The Outcome of High-Dose Corticosteroid Treatment Among Coronavirus Disease 2019 Patients

A Retrospective Cohort Study

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Abstract: This study aimed to demonstrate the association between high-dose corticosteroid administration and adverse outcomes in coronavirus disease 2019 patients. Data were collected retrospectively from medical records. The primary outcome was invasive mechanical ventilation or death, whichever occurred first. The secondary outcome was all-cause in-hospital mortality. The standard dose was defined as a daily dose of ≤1.5 mg/kg of prednisolone or equivalent, and the high-dose was defined as ≥250 mg of prednisolone or equivalent. Data were analyzed using frequentist and Bayesian logistic models. In addition, a propensity score–matched subgroup was analyzed for the association between high-dose corticosteroid use and adverse outcomes. A total of 1072 patients hospitalized between September 29, 2020, and April 20, 2021, were enrolled in the study. Of these, 188 patients (18%) had a primary outcome; 55 patients (29%) died, and 133 (71%) required invasive mechanical ventilation. Higher age was associated with adverse outcomes in all analyses. Standard dose corticosteroid use was found to be protective (odds ratio [95% confidence interval], 0.53 [0.35–0.81]) in the final logistic model. Point estimates in the propensity score–matched subgroup did not encourage high-dose corticosteroid use (odds ratio [95% confidence interval], 3.06 [0.98–9.50]). The posterior probability density distributions generated by the Bayesian logistic model implicated standard-dose corticosteroid use as protective (80% credible intervals, −0.839 to −0.313), whereas it implicated high-dose corticosteroid use as associated with adverse outcomes (80% credible intervals, 0.163–0.941). This study found high-dose corticosteroid (≥250 mg prednisolone daily) use associated with adverse outcomes.

Key Words: corticosteroids, prednisolone, propensity score, COVID-19

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Although it has been more than a year since coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China, it remains a top-priority health care problem because it was declared a pandemic. The immunopathology of the disease, which is not yet entirely elucidated, is highly variable.[1] The course of the disease consists of 3 consecutive stages: (1) viral replication, (2) organizing pneumonia, and (3) late complications, including necrotizing pneumonia, suppurative bronchopneumonia, and other secondary infections.[2] Postmortem examinations frequently documented diffuse alveolar damage, thrombosis, organizing pneumonia, and bronchopneumonia. In other words, postmortem studies suggest that nonviral etiologies might be at least partly responsible for disease severity.[3] In addition, recent studies have documented an association between dysregulated immune responses and tissue injury in COVID-19 patients.[4] Therefore, immunomodulatory drugs have attracted considerable interest during the COVID-19 pandemic.

Immunomodulatory drugs are promoted to regulate excess inflammation. Among the various immunomodulatory drugs, corticosteroids seem to be the most promising.[5] Corticosteroids readily cross cell membranes, bind to a soluble receptor, and control the expression of multiple genes.[6] Corticosteroids also inhibit endothelial adhesion molecules and suppress the accumulation of neutrophils in the inflammation site.[7] However, the appropriate dosage and duration of corticosteroids for COVID-19 patients are still debatable.[8,9] Therefore, we aimed to conduct a retrospective study to elucidate the association between high-dose corticosteroid treatment and adverse outcomes in COVID-19 patients.

MATERIALS AND METHODS

The Setting, Study Design, and Data Collection

Our institution is a 740-bed tertiary care hospital affiliated with a university medical school. Depending on the daily infection rates in our city, our hospital administration accommodated the number of reserved beds for COVID-19 patients.

This is a retrospective cohort study that followed the STROBE guides.

We primarily hospitalize patients with moderate-to-severe COVID-19.[10] Oxygen is delivered using a nasal cannula with or without bag-valve-mask in regular wards, a high-flow nasal cannula in the second-level intensive care unit (ICU), and invasive mechanical ventilation (IMV) in the third-level ICU.

In our institution, doctors from different departments manage COVID-19 patients independently. As a result, some patients receive high-dose corticosteroids (HD-CS), whereas others are administered standard-dose corticosteroids (SD-CS). In addition, the emergency department team allocates patients to the departments according to bed availability. Thus, we were able to compare the efficacy of HD-CS in quasirandomized patients.

Medications, laboratory, and outcome data were obtained from the electronic hospital records. In addition, patients' baseline status was extracted from the medical notes of the emergency department. The patients were discharged from the hospital on the third consecutive stable day. Patients who were not stable for discharge and were therefore transferred to another hospital were excluded from the analysis.

