

# Real-world evidence of the use of glucocorticoids for severe COVID-19

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## Abstract

**Introduction:** Currently, only glucocorticoids have proved to impact adverse outcomes in COVID-19. However, their risk/benefit balance remains inconclusive and populations' characteristics should be considered.

**Objective:** The objective was to evaluate the real-life use of glucocorticoids in patients with severe COVID-19 hospitalized in a third-level referral center and to determine the type, accumulated doses, and the in-hospital outcomes related with their use.

**Methods:** We evaluated a retrospective cohort of 737 patients with criteria for severe COVID-19 and a positive polymerase chain reaction (PCR) test for SARS-CoV-2. We extracted data for epidemiological analysis, medical history, and medications, as well as baseline laboratory tests. Data were analyzed using SPSS 21.0 and nonparametric tests, medians, and interquartile ranges (IQR). A  $p < 0.05$  was considered significant.

**Results:** A total of 65.3% were men, with a median age of 59 years (IQR 46–70) and a median of 10 days of hospital stay (IQR 6–16), more than 40% had diabetes, hypertension, and/or obesity, and 0.8% used steroids chronically. At the time of the study, 54.0% had been discharged due to improvement and 40.8% died. The most common treatment used was dexamethasone 6 mg/day/10 days (46.6%). Patients with a complete dexamethasone scheme [as proposed by the Randomized Evaluation of COVID-19 Therapy (RECOVERY) study] had a lower mortality risk [hazard ratio (HR) 0.441, 95% confidence interval (CI) 0.232–0.840] in comparison with patients with lower doses (HR 1.803, 95% CI 1.080–3.012). Patients with methylprednisolone or several steroids tended to have higher cumulative doses (equivalent to >675 mg of prednisolone).

**Conclusion:** The use of steroids in severe COVID-19 reduces mortality only at the dose proposed in the RECOVERY study in the younger population. No benefit of the use of steroids was observed in patients with older age or higher number of comorbidities.

**Keywords:** dexamethasone, SARS-CoV-2, therapeutics

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## Introduction

Glucocorticoids are recommended in the management of sepsis because they help to downregulate the excessive pro-inflammatory response, while preserving innate immunity.<sup>1</sup> Nonetheless, there is no consensus regarding the type of steroid, dose, or treatment duration<sup>1,2</sup> due to the different causes of sepsis evaluated, age, and comorbidities of the patients, as well as the use of adjunctive therapies and their inflammatory profile.<sup>3</sup> The Surviving Sepsis Campaign (SCC)

published recommendations for COVID-19, suggesting a short course of systemic steroids for adults with severe or critical disease, with preference for dexamethasone over other corticosteroids (6 mg/day for a maximum of 10 days),<sup>4</sup> based on previous recommendations for Acute Respiratory Distress Syndrome. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) Trial aimed to test this recommendation in hospitalized patients.<sup>5</sup> They found improvement in mortality and mechanical ventilation rates; however,

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this was limited to patients under invasive mechanical ventilation or those who required oxygen through invasive or not invasive ventilation. However, in this trial, important clinical information of the patients' characteristics was lacking. Nonetheless, this recommendation became mainstay for the treatment of severe COVID-19 worldwide in the second half of 2020, considering also that other promising therapies failed to prove efficacy and vaccines were not available for the general population yet.

The routine use of corticoids in severe respiratory diseases has been questioned by other authors.<sup>6,7</sup> Steroid use should be tailored to the patient's needs, along with a careful and dynamic clinical evaluation to limit their adverse effects. Important acute adverse events, such as hyperglycemia, hypertension, electrolyte disturbances, susceptibility to secondary infections, arrhythmias, gastric ulcer formation, and bleeding, and even psychosis may complicate the evolution of severe COVID-19 patients.<sup>8</sup> Concerns have also risen because of contradictory results in different ethnicities, ages, and comorbidities. Clinical evidence in patients with previous use of steroids or with metabolic comorbidities is scarce.<sup>9–11</sup> Endocrine guidelines warn about adrenal suppression in any patient who used prednisolone 7.5 mg per day for 90 days or more or its equivalent (675 mg), which may affect long-term outcomes, and it can be related with post-COVID-19 syndrome, hyperpigmentation, hypotension, hypoglycemia, or recurrent shock.<sup>12,13</sup> However, the number of patients that may be at risk of these complications has not been described

