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Steroids and mortality in non-critically ill COVID-19 patients: a propensity score-weighted study in a Chilean cohort

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ABSTRACT

Objectives: The aim of this study was to evaluate the impact on 30-day mortality of early use of corticosteroids in COVID-19 patients with supplementary oxygen requirements and without invasive mechanical ventilation at the initiation of therapy.

Methods: All patients hospitalized with COVID-19 between April 15 and July 15, 2020, and requiring supplementary oxygen, were prospectively included in a database. Patients who died or required intubation within the first 48 hours were excluded. Patients who received corticosteroids within the first 5 days of hospitalization and at least 24 hours prior to intubation were allocated to the 'early corticosteroids' group. To compare both populations and adjust for non-random treatment assignment bias, a weight-adjusted propensity score model was used.

Results: In total, 571 patients met the inclusion criteria, 520 had sufficient information for the analysis. Of these, 233 received early corticosteroids and 287 did not. Analysis showed a reduction of 8.5% ($p = 0.038$) in 30-day mortality in the early corticosteroid group. The reduction in mortality was not significant when patients with corticosteroid initiation between day 5 and day 8 of hospitalization were included.

Conclusion: Early corticosteroid use reduced mortality in patients with pneumonia due to COVID-19, who required supplementary oxygen but not initial invasive mechanical ventilation.

Introduction

Chile's first patient with COVID-19 was diagnosed in March 2020. The disease spread rapidly, causing a first wave of infections that had its peak at epidemiological week 27, corresponding to the week of May 28, 2020, and mainly affecting the capital, Santiago.

Hospital Barros Luco Trudeau located in Santiago is one of the main adult care centers in the country, providing care to 1.5 million people. Before the first wave, it had 22 critical beds enabled to provide mechanical ventilation. After subsequent conversions, the number of beds with invasive ventilation capacity reached 85.

The use of corticosteroids in patients with COVID-19 is supported by several studies and a meta-analysis (Sterne et al., 2020; Van Paassen et al., 2020; Sai Pulakurthi et al., 2021), which have shown a reduction in mortality with the use of corticosteroids. Most of the included studies involved critically ill patients, and only two of the 44 studies reported on the Latin American population (Jeronimo et al., 2020; Tomazini et al., 2020). Both of these studies were randomized, but only one evaluated non-critically ill patients, and no reduction in mortality with the use of corticosteroids was observed. Of the studies included in the meta-analysis, only a minority managed to establish a benefit with statistical significance, and the estimators were highly influenced by the weight of the RECOVERY trial (The RECOVERY Collaborative

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Group et al., 2021). In the RECOVERY study, a reduction in mortality of 12.3% was observed for patients on mechanical ventilation, while for those with oxygen requirements but without invasive ventilation the figure was 4.2%. The RECOVERY study was carried out in the United Kingdom, where the epidemiological characteristics and conditions of care were not comparable with those in Latin America. For this reason, it was necessary to establish whether this small margin of benefit in the population without invasive mechanical ventilation was maintained, despite demographic variations observed across different populations.

Materials and methods

Between April 15 and July 15, 2020, data were prospectively recorded for all adult hospitalized patients with a diagnosis of COVID-19 and oxygen requirements. Infection was documented by positive PCR test for SARS-CoV-2 through nasopharyngeal swab performed on admission. Patients who died or required intubation within the first 48 hours of hospitalization were excluded.

The information collected included days of symptoms, date of hospital admission, demographic characteristics such as age and sex, and comorbidities — hypertension (HT), diabetes (DM2), chronic kidney disease (CKD), chronic liver disease, solid or hematological cancer, HIV infection, pharmacological immunosuppression, and chronic lung disease.

Laboratory results were recorded for the first 5 days of hospitalization, including leukocyte cell counts, lymphocytes, neutrophils, platelets, lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer, ferritin, blood urea nitrogen (BUN), creatinine, aspartate transaminase (AST), alanine aminotransferase (ALT), and lactic acid. The worst result for each variable found within the first 5 days of hospitalization was used for analysis. These comprised the lowest lymphocyte and platelet counts, and the highest values for the rest of the laboratory results.

