

Effect of Corticosteroids on Mortality in Hospitalized COVID-19 Patients Not Receiving Invasive Mechanical Ventilation

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The most beneficial effect of corticosteroid therapy in COVID-19 patients has been shown in subjects receiving invasive mechanical ventilation (IMV), corresponding to a score of 6 on the World Health Organization (WHO) COVID-19 Ordinal Scale for Clinical Improvement (OSCI). The aim of this observational, single-center, prospective study was to assess the association between corticosteroids and hospital mortality in coronavirus disease 2019 (COVID-19) patients who did not receive IMV (OSCI 3–5). Included were 1,311 COVID-19 patients admitted to nonintensive care wards, and they were divided in two cohorts: (i) 480 patients who received corticosteroid therapy and (ii) 831 patients who did not. The median daily dose was of 8 mg of dexamethasone or equivalent, with a mean therapy duration of 5 (3–9) days. The indication to administer or withhold corticosteroids was given by the treating physician. In-hospital mortality was similar between the two cohorts after adjusting for possible confounders (adjusted odds ratio (ORadj) 1.04, 95% confidence interval (CI), 0.81–1.34, $P = 0.74$). There was also no difference in Intensive Care Unit (ICU) admission (ORadj 0.81, 95% CI, 0.56–1.17, $P = 0.26$). COVID-19 patients with noninvasive mechanical ventilation (NIMV) had a lower risk for ICU admission if they received steroid therapy (ORadj 0.58, 95% CI, 0.35–0.94, $P = 0.03$). In conclusion, corticosteroids were overall not associated with a difference in hospital mortality for patients with COVID-19 with OSCI 3–5. In the subgroup of patients with NIMV (OSCI 5), corticosteroids reduced ICU admission, whereas the effect on mortality requires further studies.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The efficacy of corticosteroids in the treatment of patients with novel coronavirus disease 2019 (COVID-19) requiring invasive mechanical ventilation (IMV) and oxygen therapy has been demonstrated in randomized clinical trials and their meta-analyses.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ What is the association between treatment with corticosteroids and in-hospital mortality in noncritically ill COVID-19 patients who did not receive invasive mechanical ventilation?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Differently from mechanically ventilated COVID-19 patients, there is no association between corticosteroids and mortality in COVID-19 patients who did not receive IMV.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This study shows that corticosteroid therapy is not useful in COVID-19 patients not receiving IMV. Of note, our data is conflicting with results from the RECOVERY trial, and therefore gathering more evidence on the subject would be desirable.

In the past months, the spotlight has been on the effects of corticosteroid therapy on hospitalized patients with novel coronavirus disease 2019 (COVID-19), with many randomized clinical trials being conducted on the subject.^{1–5}

Many of the ongoing trials were stopped early, due to the results of the preliminary report from the RECOVERY Collaborative

Group, which showed that the use of dexamethasone was associated with a lower 28-day mortality in patients who were receiving either invasive or noninvasive mechanical ventilation or oxygen therapy, compared with standard care.⁵

While the evidence in favor of corticosteroid therapy in patients with acute respiratory distress syndrome (ARDS) from

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any cause⁵⁻⁹ seems to be confirmed also in ARDS secondary to COVID-19, the RECOVERY Collaborative Group Preliminary Report results were consistent with dexamethasone being possibly harmful in patients not receiving oxygen therapy.⁵

The aim of this study was to assess the association between corticosteroid therapy and hospital mortality in noncritically ill COVID-19 patients, who had been admitted to the ward for more than 24 hours and who did not need invasive mechanical ventilation (with a score of 3, 4, and 5 on the World Health Organization (WHO) COVID-19 Ordinal Scale for Clinical Improvement (OSCI)).

MATERIAL AND METHODS

In this observational cohort study, data were prospectively collected from the electronic medical records of patients admitted between February 20 and May 10, 2020 to Poliambulanza Foundation Hospital, a 600-bed tertiary care hospital in Northern Italy. The study protocol was approved by the Ethics Committee of Brescia.

Patients were included in the study if they had a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive reverse transcriptase real-time polymerase chain reaction test on biological material obtained from a nasopharyngeal swab, if they had been admitted to a nonintensive ward, and if they did not receive invasive mechanical ventilation at the time of enrollment. Patients with a score of 3, 4, and 5 on the WHO COVID-19 OSCI were included.¹⁰ Patients with a score of 3 were hospitalized patients not receiving oxygen therapy, patients with a score of 4 were hospitalized patients receiving oxygen by mask or nasal prongs, and patients with a score of 5 were patients receiving noninvasive positive pressure ventilation or high-flow oxygen.