We aimed to describe real-world evidence (RWE) of the use of glucocorticoids in a Mexican cohort of patients with severe COVID-19. We evaluated the frequency of patients who have comorbidities that may be affected by the use of steroids, as well as their outcomes (such as requirement for mechanical ventilation, days of hospitalization, and mortality rate) and the number of patients who were treated with a higher or lower dose of glucocorticoids during hospitalization and described the most commonly used biochemical biomarkers for each group.

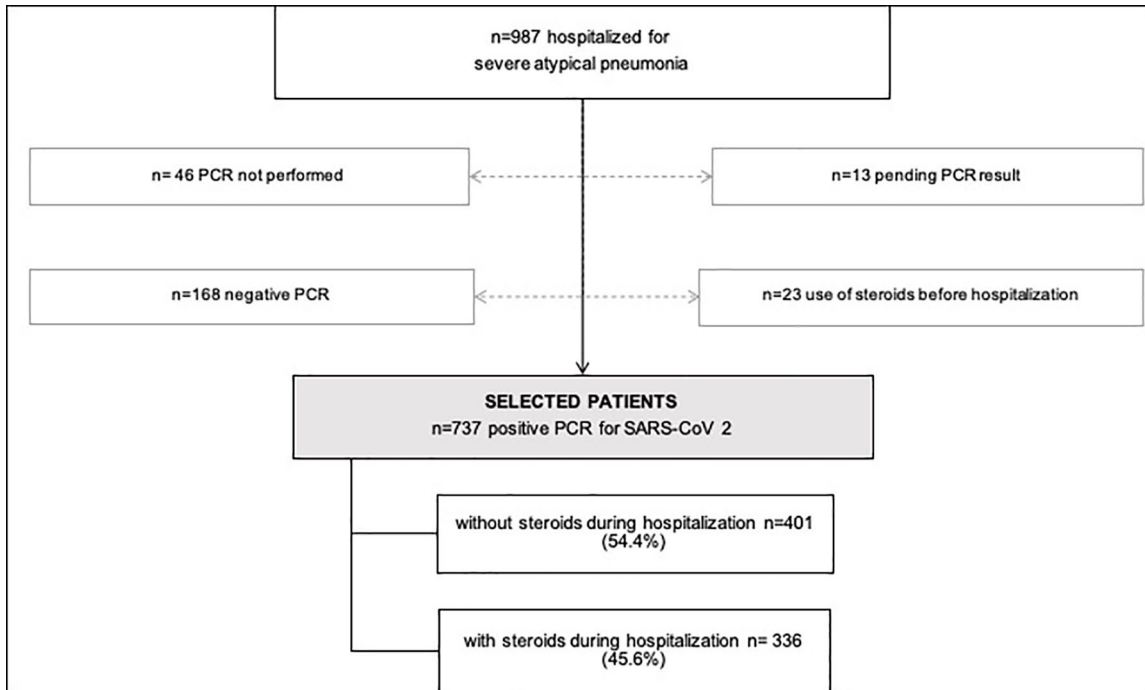
## Methods

We performed a retrospective evaluation of the files of hospitalized patients from February 2020