Follow-up data on 30-day mortality were extracted from national registries. The final search was performed 4 months after recruitment of the last patient in order to avoid loss of deceased due to delays in registration. The date of intubation was obtained from our intensive care unit records.

The correlative variable 'day of admission' was established by taking April 15 as 'day 0' and July 15 as 'day 91'.

On June 15, 2020, a local management guideline was published that protocolized the use of corticosteroids in patients with COVID-19. The protocol was based on a study demonstrating the benefits of early use of short courses of corticosteroids (Fadel et al., 2020), and proposed the use of 8–16 mg/day of dexamethasone or 40–80 mg/day of methylprednisolone for 3 days. Final doses were defined by the treating physician according to the patient's weight and comorbidities; no need for progressive reduction of corticosteroids was specifically established. Use was indicated in patients who met all the following criteria: more than 7 days of symptoms, acute respiratory failure, and showing inflammatory markers in the lab profile. The protocol is described in full in Table 1. These guidelines was widely distributed in the hospital, especially within the emergency department, to achieve early indication from the moment the patient was admitted.

Corticosteroid use was established according to pharmacy and clinical records. Early corticosteroid use was defined as an indication of at least one dose of methylprednisolone or dexamethasone within the first 5 days of hospitalization, and at least 1 day before the start of invasive mechanical ventilation.

Total corticosteroid dose was calculated by adding the doses of methylprednisolone and/or dexamethasone administered to each patient during the observation period, based on an equivalence of 6.7 mg and 1.3 mg of prednisone for each mg of dexamethasone and methylprednisolone, respectively.

Table 1
Criteria for starting corticosteroids in confirmed COVID-19 patients.

All the following:
1. > 7 days of symptoms
2. Respiratory failure, defined as one of the following:
PaO_2 < 60 mmHg or O_2 sats < 94% with ambient oxygen
Respiratory rate > 30 bpm
Use of accessory muscles
3. At least two of the following:
Elevated CRP
Elevated leucocytes
Lymphocytes < 1000 cells/mm^3
Elevated ferritin
Elevated LDH

PaO2: partial pressure of arterial oxygen; O_2 sats: oxygen saturation; CRP: C-reactive protein; LDH: lactate dehydrogenase

None of the patients received any other type of antiviral, immunomodulatory treatment, or vaccination against COVID-19 during the period of observation.

Statistical analysis

Continuous variables were reported as median and interquartile range, and the differences between treated and untreated groups were assessed using the Mann-Whitney test. Categorical variables were reported as percentages and the differences between treated and untreated groups were assessed using a chi-squared test.

Two different propensity score weighting models were tested to adjust for bias due to non-random treatment assignment. One involved overlap weights (overlap) and the other, inverse probability weights (IPW), both of which were evaluated according to the balance of variables achieved by each model (Li et al., 2018; Li and Thomas, 2019; T. Zhou et al., 2020).

Propensity scores were estimated by logistic regression using the following variables: age, correlative day of admission, days of symptoms, sex, pharmacological immunosuppression, HT, DM2, CKD, chronic liver disease, platelets, LDH, CRP, and lymphocytes.

Age and correlated day of admission were included in this study using natural cubic spline with four degrees of freedom, and laboratory variables were included by quintiles.

To compare the difference in treatment effect between the two groups, the average treatment in the overlap population (ATO) was used with the overlap model and the average treatment effect (ATE) was used in the IPW model; both were estimated using the R package PSweight (Li and Thomas, 2019; Thomas et al., 2020).

The primary endpoint was the mortality rate at 30 days from admission to the hospital.

Results

In total, 571 patients were recruited, of whom 520 provided sufficient data for propensity score analysis. Of these, 233 were in the early corticosteroid group and 287 in the no early corticosteroid group.