This study was performed per the principles of the Declaration of Helsinki. Accordingly, approval was granted by the Ethics Committee of the Institute (2021/0286), with a waiver for informed consent.

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Definitions and Baseline Variables

Coronavirus disease 2019 was diagnosed when a patient presented with compatible symptoms and a positive polymerase chain reaction test (confirmed case) or computerized thorax imaging resembling COVID-19 pneumonia (probable case). Disease severity was assessed by consulting infectious disease physicians according to O_2 saturation, respiratory rate per minute, older age, and computerized thorax findings. Patients were considered stable if they had no high fever (≥38°C) and no requirement for oxygen support.

The primary outcome was a composite of death or IMV, whichever occurred first, and the secondary outcome was all-cause death during the hospital stay. Patients who were intubated immediately at admission to the hospital were excluded.

We defined SD-CS as a daily dose of ≤1.5 mg/kg of prednisolone or equivalent and HD-CS as ≥250 mg of prednisolone or equivalent.[11,12]

We collected demographic data and baseline variables at admission to the hospital to assess case severity. The baseline variables were O_2 saturation at ambient air, respiratory rate per minute, delayed time from the onset of symptoms, and lymphocyte and neutrophil counts.

Statistical Analysis

We performed data cleaning and statistical analysis using R statistical software (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables that were not normally distributed were reported as medians and interquartile ranges, and groups were compared using the Mann-Whitney *U* test. Categorical variables were reported as frequencies and percentages (%), and groups were compared using Pearson χ^2 test.

Our data were not suitable for survival analysis because we discharged stable patients and discontinued follow-up because these patients were no longer at risk of developing the outcome. The data thus did not satisfy the assumption that censoring was noninformative.[13] That censored individuals were equally at risk of experiencing the outcome as the rest of the study population at the time of censoring.[14] We, therefore, used logistic regression models to explore the data.

We applied both Bayesian and frequentist logistic regression models to estimate the association between corticosteroid dosage and the outcomes. We imputed missing observations and combined the estimates using Rubin's rules. Variables that were statistically significant ($P < 0.05$) in the univariate analysis were included in the initial model, and variables in the final model were selected

TABLE 1. Comparison of Demographics and Baseline Severity Features of Cases to Controls

		IMV or Death*		
Features	**n**	**No n = 884 (82%)‡**	**Yes n = 188 (18%)‡**	***P*†**
Age, y	1072	57 (46–68)	68 (59–76)	<0.001
Male sex	1072	449 (51)	118 (63)	0.003
Delayed time to admission	1029	6.0 (3.0–8.0)	4.0 (2.0–7.0)	<0.001
Respiration rate per minute	1033	26.0 (22.0–30.0)	28.0 (24.0–32.0)	<0.001
O_2 saturation	1051			<0.001
<88		148 (17)	79 (45)	
88–93		349 (40)	56 (32)	
>93		380 (43)	39 (22)	
Neutrophils, $\times 10^9$/L	1054	4.4 (3.2–6.9)	5.9 (4.0–9.1)	<0.001
Lymphocytes, $\times 10^9$/L	1053	1.10 (0.70–1.50)	0.70 (0.40–1.10)	<0.001
Corticosteroids	1072			<0.001
Not used		196 (78)	54 (22)	
Standard dose (≤1.5 mg/kg/d)		630 (86)	104 (14)	
High dose (≥250 mg/d)		58 (66)	30 (34)	
Antiviral treatment	1072			0.2
No antiviral		566 (84)	108 (16)	
Favipiravir		73 (82)	16 (18)	
Lopinavir-ritonavir		245 (79)	64 (21)	
ICU admittance	1072	50 (5.7)	161 (86)	
Event type	1072			
Died before mechanical ventilation		0 (0)	55 (29)	
Required mechanical ventilation		0 (0)	133 (71)	
Discharged stable		884 (100)	0 (0)	
Died overall	1072	0 (0)	157 (84)	

*Invasive mechanical ventilation or death, whichever comes first.

†Wilcoxon rank sum test; Pearson χ^2 test.

‡Median (interquartile range); n (%).

by a stepwise backward elimination procedure using the rms and Hmisc packages.[15] The final model was calibrated using various transformations and internally validated using bootstrapping. Overfitting was identified using a heuristic shrinkage factor of >90. We tested for multicollinearity according to the variance inflation factor and excluded the less significant of the 2 variables, if necessary.