to December 2020 due severe COVID-19. The patients were treated by their physicians according to the available guidelines and information published at the time. The investigators did not decide on the treatments during their hospitalization. The hospital is a third-level referral center for patients from the central and south areas of Mexico. A special area for triage and hospitalization for COVID-19 patients was created since the beginning of the pandemic. The patients were evaluated by internal medicine specialists in this area, as well as other subspecialists as required. A full routine laboratory and imaging workup was performed in suspicious cases and only those fulfilling the criteria for severe COVID-19 were admitted. Severity was defined using international epidemiologic consideration, in adults with the presence of dyspnea, a respiratory rate of 30 or more breaths per minute, a blood oxygen saturation of 93% or less, a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ( $\text{PaO}_2:\text{FiO}_2$ ) of less than 300 mmHg, or evidence of lung infiltration more than 50%.<sup>14</sup> All patients hospitalized were tested for SARS-CoV-2 infection with a polymerase chain reaction (PCR) of nasal secretion, which was analyzed by the National Reference Laboratory [Instituto de Diagnóstico y Referencia Epidemiológicos (InDRE)]. For the final analysis, we included only those patients with positive PCR who had not been treated with steroids for COVID-19 before hospitalization. The study was approved by the Local Ethics Committee (registration number R-2020-3601-241). All the patients or their legal representatives signed the informed consent to participate in the study protocol before admission.

## Statistical analysis

We analyzed the data using SPSS version 21.0 using nonparametric statistics due to data distribution. The results are expressed in medians and interquartile ranges (IQR) or percentages according to the variable characteristics. Group differences were analyzed using the Mann–Whitney *U* test or chi-square test. Comparison among more than three groups was performed using analysis of variance (ANOVA). Logistic regression model performance was evaluated using the Nagelkerke  $R^2$  test. Furthermore, a Cox proportional hazard regression model was performed to evaluate the risk of death at follow-up comparing the different types and doses of steroids adjusted for those variables that were significant in the bivariate



**Figure 1.** Patient selection flowchart. Only patients with positive PCR for SARS-CoV-2 that had not received steroids for COVID-19 as outpatients were included. PCR, polymerase chain reaction.

analysis. We considered a value of  $p < 0.05$  to be statistically significant.

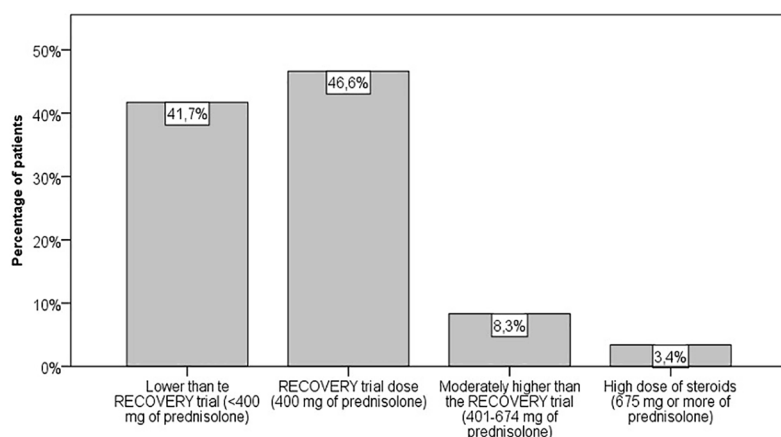
## Results

A total of 987 patients were hospitalized for suspected severe atypical pneumonia. The PCR test for SARS-CoV-2 was not performed in 4.7% of the patients, was pending in 2.5%, was negative in 16.9%, and positive in 75.9% (Figure 1).

We analyzed 737 patients with a positive PCR for SARS-CoV2, 65.3% were men, with median age of 59 years (IQR 46–70 years), and a median of 10-day hospital stay (IQR 6–16 days). At the time of evaluation, 54.0% had been discharged due to improvement, 40.8% died, 2.6% remained hospitalized, and in 2.6%, the outcome could not be ascertained. Only 0.8% of the patients used steroids chronically for other diseases before the diagnosis of COVID-19, and most of them were on prednisone with a median dose of 12.5 mg per day (IQR 5–25 mg/day) for more than 3 months.