Patients were excluded if they were younger than 18 years, had been admitted directly to the intensive care unit (ICU), or had a length of stay on the ward of < 24 hours. Oxygen therapy was started if oxygen saturation was < 90%; noninvasive mechanical ventilation was indicated in the presence of dyspnea or with oxygen saturation < 90% despite oxygen therapy. ICU admission and invasive mechanical ventilation were indicated if, despite noninvasive ventilation, any of the following were present: ratio of arterial oxygen partial pressure to fractional inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) < 100 mmHg, dyspnea, respiratory rate > 40 breaths per minute, or tidal volume > 10 ml/kg.

Patients were divided into two cohorts: (i) patients who received corticosteroid therapy on the ward and (ii) patients who did not receive corticosteroid therapy on the ward.

Corticosteroid therapy with drugs different from dexamethasone was converted to the equivalent dose.¹¹ The choice of patients' treatment plan and the decision to start or withhold corticosteroid therapy was made by the attending physician, since there was no clear evidence in favor or against the use of corticosteroids in COVID-19 patients at the time of the study.

Primary outcome was association between corticosteroid use and in-hospital mortality. The association between corticosteroid therapy and ICU admission was the secondary outcome.

For secondary analyses, patients were divided according to the need of positive pressure support: The noninvasive mechanical ventilation (NIMV) group included all patients with a score of 5 on the WHO COVID-19 OSCI, that is to say patients that received noninvasive positive pressure ventilation (continuous positive airway pressure or pressure support ventilation), while the group of patients not on NIMV included all patients with a score of 3 or 4 on the WHO COVID-19 OSCI, i.e., patients that did not receive positive pressure ventilation (spontaneously breathing patients, with or without oxygen therapy).

Statistical analysis

One thousand fifty four patients were needed to obtain a power of 80% to detect an odds ratio of 0.7, assuming mortality was 25% in those

receiving corticosteroids, with one patient treated with corticosteroids for every three patients admitted to the hospital and alpha error = 0.05.

Continuous variables are expressed with mean (standard deviation, SD) or median (1st quartile–3rd quartile) as appropriate, discrete variable as count (percentage). Bivariate analysis of the outcome was performed with Fisher's exact test for factorial variables and Student's *t*-test for continuous ones. Association with corticosteroid treatment was assessed, and a propensity score was estimated using variables that were associated with treatment allocation and survival. The overlap weight method was used for balancing variables between the corticosteroids cohort and control cohort.¹² Association with hospital survival was assessed with logistic regression; odds ratios (ORs) with 95% confidence interval (CI) are reported. A second analysis was conducted with proportional hazard ratios. Patients were considered alive after hospital discharge and the results were reported in explicative figures.

Collinearity was assessed with variation inflation factor, and variables were excluded from the multivariate model if variation inflation factor was > 3 and if there was correlation with other explanatory variables (for example, $\text{PaO}_2/\text{FiO}_2$ and PaO_2). Missing values, in covariates, were assessed and replaced with mean substitution. A sensitivity analysis including only complete cases was conducted to evaluate the effect of missing values.

Planned secondary analyses were conducted according to the daily dosage of corticosteroids used: more than 8 mg of dexamethasone/*die* (the median daily dose) and less than or equal to 8 mg/*die*, and assessing the effect of corticosteroids in patients with or without noninvasive ventilation.

Statistical analysis was performed using R Studio software version 4.0.0 (R Core Team, Vienna, Austria, 2014) and packages "psw" and "survival" for overlap weight propensity score and Cox's model estimation, respectively.

RESULTS

As shown in **Figure 1**, 11,671 patients visited Fondazione Poliambulanza's emergency room during the study period, 2,053 of them tested positive for SARS-CoV-2, and 1,403 of those were admitted to the hospital. Forty-one of them were admitted directly to the ICU, while 1,362 were admitted to a nonintensive ward. In the first 24 hours of hospital stay, 37 patients went to intensive care, and 14 died or were discharged: They were therefore excluded from analyses. Of the 1,311 remaining patients, 480 were exposed to steroids, and 831 were not (**Figure 1**). Three hundred ninety patients underwent noninvasive mechanical ventilation on the nonintensive care wards; 203 of them received corticosteroid therapy and 187 did not.

The median daily equivalent dose of dexamethasone was 8 (4–17) mg per day.

Duration of corticosteroid therapy was 5 (3–9) days, and corticosteroid therapy was started on day 2 (2–5) of the hospital stay.

Characteristics of patients in the corticosteroid and in the no corticosteroid cohorts are presented in **Table 1**.

Table 2 shows the characteristics of survivors and nonsurvivors, with nonsurvivors being older, more frequently male, with a higher incidence of diabetes mellitus and a more severe respiratory dysfunction at baseline.