The median age was 64 years and 55% were male. The prevalence of comorbidities was 55.2% for HT, 37.9% for DM2, 6.5% for CKD, 2.5% for chronic liver disease, 2.7% for solid or hematologic cancer, 0.2% for HIV, and 8.9% for chronic lung disease. There were no differences between the two groups, except for the history of pharmacological immunosuppression, for which only one of the 15 patients was included in the early corticosteroid group ($p = 0.003$).

Mortality was similar in both groups — close to 28% — with the analysis of the crude data showing a risk difference of 0.012 (CI −0.065 to 0.90) against the use of early corticosteroids.

Table 2
Demographic characteristics and percentages of early corticosteroid use for each period.

	No ECU	ECU	Total	*p*-value
n (%)	287 (55%)	233 (45%)	520 (100%)	
Age, median (IQR)	63 (54–72)	64 (55–72)	64 (54–72)	0.975[a]
n (% total cases)				
Male	147 (51.2)	139 (59.7)	286 (55.0)	0.054[b]
HT	156 (54.4)	131 (56.2)	287 (55.2)	0.670[b]
DM2	101 (35.2)	96 (41.2)	197 (37.9)	0.160[b]
CKD	19 (6.6)	15 (6.4)	34 (6.5)	0.933[b]
Chronic liver disease	8 (2.8)	5 (2.2)	13 (2.5)	0.641[b]
Solid or hematologic cancer	9 (3.1)	5 (2.2)	14 (2.7)	0.488[b]
HIV	0 (0.0)	1 (0.4)	1 (0.2)	0.267[b]
Pharmacological immunosuppression	14 (4.9)	1 (0.4)	15 (2.9)	0.003[b]
Chronic pulmonary disease	22 (7.7)	24 (10.3)	46 (8.9)	0.293[b]
30-day mortality	79 (27.5)	67 (28.8)	146 (28.1)	0.756[b]
Intubation after 48 hrs from admission	19 (6.6)	56 (24.0)	75 (14.4)	< 0.0001[b]
Number of patients admitted every 30 days, *n* (% for the period)				
0–30	101 (98.1)	2 (1.9)	103 (19.8)[c]	<0.0001[b]
31–60	143 (58.4)	102 (41.6)	245 (47.1)[c]	<0.0001 b
61–91	43 (25.0)	129 (75.0)	172 (33.1)[c]	<0.0001 b

No ECU: no early corticosteroid use; ECU: early corticosteroid use; HT: hypertension; DM2: diabetes mellitus; CKD: chronic kidney disease; HIV: human immunodeficiency virus; IQR: interquartile range
[a] Mann-Whitney test
[b] chi-squared test
[c] *n* (% of total cases)

Table 3
Laboratory results.

Laboratory results (*n*)	No ECU	ECU	Total	*p*-value[a]
Median (IQR)				
Leukocytes (520) × 10^3/μL	9.36 (6.87–12.95)	11.5 (9.38–14.64)	10.42 (7.93–14.06)	0.0001
Lymphocytes (520) cells/μL	901 (594–1222.8)	682.5 (522.5–949.2)	774.25 (552–1123.7)	0.0001
Platelets (520) × 10^3/μL	210 (156–274)	214 (170–298)	211 (163–283.5)	0.0884
LDH (520) U/L	413 (327–527)	523 (421–672)	464 (358.5–600.5)	0.0001
Neutrophils (520) cells/μL	7426 (5022–10 483)	9683 (7560–12 967)	8452 (610–11 792)	0.0001
BUN (515) mg/dL	22 (14–40)	27 (20–40.5)	25 (17–40)	0.0008
Creatinine (519) mg/dL	1.02 (0.78–1.64)	1 (0.8–1.42)	1.02 (0.79–1.53)	0.6045
CRP (520) mg/L	157.4 (80.3–246.8)	233.1 (147.3–318.2)	183.65 (98.35–286.65)	0.0001
D Dimer (499) ng/mL	1275 (761–3277)	1954 (1088–6393.5)	1502 (906–4564)	0.0001
Ferritin (498) ng/mL	1092 (548–2000)	1506 (927–2335)	1333 (693–2171)	0.0001
AST (333) U/L	37.05 (25.9–58)	40.4 (29.8–58)	38.9 (27.9–58)	0.2552
ALT (337) U/L	27 (17.9–41.3)	32.9 (21.2–57.5)	29.5 (19.6–49.8)	0.0126
Lactic Acid (511) mg/dL	24 (19.3–29.2)	25.2 (20.8–30.5)	24.5 (19.9–30.1)	0.0449