Steroids were used in 45.6% of the patients in this cohort. The cases from April to July 2020 received

steroids only when deemed necessary by the treating physicians, according to the available sepsis guidelines at that time. From late July to December 2020, the most common indication was dexamethasone IV at a dose of 6 mg per day for 10 days, as suggested by the RECOVERY trial. In total, 46.6% of the patients completed this indication (equivalent to an accumulated dose of 400 mg of prednisolone), 41.7% of the patients had lower doses, and 11.7% had higher doses (Figure 2), equivalent to more than 401 mg of prednisolone. Even when the original indication was to complete the 10-day treatment for most patients, the ones with lower doses did not reach the full dose due to death (46.3%) or early discharge (47.1%), while the rest was still hospitalized, or the outcome was not available. The patients who were discharged due to improvement received the drugs and indications to complete the doses at home, but adherence could not be evaluated. Higher doses were indicated by the treating physician according to the patients' history and evolution. In this group, 7.4% had a previous chronic lung disease, 14.8% had a neoplasia, 11.1% had previous steroid use, 11.1% had an autoimmune disease, 44.4% improved, and the rest died.



**Figure 2.** Accumulated steroid dose at discharge. All treatments were transformed to the equivalent dose in prednisolone for comparison. An accumulated dose of 675 mg is equivalent to 7.5 mg of prednisolone per day for 90 days.

RECOVERY, Randomized Evaluation of COVID-19 Therapy.

The median accumulated dose for dexamethasone was an equivalent to 400 mg of prednisolone (IQR 280–400 mg), for prednisone 118 mg (IQR 51–184 mg), for hydrocortisone 280 mg (IQR 199–450 mg), for methylprednisolone 375 mg (IQR 225–500 mg), and for patients with several steroids 500 mg (370–850 mg). The patients who were indicated methylprednisolone pulses and several different steroids were more likely to have a ‘high’ accumulated dose (over 675 mg of prednisolone) 81.8% *versus* 18.2% with an odds ratio (OR) of 38.45 [95% confidence interval (CI) 7.96–185.58,  $p < 0.001$ ]. The patients with lower doses of steroids tended to have lower death rates (41.3% *versus* 63.6% with high doses) but this was not significant ( $p = 0.340$ ). The use of methylprednisolone or several steroids was not more common in patients with autoimmune diseases or transplants and it did not change the mortality rate ( $p = 0.537$ ).

When we compared the patients who were discharged due to improvement *versus* those who died, we observed that the former group had more patients who completed the steroid scheme proposed by the RECOVERY trial. Completing the RECOVERY steroid scheme resulted in lower probabilities of death compared with the patients who had lower or higher steroid doses (49.4% improved *versus* 37.2% died;  $p = 0.035$ ).