Table 3 shows that the OR for in-hospital mortality is not statistically different between the cohort of patients receiving and the one not receiving corticosteroids (adjusted odds ratio (OR_{adj}) 1.04, 95% CI, 0.81–1.34, $P = 0.74$) after adjusting for possible confounders. This finding was confirmed by the survival analysis (**Figure 2**). There is also no difference for the secondary outcome of ICU admission (OR_{adj} 0.81, 95% CI, 0.56–1.17, $P = 0.26$). In the planned subgroup analysis, corticosteroid therapy was not found to increase

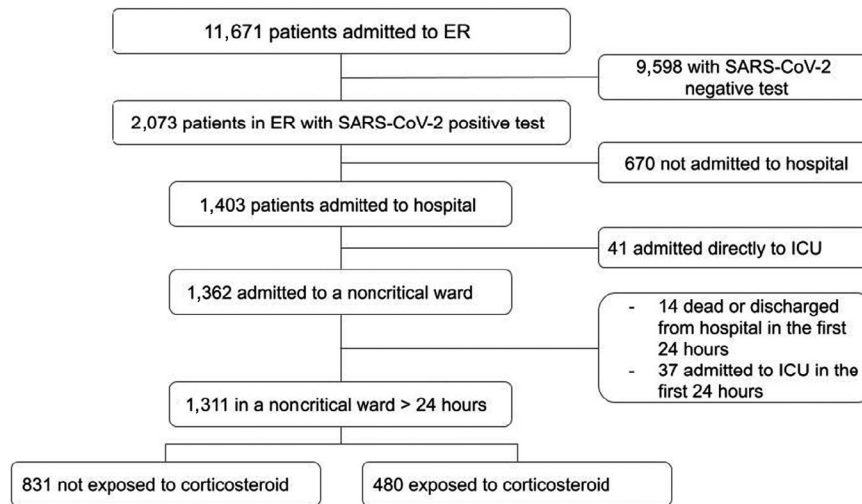


Figure 1 Flow diagram of study patients. ER, emergency room; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

survival in patients with a score of 3 and 4 on the WHO COVID-19 OSCI (ORadj 0.95, 95% CI, 0.66–1.35, $P = 0.78$) nor in patients with a score of 5 on the WHO COVID-19 OSCI (ORadj 0.79, 95% CI, 0.53–1.17, $P = 0.24$) (Figure 3). Patients on noninvasive mechanical ventilation (score of 5 on the WHO COVID-19 OSCI) who received corticosteroids were less likely to be admitted to the ICU (ORadj 0.58, 95% CI, 0.35–0.94, $P = 0.03$).

Figure 4 shows the overall survival probability in patients not needing invasive mechanical ventilation, treated with more than 8 mg of dexamethasone/die and less than or equal to 8 mg/die, or

not treated with corticosteroids; no difference in mortality was found in either cohort.

Analyses of completed cases were in agreement with what has been reported with substitution of missing values by the mean.

DISCUSSION

Our findings show that corticosteroid therapy is not associated with any difference in hospital mortality for patients with COVID-19 who score 3, 4, or 5 on the WHO COVID-19 OSCI, i.e., not receiving invasive mechanical ventilation.

Table 1 Patients' characteristics

		No corticosteroids	Corticosteroids	<i>P</i>
Number of patients	<i>N</i> (%)	831 (63)	480 (37)	
Age	years	69 (15)	69 (12)	0.29
Body mass index	kg/m ²	26.3 (5.0)	26.9 (4.4)	0.050
Female sex	<i>N</i> (%)	282 (34)	175 (37)	0.39
Arterial hypertension	<i>N</i> (%)	280 (34)	209 (44)	< 0.001
Diabetes mellitus	<i>N</i> (%)	165 (20)	117 (24)	0.064
PaO ₂	mmHg	59.3 (22.0)	53.0 (16.0)	< 0.001
pH		7.47 (0.6)	7.49 (0.5)	< 0.001
PaCO ₂	mmHg	34.7 (6.6)	34.0 (7.0)	0.049
PaO ₂ /FIO ₂	mmHg	272 (73)	244 (69)	< 0.001
HCO ₃ ⁻	mmol/L	24.6 (3.8)	24.9 (3.5)	0.29
Lactate	mmol/L	1.3 (1.1)	1.3 (0.9)	0.97
Leukocytes	10 ⁹ /L	7.9 (4.1)	8.4 (4.3)	0.04
Lymphocytes	10 ⁹ /L	1.2 (1.3)	1.0 (0.7)	0.005
Platelets	10 ⁹ /L	194.3 (91.0)	204.3 (95.8)	0.07
C-reactive protein	mg/dL	98.0 (79.3)	129.8 (89.6)	< 0.001
Lactic dehydrogenase	U/L	427.7 (240.6)	501.0 (184.7)	0.20
Bilirubin	mg/dL	0.8 (0.5)	0.9 (0.5)	0.15
Treated with enoxaparin	<i>N</i> (%)	359 (43)	364 (76)	< 0.001

Data are presented as mean (standard deviation) or as count (percentage).

FIO₂, fractional inspired oxygen; HCO₃⁻, bicarbonate; ICU, intensive care unit; PaCO₂, partial pressure of carbon dioxide; PaO₂, arterial oxygen partial pressure.