We also conducted a propensity score–matched analysis to minimize baseline imbalance between the patients administered HD-CS and the other patients. Propensity scores were generated using a logistic regression model that included age, sex, O_2 saturation in ambient air, lymphocyte and neutrophil counts on admission, and the administration of antiviral drugs. High-dose corticosteroids patients were matched with controls in a 1:1 ratio by the nearest neighbor method using the MatchThem software package.[16]

We conducted Bayesian logistic analysis using the brms package, which uses Markov Chain Monte Carlo sampling using the Stan language.[17] We checked the output for sampling efficiency and potential scale-reduction factors using the Rhat convergence diagnostic. In addition, we carried out sensitivity analyses using variables with informative and weakly informative prior distributions.

RESULTS

A total of 1072 patients hospitalized between September 29, 2020, and April 20, 2021, were enrolled in the study. During the study period, 157 patients (14.6%) died. Of these, 55 patients died in the ICU while on noninvasive ventilator support. In addition, 250 patients did not receive corticosteroids (no-CS), 734 patients received SD-CS, and 88 patients received HD-CS.

Table 1 presents the demographics and baseline features of the patients with composite primary outcomes. Briefly, older age and male sex were associated with adverse events. Delayed time to admission and higher respiratory rate per minute were also significant among the cases. However, O_2 saturation at admission was remarkable. We found that 45% of patients who experienced adverse outcomes presented with an O_2 saturation of <88%. Of 1072 patients, 22% of patients in the no-CS group, 14% in the SD-CS group, and 34% of the HD-CS-treated patients had the primary outcome.

Mostly, the infectious diseases department used lopinavir, whereas others used favipiravir. However, patients admitted after the 8th day of the disease did not use antivirals, or some patients admitted were already on an antiviral drug (favipiravir used widely in Turkey). Briefly, antiviral usage varies among patients. However, antivirals had no significant effect on the outcome and therefore was eliminated during the variable selection routine.

We constructed a full logistic model with age, sex, corticosteroid use, O_2 saturation (categorized as <88, 88–93, and >93), respiratory rate per minute, lymphocyte count, and neutrophil count. Stepwise evaluation eliminated lymphocyte count. We discarded the variable respiratory rate per minute because of collinearity. The final model and point estimates are presented in Table 2. Briefly, higher age and male sex were significantly associated with the primary and secondary outcomes. On the other hand, higher O_2 saturation at admission and SD-CS use were protective for both outcomes. A higher neutrophil count was only associated with the primary outcome.

Propensity scores were generated using the following covariates: age, sex, delayed time to admission, O_2 saturation, neutrophil count, and antiviral treatment. Eventually, the HD-CS–treated patients (n = 88) were 1:1 matched with controls (n = 88). Figure 1 displays the covariate balance, and Table 3 shows the point estimates for adverse outcomes in the propensity score–matched subgroup.

TABLE 2. Point Estimates From the Final Logistic Model for Primary and Secondary Outcomes

	IMV or Death*			All-Cause Mortality*		
Characteristic	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age	1.04	1.03–1.05	**<0.001**	1.05	1.04–1.07	**<0.001**
Male sex	1.83	1.27–2.62	**0.001**	2.00	1.35–2.96	**<0.001**
Corticosteroids†						
Not used	—	—		—	—	
SD-CS	0.53	0.35–0.81	**0.003**	0.51	0.32–0.80	**0.003**
HD-CS	1.57	0.85–2.92	0.2	1.71	0.90–3.27	0.10
O_2 saturation						
88–93	0.35	0.23–0.54	**<0.001**	0.38	0.24–0.59	**<0.001**
>93	0.26	0.16–0.41	**<0.001**	0.24	0.14–0.41	**<0.001**
Neutrophil count	1.05	1.01–1.09	**0.018**	1.03	0.98–1.07	0.2

Estimates <0.05 is shown in boldface.

*Composite of IMV or death is the primary outcome. All-cause mortality in the hospital is the secondary outcome.

†Standard-dose corticosteroid use (≤1.5 mg/kg per day); HD-CS use (≥250 mg/day).

CI indicates confidence interval; OR, odds ratio.

Briefly, older age was associated with adverse outcomes in the propensity score–matched subgroup. The estimated credible intervals of HD-CS in the matched subgroup shifted to the right compared with the estimates from the unmatched comparison. This difference was due to the higher proportion of SD-CS–treated patients in the matched subgroup than in the cohort.