### Physical examination and laboratory tests

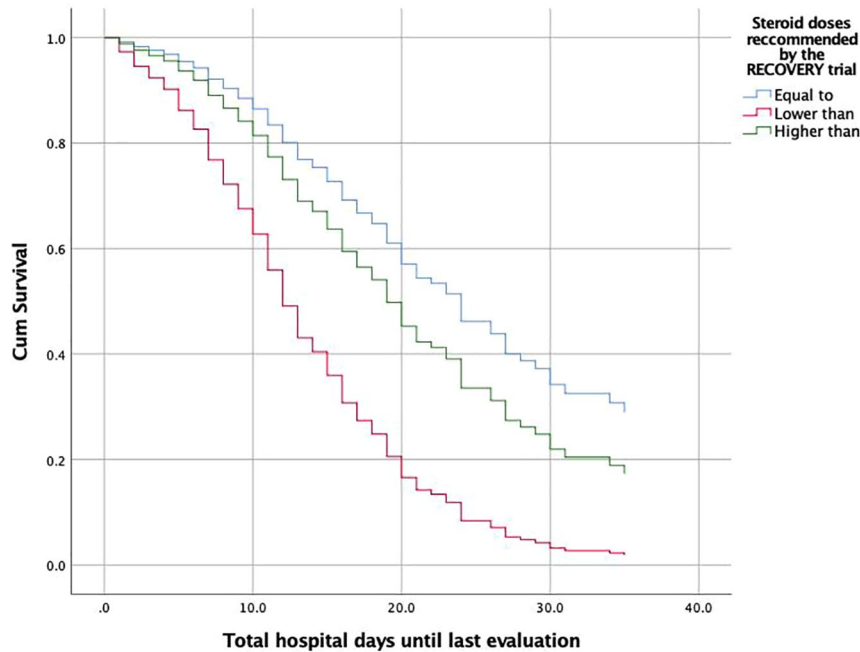
We analyzed the characteristics of patients with severe COVID-19 who died or improved comparing groups with and without steroid treatment. The patients who received steroids were older, with lower  $SO_2$  at the first evaluation, and were less likely to have metabolic comorbidities such as diabetes, hypertension, and kidney disease. There were no differences in the frequency of comorbidities as obesity, autoimmune diseases, and heart or lung diseases. Patients who received steroids and died had lower median oxygen saturations at their arrival to the respiratory triage, lower lymphocytes, and 25-OH vitamin D compared with the survivors; they also had higher total leukocytes, fibrinogen, lactic dehydrogenase, C-reactive protein, procalcitonin, and ferritin levels (Table 1). No differences were observed in quick Sepsis-related Organ Failure Assessment (qSOFA) score or in Acute Physiology and Chronic Health Evaluation II (APACHE II) score among groups.

When comparing those clinical data among different types of steroids or low and high doses, no differences were observed (data not shown).

### Multivariate analysis

We performed a multivariate analysis including patients in whom the final outcome could be assessed (death/alive,  $n = 699$ ). First, we aimed to explore whether certain clinical characteristics or previous diseases influenced the decision to prescribe steroids. For this purpose, we included those variables depicted in Table 1 with a value of  $p < 0.10$ . We observed that older patients (OR 1.02, 95% CI 1.01–1.04) and those with hypertension (OR 1.93, 95% CI 1.26–2.97) and hyperlipidemia (OR 1.98, 95% CI 1.19–3.30) were less likely to receive steroids.

We also evaluated whether the risk of death was increased based on the variables with a value of  $p < 0.10$  depicted in Table 1. We observed that older patients (OR 1.05, 95% CI 1.010–1.10), those who required mechanical ventilation (OR 61.4, 95% CI 11.8–319.3), and those with hypertension (OR 3.73, 95% CI 1.095–12.75) were more likely to die. We did not find a cutoff point for age or lipid profile that would predict



**Figure 3.** Cox proportional hazard model for mortality depending on steroid doses. A dose lower than that proposed by the RECOVERY trial increased the mortality rate. The analysis was adjusted by those variables that were significant in the bivariate analysis. RECOVERY, Randomized Evaluation of COVID-19 Therapy.

mortality, but patients with more than 10 years with hypertension had more probabilities to die when associated with acute or chronic kidney disease.

#### *Mortality risk depending on type and steroid doses*

Using a Cox proportional regression model (Figure 3), we observed that those patients who completed a steroid scheme as that reported in the RECOVERY trial had a lower mortality risk with a hazard ratio (HR) of 0.441 (0.232–0.840); meanwhile, lower doses had an HR of 1.803 (1.080–3.012). No statistical differences were observed in mortality risk using higher doses (HR 1.41, 0.856–2.332). No differences were observed in mortality risk depending on steroid types.

Furthermore, we observed that despite the use of steroids, an older age had an HR of 1.02 (1.009–1.947), higher  $\text{SaO}_2$  at the first evaluation had an HR of 0.980 (0.964–0.997), hypertension had an HR of 2.24 (1.19–4.23), and the presence of any neoplasia had an HR of 2.19 (1.21–6.99), for mortality.