Table 2 Characteristics of survivors and nonsurvivors

		Alive	Dead	P
Number of patients	N (%)	1,006 (76)	305 (24)	
Age	years	66 (14)	78 (9)	< 0.001
Body mass index	kg/m ²	26.4 (4.7)	26.7 (5.2)	0.41
Female sex	N (%)	362 (37)	83 (27)	0.003
Arterial hypertension	N (%)	370 (37.6)	119 (39.1)	0.67
Diabetes	N (%)	200 (20.3)	82 (27.0)	0.017
PaO ₂	mmHg	59.1 (19.1)	50.2 (21.6)	< 0.001
PaCO ₂	mmHg	34.8 (6.5)	33.4 (7.1)	0.003
PaO ₂ /FIO ₂	mmHg	275.1 (66.1)	217.2 (73.9)	< 0.001
pH		7.48 (0.5)	7.47 (0.6)	0.001
HCO ₃ ⁻	mmol/L	25.1 (3.4)	23.5 (4.4)	< 0.001
Lactate	mmol/L	1.2 (0.7)	1.7 (1.5)	< 0.001
Leukocytes	10 ⁹ /L	7.9 (3.7)	8.6 (5.4)	0.009
Lymphocytes	10 ⁹ /L	1.2 (1.0)	0.9 (1.2)	0.002
Platelets	10 ⁹ /L	204.6 (91.4)	175.3 (88.1)	< 0.001
C-reactive protein	mg/L	97.9 (80.1)	149.2 (87.9)	< 0.001
Lactic dehydrogenase	U/L	432.9 (178.6)	611.7 (306.9)	0.016
Bilirubin	mg/dL	0.8 (0.5)	0.9 (0.6)	0.13
Treated with enoxaparin	N (%)	544 (55)	165 (54)	0.82
Treated with corticosteroid	N (%)	350 (36)	125 (41)	0.09
Outcome: ICU admission	N (%)	42 (4)	59 (19)	< 0.001

Data are presented as mean (standard deviation) or as count (percentage). FIO₂, fractional inspired oxygen; HCO₃⁻, bicarbonate; ICU, intensive care unit; PaCO₂, partial pressure of carbon dioxide; PaO₂, arterial oxygen partial pressure.

At the beginning of the COVID-19 pandemic, caution was advised when prescribing corticosteroids, due to the possibility of a more prolonged viral shedding and delayed viral clearance,¹³ which was also shown for other similar viral infections, like Middle

Eastern respiratory syndrome.¹⁴ Many guidelines did not recommend the use of corticosteroids in COVID-19 patients,¹⁵ and the World Health Organization initially discouraged corticosteroid use in COVID-19 due to the absence of any survival benefit and the possibility of harmful effects (avascular necrosis, psychosis, or diabetes) found in patients with SARS.¹⁶

In the following months, evidence specific to SARS-CoV-2 emerged from randomized clinical trials, showing the benefit of corticosteroid treatment on critically ill COVID-19 patients with severe forms of the disease.^{14,15} These patients underwent invasive or noninvasive mechanical ventilation for severe hypoxemia in a disease characterized by diffuse viral pneumonia, suggesting that most of them could be classified as patients with moderate to severe ARDS. Therefore the results of clinical trials on the use of steroids in severe COVID-19 appear to be in agreement with current treatment guidelines for ARDS patients, like the ones produced by the Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) in 2017, which recommend the use corticosteroids in patients with early moderate to severe acute respiratory distress syndrome.¹⁷ Moreover, a recent study by Villar *et al.* found that early administration of dexamethasone could reduce duration of mechanical ventilation and overall mortality in patients with established moderate to severe ARDS.⁷ The benefit of corticosteroid treatment in patients with ARDS could be due to their effect on the inflammatory state that is a hallmark of the disease,¹⁸ since corticosteroids affect numerous steps in the inflammatory pathway.¹⁹

In patients who are not critically ill, the evidence is less compelling. In community acquired pneumonia, dexamethasone could reduce length of hospital stay when added to antibiotic treatment in nonimmunocompromised patients,²⁰ and it could reduce mortality and the need for mechanical ventilation.²¹ But evidence in influenza, another viral disease that can cause severe respiratory symptoms, shows that corticosteroid treatment is associated with increased mortality and hospital-acquired superinfection.²² In COVID-19, data from the RECOVERY Collaborative Group Preliminary Report showed no benefit (and the possibility of harm) among patients who did not receive oxygen therapy.⁵ Our data suggest that corticosteroids are not beneficial in patients without invasive mechanical ventilation (with a score of 3,4, or 5 on the WHO COVID-19 OSCI¹⁰). In particular, this appears to be