No ECU: no early corticosteroid use; ECU: early corticosteroid use; LDH: lactate dehydrogenase; BUN: blood ureic nitrogen; CRP: C-reactive protein; AST: aspartate transaminase; ALT: alanine aminotransferase
[a] Mann-Whitney test

Intubation rate was 3.6 times higher in patients who used early corticosteroids compared with those who did not (6.62% vs 24%; $p < 0.001$).

It is also noteworthy that early corticosteroid use increased as the observation period progressed, being prescribed in 2%, 42%, and 75% of total admissions for each 30-day observation period. The clinical and demographic characteristics are shown in Table 2.

Patients in the early corticosteroid group had significantly more lymphopenia and higher leukocyte, LDH, neutrophil, BUN, CRP, D-dimer, ferritin, and ALT values (Table 3).

Patients were admitted with a median of 7 days of symptoms and received steroids between days 7 and 12 from symptom onset, with a median of 9 days. Fifty-seven patients in the no early corticosteroid group received corticosteroids during their hospitalization after medians of 13 days of symptoms and 7 days of hospitalization (Table 4).

Of the early corticosteroid users, 89.7% received dexamethasone, 3.4% received methylprednisolone and 6.9% of patients had no data. Patients without information corresponded mostly with those who received treatment in the emergency room and therefore did not appear in the pharmacy register.

The median duration of treatment was 3 days (IQR 2–4), and the median total dose of prednisone was 293 mg (RIQ 160–453), equivalent to 15 mg/day of dexamethasone for 3 days (Table 5).

Results of the statistical analysis

A logistical model was selected with an equation able to predict steroid use with a discriminant value of 0.90 (area under the curve) and a pseudo R2 of 0.42.

Figure 1 shows the standardized mean differences of the variables included in the model. In the crude data analysis, most of the variables showed differences of over 10%, reflecting allocation bias. After adjustment using the overlap weights model, all variables reduced their differences to under 10%, allowing evaluation of the effect of corticosteroids.

After comparing the IPW and overlap methods, it was decided to select the latter because it represented considerably better balance, especially of the variables that determine the severity of this disease (Figure 1).

Figure 2 compares the difference in treatment effect of the two methods tested (IPW and overlap) and the two different periods

Table 4
Days of symptoms on admission, and days since admission and with symptoms before corticosteroids where initiated.

Total (*n*)	No ECU (287)	ECU (233)	Total (519)	*p*-value[a]
Days of symptoms at admission, median (IQR)	7 (3–10) No ECU (57)	7 (5–10) ECU (233)	7 (4–10)	0.0021
Days of symptoms before initiation of corticosteroids, median (IQR)	13 (10–16)	9 (7–12)	10 (7–13)	0.0001
Days of hospitalization before initiation of corticosteroids, median (IQR)	7 (6–10)	2 (1–3)	2 (1–4)	0.0001

No ECU: no early corticosteroid use; ECU: early corticosteroid use; IQR: interquartile range
[a] Mann-Whitney test

Table 5
Details of corticosteroid use.