#### **Discussion**

Our study shows that the use of steroids in severe COVID-19 benefits only a group of patients and only at the same doses proposed by the RECOVERY trial. This group represents the extreme of the disease spectrum, where patients were older (59 years) than the mean age for infection reported for our country ( $46.47 \pm 15.62$  years).<sup>15</sup> The patient in our cohort had other risk factors for hospitalization, such as high frequencies of diabetes and hypertension (around 40% for each disease); greater than 40% had some degree of obesity and kidney, lung, or heart disease; or a previous neoplasia was also common. The comorbidities that were diagnosed at hospital admission for COVID-19 were 69 cases of diabetes, 20 of hypertension, 35 of hyperlipidemia, and 16 of heart disease. The group that died had a greater number of poor prognostic factors for COVID-19, including an adverse biomarker profile in which use of steroids and other treatments was not enough to counteract their inflammatory status. The group that benefited most from the careful use of steroids were the youngest and with better laboratory profiles. Special attention to steroid management should



**Table 1.** Characteristics of patients with severe COVID-19 who died or improved comparing groups with and without steroid treatment.

	Improved (n = 398)		Death (n = 301)		p value
	Without steroid n = 233 (59%)	With steroid n = 165 (41%)	Without steroid n = 162 (54%)	With steroid n = 139 (46%)	
Age, years	53 (42–62)	56 (45–69)	64 (53–71)	67 (55–75)	<0.001
Male, %	63	64	67	68	0.287
Tobacco use, %	9	9	12	2	0.041
Days from symptoms to hospitalization	8 (4–13)	9 (6–12)	8 (5–14)	7 (5–11)	0.640
Total days in hospital	9 (6–15)	11 (8–16)	9 (4–14)	11 (7–18)	0.055
SBP, mmHg	134 (125–148)	136 (127–145)	131 (128–141)	140 (125–157)	1.000
DBP, mmHg	80 (70–86)	80 (70–85)	73 (69–82)	78 (70–89)	1.000
Median BP, mmHg	97 (90–104)	97 (88–104)	94 (90–104)	97 (85–112)	1.000
Heart rate	105 (92–117)	102 (86–112)	101 (91–116)	92 (104–118)	0.669
Respiratory rate	24 (22–28)	24 (22–28)	28 (24–32)	28 (24–31)	0.013
pCO <sub>2</sub> , mmHg	31 (27–36)	31 (28–36)	31 (24–37)	31 (25–37)	0.777
pO <sub>2</sub> , mmHg	62 (41–73)	61 (34–76)	59 (46–75)	46 (37–54)	0.794
SaO <sub>2</sub> at the first evaluation, %	87 (75–93)	80 (70–89)	67 (54–82)	66 (48–82)	<0.001
Leukocyte, 10 <sup>3</sup> /μL	7.89 (5.87–12.36)	9.23 (6.79–12.31)	10.56 (7.2–15.47)	11.41 (7.53–15.7)	<0.001
Lymphocytes, 10 <sup>3</sup> /μL	0.84 (0.59–1.24)	0.83 (0.61–1.16)	0.71 (0.46–0.98)	0.73 (0.48–1.03)	0.330
D-dimer, μg/dL	1.1 (0.69–2.55)	1.25 (0.66–2.32)	2.5 (1.17–5.13)	2.13 (1.03–5.57)	0.390
Fibrinogen, mg/dL	671 (529–771)	636 (502–774)	697 (591–798)	703 (593–796)	0.015
Fasting glucose, mg/dL	103 (85–135)	112 (95–158)	118 (91–188)	133 (103–190)	0.028
hsCRP, mg/dL	8.77 (3.04–18.97)	8.2 (3.63–14.57)	20.1 (11.4–28)	16.9 (8.82–21.8)	<0.001
Procalcitonin, ng/mL	0.23 (0.10–0.605)	0.15 (0.08–0.42)	1.8 (0.62–5.92)	0.51 (0.19–1.57)	<0.001
Ferritin, ng/mL	925 (475–1568)	853 (389–1391)	1067 (555–1885)	1178 (670–2140)	0.55
Albumin, mg/dL	3.3 (3.0–3.6)	3.4 (3.1–3.7)	3.1 (2.7–3.3)	3.0 (2.7–3.3)	<0.001
LDH, U/L	363 (278–476)	408 (303–529)	552 (384–710)	502 (388–662)	<0.001
Vitamin D, ng/dL	15.3 (10.4–18.4)	16.1 (10.8–26.6)	12.3 (8.3–15.4)	13.8 (8.9–18.6)	0.020
Mechanical ventilation, %	32	19	78	82	<0.001
Vasoactive treatment, %	6	5	17	44	<0.001
Received antibiotic, %	85	67	43	90	<0.001
Received antivirals, %	11	9	8	5	1.000