Table 3 Adjusted odds ratio

Outcome	No corticosteroids (number/total (%))	Corticosteroids (number/total (%))	Estimate (95% CI)	P value
In-hospital death	179/831 (22)	125/480 (26)	1.04 (0.81–1.34)	0.74
In-hospital death in NIMV patients	85/187 (45)	83/203 (41)	0.79 (0.53–1.17)	0.24
In-hospital death in patients not receiving NIMV (with/without oxygen)	94/644 (15)	42/277 (15)	0.95 (0.66–1.35)	0.78
ICU admission	56/831 (7)	53/480 (11)	0.81 (0.56–1.17)	0.26
ICU admission in NIMV patients	38/187 (20)	41/203 (20)	0.58 (0.35–0.94)	0.03
ICU admission in patients not receiving NIMV (with/without oxygen)	18/644 (3)	18/277 (6)	0.88 (0.45–1.70)	0.71

Patients on NIMV are patients with a score of 5 on the WHO COVID-19 Ordinal Scale For Clinical Improvement; patients not receiving NIMV are patients with a score of 3 and 4 on the WHO COVID-19 Ordinal Scale For Clinical Improvement.

CI, confidence interval; ICU, intensive care unit; NIMV, noninvasive mechanical ventilation.

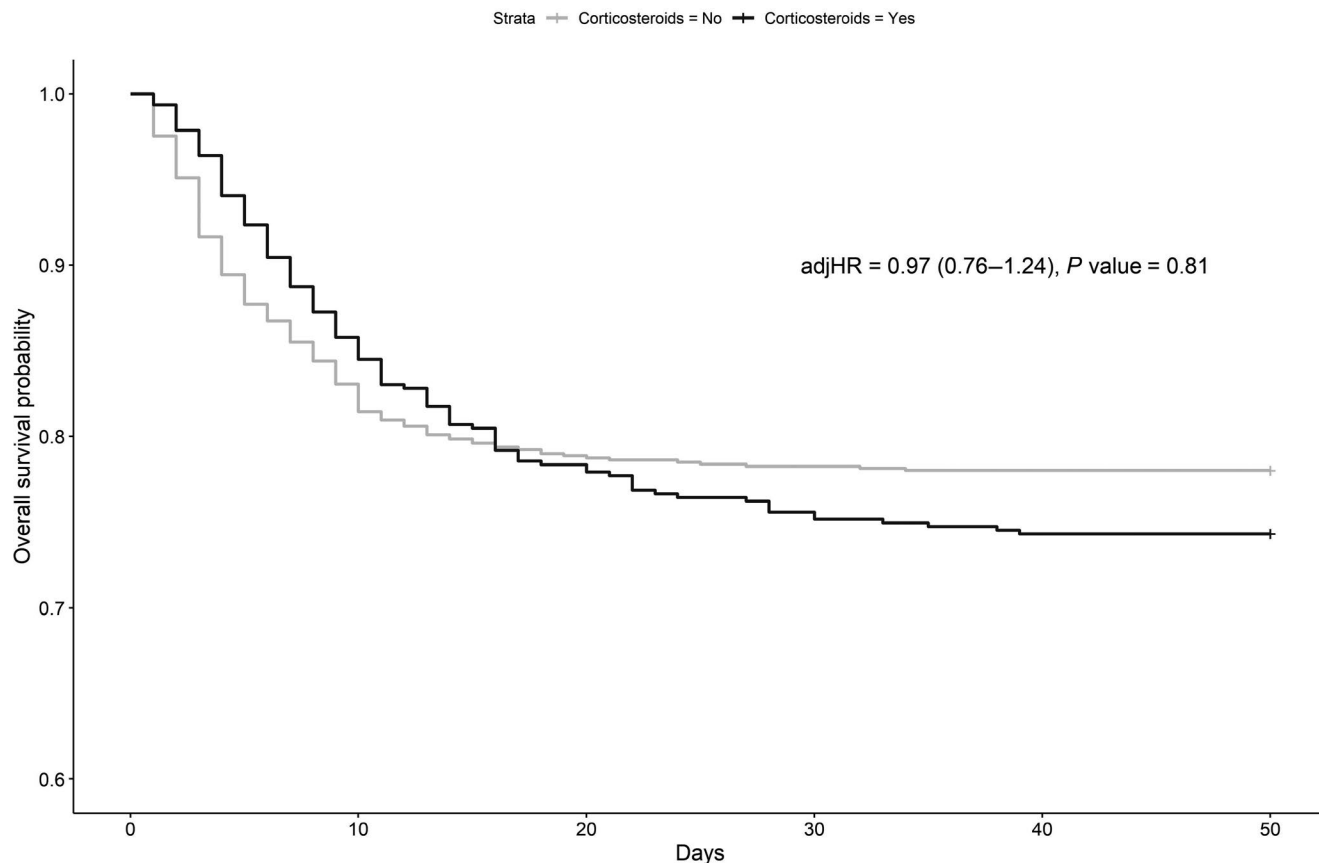


Figure 2 Overall survival probability in patients not receiving invasive mechanical ventilation, both treated and not treated with corticosteroids. adjHR, adjusted hazard ratio.