The Bayesian model was run with a weakly informative prior distribution for 1000 warmup and 40,000 total postwarmup samples. Figure 2 displays the posterior 80% and 95% high probability density intervals (HPDIs) generated by the model. Briefly, HPDIs of HD-CS use and age reside outside and on the right, and the HPDIs of SD-CS and O_2 saturation reside outside and on the left of zero intercepts. These posterior distributions suggest that with 80% probability, future studies (future samplings) would find HD-CS use and age to be significantly associated with the primary outcome. On the other hand, the posterior distribution from the Bayesian model suggests that, with high probability, future studies would find SD-CS and higher O_2 saturation as protective factors.

DISCUSSION

Although there is a broad consensus on corticosteroid use in treating COVID-19 patients, the timing, dosage, and duration of corticosteroids remain debatable.[18] For example, one randomized controlled trial (RCT) found that corticosteroid use before ICU admission was beneficial,[8] whereas another placebo-controlled RCT failed to reproduce this effect.[19] In addition, one RCT found that high-dose methylprednisolone was beneficial.[20] However, at the same time, another failed to prove its benefits among COVID-19 patients with acute respiratory distress syndrome.[12] One other study found 6 mg of dexamethasone as effective as 12 mg of dexamethasone.[21] Hence, studies addressing the timing, dosage, and duration of corticosteroid use are of scientific interest and are important during the ongoing COVID-19 pandemic.

Using both frequentist and Bayesian approaches, we found that SD-CS is protective against adverse outcomes. However, this study point estimates failed to demonstrate a favorable effect of HD-CS use. In the propensity score–matched subgroup, the effect directions of HD-CS suggest some association with adverse outcomes. Furthermore, credible intervals estimated by the Bayesian

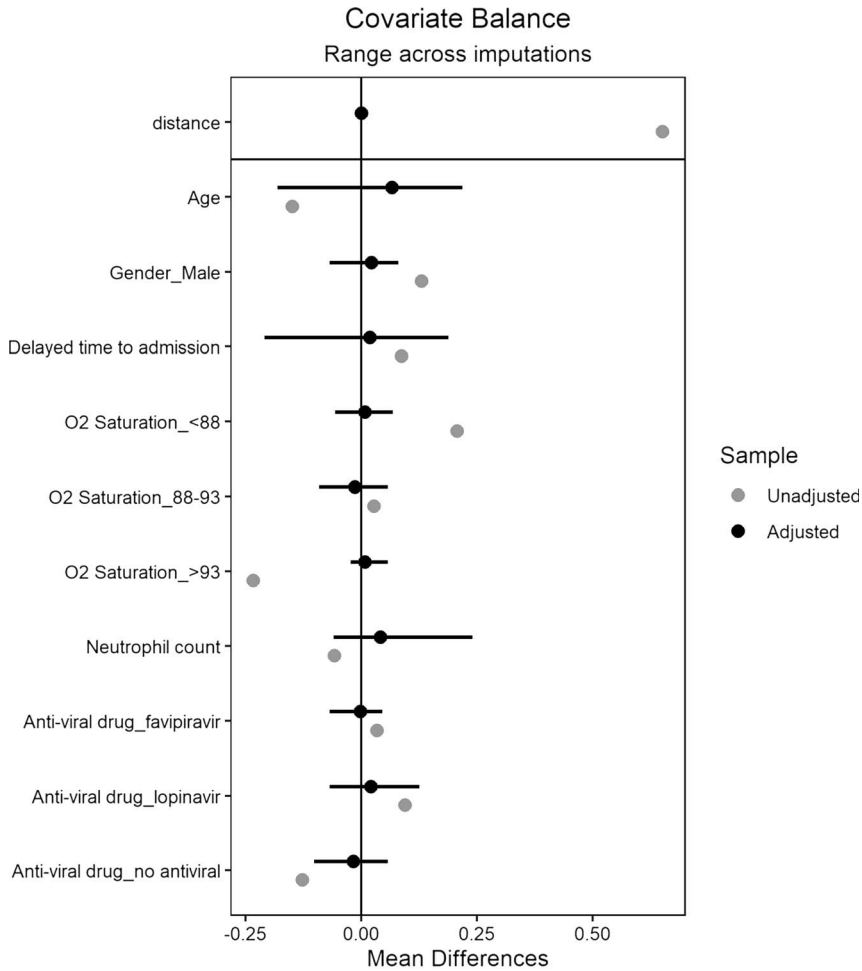


FIGURE 1. The covariate balance obtained before and after adjusting with propensity score matching. Estimates and ranges were combined across multiple imputed data sets.

model suggested an 80% probability that future studies would not favor HD-CS use.

