, Peng Z, et al. Clinical Use of Short-Course and Low-Dose Corticosteroids in Patients With Non-severe COVID-19 During Pneumonia Progression. Front Public Health 2020;8:355.