evident in all patients with a score of 3 or 4, i.e., patients with or without oxygen therapy who are not on positive pressure noninvasive ventilation. Since ARDS diagnostic criteria include the use of at least 5 centimeters of water of end-expiratory pressure, patients receiving oxygen therapy but not on NIMV / continuous positive airway pressure and patients not receiving oxygen cannot have an ARDS diagnosis.²³

Differently from previous trials on corticosteroids in COVID-19 patients,^{1–3,5} we assessed patients who received noninvasive ventilatory support (with a score of 5 on the WHO COVID-19 OSCI) as a separate group from patients who score 3 or 4 on the same scale. With this stratification of study sample, corticosteroids showed a protective effect against the need for ICU admission for patients with a score of 5 on the WHO scale (i.e., noninvasively mechanically ventilated patients). Differently from the RECOVERY trial,⁵ we did not find any mortality reduction in patients receiving steroid therapy. This could depend on the exclusion of patients with a score of 6 on the WHO COVID-19 scale of clinical improvement (invasive mechanical ventilation patients), which were the stratum with the most benefit in survival with steroids. The secondary analysis on patients with score of 3, 4, and 5 is not comparable with the one in the RECOVERY trial, because we aimed to assess the effect of steroids in ventilated (score of 5) versus nonventilated (with a score of 3 and 4) patients, whereas RECOVERY separately

analyzed patients without oxygen therapy (with a score of 3) separately from patients with oxygen therapy (with a score of 4 and 5). The subgroup analysis in patients without mechanical ventilation (score of 3 and 4) clearly confirms the absence of effect of steroids on mortality, confirming the primary analysis. The effect of steroids on survival is more complex to interpret in patients on NIMV (with a score of 5), because a trend toward the improvement could be detected and the sample size of the NIMV patients (390 patients) gives a low statistical power ($\beta = 0.553$). In absence of further evidence on COVID-19 patients with noninvasive mechanical ventilation, we think that steroid use should be suggested in these patients because it reduces ICU admission and it can possibly have an effect on mortality reduction. It should be noted that COVID-19 requiring noninvasive mechanical ventilation probably met all moderate to severe ARDS diagnostic criteria (acute onset, $\text{PaO}_2/\text{FIO}_2$ lower than 200, bilateral lung infiltrates, and absence of cardiogenic origin of respiratory failure).²³ Therefore our data show once more how corticosteroid efficacy seems to be linked to the more severe disease stages of COVID-19. Since corticosteroid treatment is not exempt from side effects, and has been associated with complications such as increased infection rate,²⁴ hyperglycemia,^{20,25} hyponatremia,²⁶ and ICU-acquired weakness,²⁷ we think that caution should be exercised when prescribing corticosteroids to COVID-19 patients who are not receiving ventilatory support.