(Continued)

**Table 1.** (Continued)

	Improved (n=398)		Death (n=301)		p value
	Without steroid n = 233 (59%)	With steroid n = 165 (41%)	Without steroid n = 162 (54%)	With steroid n = 139 (46%)	
Received chloroquine, %	23	7	15	10	0.197
Received anticoagulant, %	82	93	75	95	0.881
Received tocilizumab, %	2	2	1	2	0.748
Diabetes, %	43	34	53	44	0.015
Hypertension, %	45	34	61	46	0.001
Hyperlipidemia, %	22	10	21	12	0.868
Obesity, %	42	45	47	45	0.493
Heart disease, %	12	10	16	12	0.200
Lung disease, %	7	8	11	7	0.335
Kidney disease, %	15	9	27	24	<0.001
Liver disease, %	2	2	1	1	0.366
Coagulopathy, %	<1	3	3	2	0.596
Neoplasia, %	8	9	16	13	0.008
Transplant patient, %	3	4	3	2	0.361
Autoimmune disease, %	4	8	4	7	0.750
Accumulated steroid dose, mg equivalent to prednisolone	NA	400 [280–400]	NA	400 [233–400]	0.615
High dose of steroid, %	NA	1.9%	NA	5.1%	0.123

ANOVA, analysis of variance; DBP, diastolic blood pressure; hsCRP, high-sensitive C-reactive protein; LDH, lactate dehydrogenase; NA, not applicable; pCO<sub>2</sub>, partial pressure of carbon dioxide; pO<sub>2</sub>, partial pressure of oxygen; SaO<sub>2</sub>, oxygen saturation; SBP, systolic blood pressure. Results are presented as median (interquartile range). Differences were evaluated with ANOVA or chi-square test, accordingly.

be paid to patients receiving accumulated doses equivalent to 675 mg of prednisolone or higher, which represented 3.4% of the group and those with previous use of steroids for chronic diseases (11.1%) or comorbidities that may be affected by routine steroid use.

Corticoids are suggested in sepsis and septic shock for their unique anti-inflammatory profile<sup>16</sup>; however, there is not a single steroid or dose that has been proven to be superior to any other in critically ill patients. The preferential use of hydrocortisone infusions by critical care specialists is related to its short half-life and the possibility to stop the infusion if necessary, while dexamethasone is a powerful glucocorticoid with a simple posology but lacks mineralocorticoid effects. Patient

selection and treatment tailoring is mainstay to achieve the intended results and avoid serious adverse effects, which must be routinely evaluated considering their different potencies and effects, accumulated doses, and half-life.<sup>17</sup> High accumulated doses have been associated with diabetes,<sup>18</sup> hypertension,<sup>19</sup> and acute liver injury, among other acute and chronic side effects that affect the long-term survival of critically ill patients.

Some countries have been more severely affected by the pandemic than others,<sup>20,21</sup> due to social, economic, and cultural factors, but also related to the individual population health characteristics, which must be described. Compared with the RECOVERY trial and the Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired

Pneumonia (REMAP-CAP), our patients were younger but showed a higher frequency of metabolic comorbidities such as diabetes and obesity, a problem that has been a characteristic of developing countries. An important difference with these studies is the fact that they did not include obesity or body mass index (BMI) as a risk factor. Furthermore, BMI has been considered a risk factor for hospitalization but has not been consistently associated with mortality. Hypertension was also not reported as a single comorbidity in other studies but was grouped as cardiovascular disease. In our population, hypertension was a strong predictor for mortality even in young patients.