Certain studies, through postmortems, have documented distinct consecutive stages of COVID-19 infection.[2] The first being the viral activity stage, which is suppressed by the end of the first week, concomitant with increased T-cell activity in the lung tissue.[22,23] To some extent, the early postviral activity stage is dominated by dysregulated immune responses. Recent studies have provided evidence suggesting cytokine- or mast cell–mediated interstitial edema and tissue damage in the lung.[4,24,25]

Briefly, corticosteroids are used to reduce the adverse effects of inflammation. However, the optimal dosage is debatable. After 1 mg/kg intravenous administration, prednisolone is eliminated from the blood in 24 hours.[26] The elimination rate does not change grossly with higher doses, and nearly one fifth of the amount is excreted during the first 4 hours.[27] In other words, HD-CS use seems to result in the overexcretion of free prednisolone. However, HD-CS would also result in higher concentrations of free prednisolone in the blood.

Furthermore, the cumulative effect of corticosteroids is linear with the logarithm of the dose, and this relationship is only valid before the maximum effect is reached.[28] Therefore, higher doses would not provide benefits comparable with those expected beyond increased complications. In other words, the rationale for HD-CS use is not justified.

The main weakness of our study is its retrospective design, which leads to an imbalance in baseline confounders. We attempted to balance the baseline confounders between the cases and controls by propensity score matching. However, propensity score matching fails to account for unobserved confounders. The second

TABLE 3. Point Estimates From Propensity Score–Matched Subgroup

	IMV or Death*			All-Cause Mortality*		
Characteristic	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age	1.05	1.02–1.09	**0.003**	1.07	1.03–1.11	**<0.001**
HD-CS†	3.06	0.98–9.50	0.053	3.35	1.01–11.1	**0.048**
Oxygen saturation						
88–93	0.64	0.25–1.61	0.3	0.63	0.24–1.67	0.3
>93	0.43	0.12–1.56	0.2	0.44	0.12–1.63	0.2

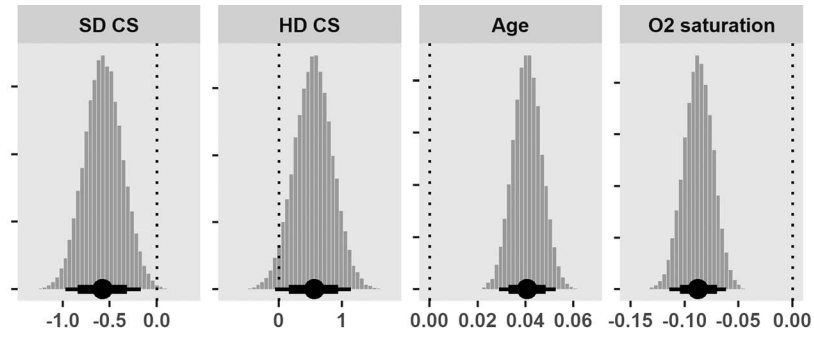
Estimates <0.05 is shown in boldface.

*Primary outcome, composite of death or IMV. Secondary outcome, all-cause mortality in the hospital.

†High-dose corticosteroid use (≥250 mg/d).

CI indicates confidence interval; OR, odds ratio.

A.



B.

names	mean	80%_HPDL	80%_HPDU
SD CS	-0.570	-0.839	-0.313
HD CS	0.545	0.163	0.941
Age	0.041	0.033	0.048
O2 saturation	-0.088	-0.104	-0.070

FIGURE 2. Posterior probability density distributions generated via a Bayesian logistic model. Standard-dose corticosteroid, ≤1.5 mg/kg of prednisolone per day; HD-CS, ≥250 mg/d of prednisolone. A, The plot of posterior probability distributions. The thick line at the base represents 80% credible intervals, and the thin line represents 95% credible intervals. B, Table displays the mean estimate and 80% credible intervals.

most critical weakness is the variability in standard of care among individual physicians. We balanced the antiviral choice between groups in the matched subgroup. Third, we could not explore complications of corticosteroid use.

Finally, this study supports SD-CS use before patients require IMV and do not promote HD-CS in COVID-19 treatment.

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