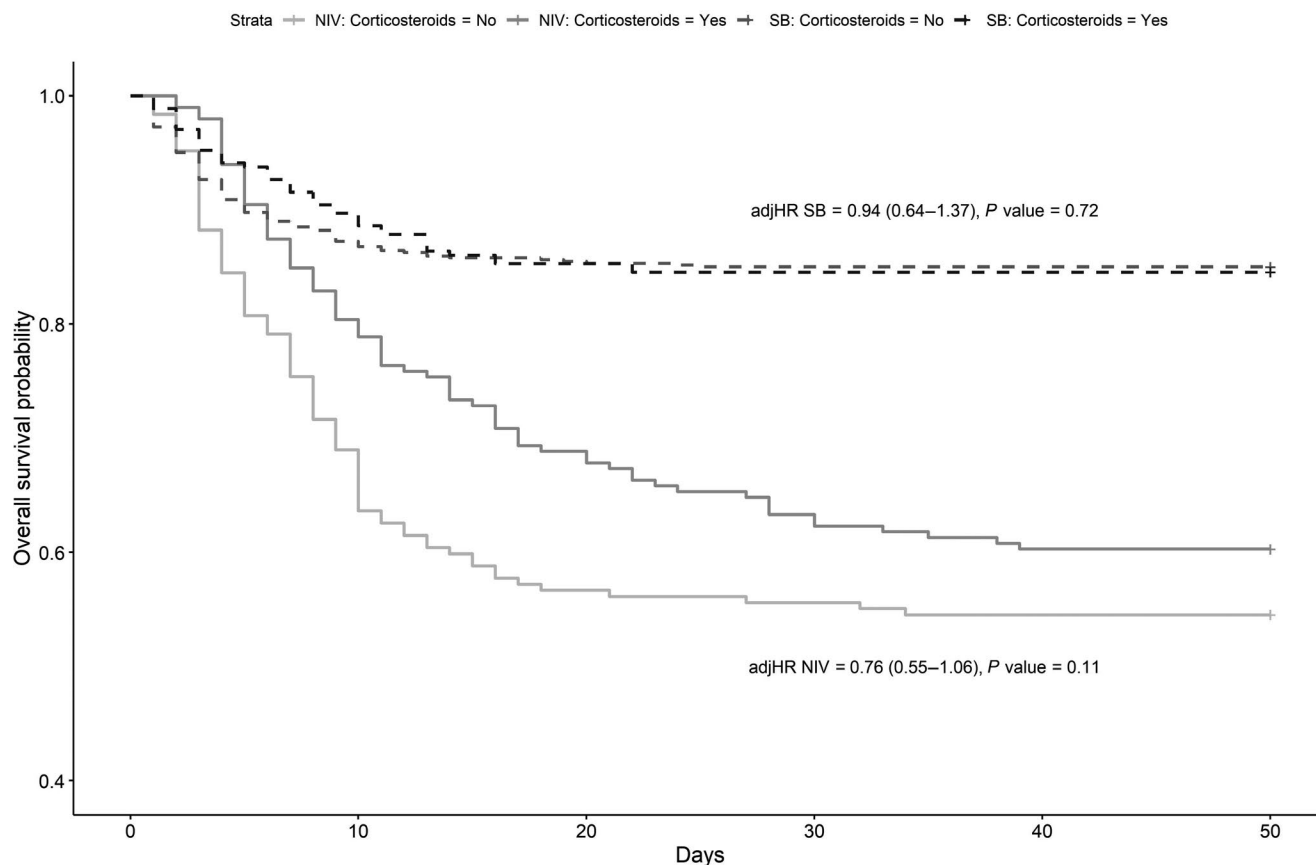


Figure 3 Overall survival probability in patients receiving or not receiving noninvasive mechanical ventilation, both treated and not treated with corticosteroids. adjHR, adjusted hazard ratio; NIMV, patients with a score of 5 on the WHO COVID-19 Ordinal Scale For Clinical Improvement; SB, patients with a score of 3 and 4 on the WHO COVID-19 Ordinal Scale For Clinical Improvement; WHO, World Health Organization.

Recent data showed that a high dose of corticosteroids, defined as higher than 1 mg/kg/day of prednisone (equivalent to 10 mg of dexamethasone a day in a 70-kg patient),¹¹ was independently associated with an increased risk of death in patients with severe COVID-19.²⁸ When conducting the planned secondary analysis dividing patients receiving higher or lower equivalent dexamethasone doses, no difference in mortality was found in our cohorts. A *post hoc* analysis was conducted, with a cutoff of 6 mg of daily dexamethasone or less (the RECOVERY trial cutoff), which did not show any difference between strata (see **Supplemental Material**). Nevertheless there appears to be a trend towards a better outcome (as compared with the higher doses) in patients treated with 6 mg of dexamethasone daily dexamethasone or less, but the study was underpowered to detect this difference. Simulating from the data that were collected during the present study to obtain a power of 0.8 with type I error rate set at 0.05, and assuming that 1 of every 2 patients will be exposed to corticosteroids in low dose, i.e., 6 mg of daily dexamethasone or less, a total of 2,339 patients would need to be enrolled to detect an adjusted hazard ratio of 0.75.

The effect of corticosteroids on outcome was adjusted for the possible associated treatment with enoxaparin, which has been shown to be associated with a reduction in mortality risk in COVID-19 patients.²⁹

We believe that our findings could be generalized to other patients with severe COVID-19, because our patients' characteristics and outcomes are comparable to what was found in other studies.^{1–3,5} Nevertheless, our study suffers from four main limitations: First, it is an observational prospective analysis of prospectively collected data; therefore the absence of randomization makes it impossible to exclude the presence of bias or unmeasured confounders. Second, it is a single-center study, so our results might not be valid for centers with different settings. Patients we have enrolled are patients with a score of 3, 4, and 5 on the WHO COVID-19 OSCI; therefore caution is advised when applying these findings to patients with a different disease severity. Nonetheless, even if multicenter randomized clinical trials (RCTs) are the gold standard in assessing a treatment's efficacy and safety, observational studies, which usually have a greater external validity than RCTs, can add information on the use of certain drugs in the clinical field and should be integrated with RCTs. Third, corticosteroid therapy was administered as per treating physicians' decision and without prespecified criteria. Fourth, in this cohort of patients, the mean duration of steroid therapy, which is of 5 (3–9) days, is shorter than the one proposed in the RECOVERY trial protocol, in which dexamethasone was prescribed for 10 days or until hospital discharge. This difference could hypothetically explain a discrepancy in hospital mortality, nevertheless the effective