In our patients, glucose control therapy had to be started and monitored when uncontrolled diabetes was present, before or after steroids were prescribed. Intravenous dexamethasone was the preferred steroid for most cases, initially indicated at 6 mg/day/10 days, with 88.3% of the patients who were indicated steroids receiving at least one dose and almost half of them completed the full 10 days. The patients with lower doses stopped the treatment due to death or quick discharge from the hospital.

The patients who improved had a higher probability of having a complete 10-day treatment with steroids, compared with the patients who died; however, this may be because some patients died before they completed the required days reflecting the disease severity and not the treatment efficacy. In our analysis, we also found that the patients who received methylprednisolone or several types of steroids had a significantly higher probability of dying, but we also consider that this is also related to the severity of the infection and comorbidities detected in these patients rather than to the steroid type itself. This was corroborated using the Cox proportional model, where mortality risk was not different depending on the type of the used steroid. These patients were also more likely to have an accumulated dose higher than 675 mg of prednisolone or several steroid schemes, which reflects a lack of response to the initial treatment or a more prolonged requirement of them.

The call from most experts and medical societies has been for a 'judicious and dynamic' use of steroids for COVID-19.<sup>22,23</sup> Siddiqi and Mehra<sup>24</sup> reflected on the need to use the treatments differentially in native and immunosuppressed

states, while the Endocrine Societies have issued special recommendations for patients with adrenal insufficiency and previous glucocorticoid use during the time of COVID-19.<sup>13,25</sup> These results support that rationale.

Our study has some limitations. First, because of the retrospective design, data were obtained from clinical records. Second, other variables, such as oxygen saturation and non-intensive care unit (ICU) intubated patient care, may have contributed to a higher mortality. However, this clinical scenario still occurs around the world because healthcare is overstretched with the new COVID variants, which have been affecting even fully vaccinated people. Third, specific biomarkers such as interleukins and cytokines are not available in our center, something that may help provide a differential profile among these patients, because all of them fulfill criteria for 'severe inflammation' but a clear-cut 'cytokine storm' could not be diagnosed. Finally, we do not have information relating long-term outcomes after steroid use. However, the patients who received high doses of steroid according to the criteria considered for this study are routinely discharged with an oral steroid, with a subsequent reduction and withdrawal in 6 weeks unless a contraindication for their use is detected. The patients with previous steroid use (for rheumatic or chronic inflammatory conditions) are tapered to their previous baseline dose and referred to their specialists for further indications.<sup>26</sup>

The main strength of this work is that is a real-life study in a third-level hospital that was adapted to treat severe COVID-19 patients. This reflects the freely prescribed treatment issued by specialized frontline physicians, according to their usual clinical practice and the scientific information available at that time. Also, we reported a relevant clinical and biochemical profile on these patients, common to several developing countries, in comparison with other clinical trials that studied steroids in COVID-19.

### Conclusion

The use of steroids in severe COVID-19 reduces mortality only at the dose proposed in the RECOVERY study in the younger population. No benefit of the use of steroids was observed in patients with older age or higher number of comorbidities.



**Author contributions**

**Alejandra Albarrán-Sánchez:** Conceptualization; Investigation; Writing – original draft.

**Claudia Ramirez-Rentería:** Data curation; Methodology; Writing – review & editing.

**Moisés Mercado:** Formal analysis; Project administration; Resources; Supervision.

**Miriam Sánchez-García:** Investigation; Methodology; Writing – original draft.

**Corazón de Jesús Barrientos-Flores:** Data curation; Investigation.

**Aldo Ferreira-Hermosillo:** Formal analysis; Supervision; Writing – review & editing.

**Conflict of interest statement**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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**Data sharing**

The data analyzed in the study are available from the corresponding author on reasonable request.

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