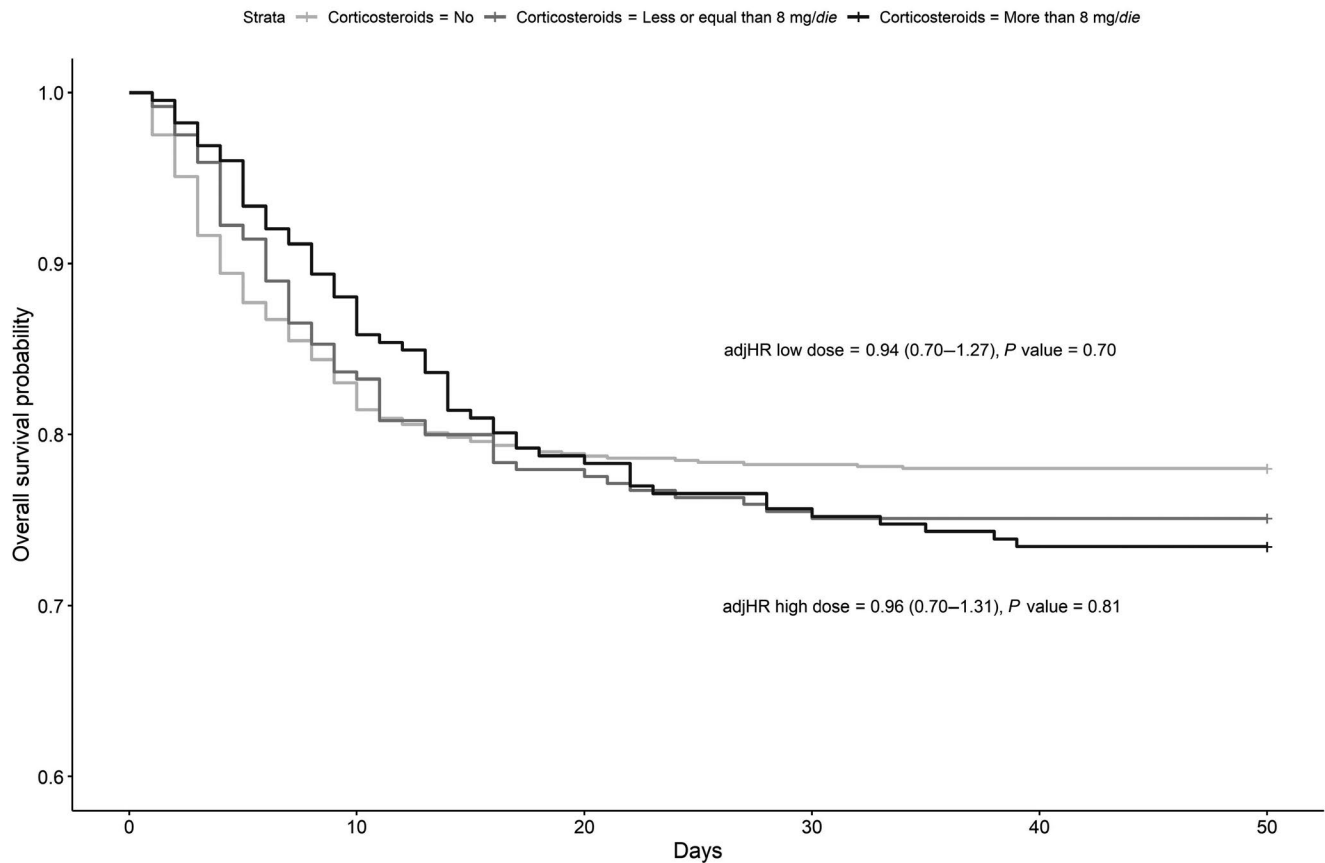


Figure 4 Overall survival probability in patients not receiving invasive mechanical ventilation, treated with high or low equivalent dose of dexamethasone or not treated with corticosteroids. adjHR, adjusted hazard ratio.

duration of steroid therapy in the RECOVERY trial was 7 days (interquartile range 3 to 10) and the possibility that just 2 more days of steroid therapy could explain these different findings is remote. A subgroup analysis for corticosteroid therapy duration was not feasible because it would inevitably lead to immortal patient bias,³⁰ by selecting patients who survived for more than 7 days in the steroids group, thus leading to a biased association with reduced mortality.

CONCLUSION

In conclusion, data from our observational, prospective, single-center study show that treatment with corticosteroids is not associated with in-hospital mortality reduction in patients admitted for COVID-19 who did not receive invasive mechanical ventilation. In the subgroup of COVID-19 patients treated with noninvasive mechanical ventilation, corticosteroid therapy is associated with a lower OR for ICU admission, whereas the effect on mortality has to be addressed in further studies.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

G.N., F.F., and F.A. wrote the manuscript. G.N., F.A., and F.F. designed the research. All the authors performed the research. F.A. and G.N. analyzed the data.

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