Type of steroid use	No ECU (57)	ECU (233)	Total	*p*-value
Dexamethasone n (%)	37 (64.9%)	209 (89.7%)	240	< 0.001[a]
Methylprednisolone n(%)	16 (28.1%)	8 (3.4%)	22	
Without information n(%)	4 (7%)	16 (6.9%)	16	
Days of steroid use, median (IQR)	2 (1–3)	3 (2–4)	3 (2–4)	0.0197[b]
Total doses of prednisone, mg (IQR)	320 (160–640)	293 (160–453)	310 (160–480)	0.4767[b]

[a] Chi-squared test
[b] Mann-Whitney test

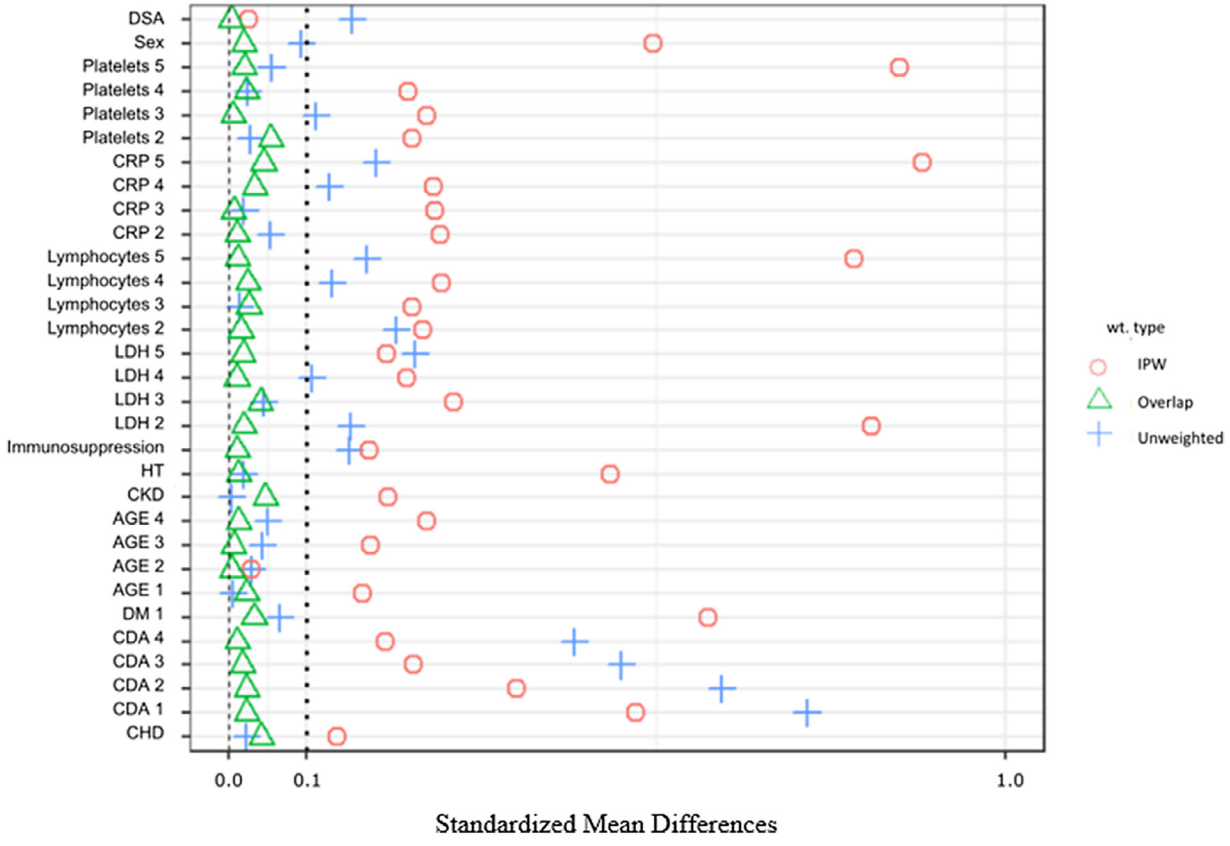


Figure 1. Balance of variables between the inverse probability (IPW) and overlap propensity score-weighted models compared with the unweighted population
Differences between the early and non-early corticosteroid use groups are represented using the standardized mean differences for each variable included in the model. The crude analysis (unweighted) showed important differences between the two groups in most of the variables included. After adjusting for the overlap-weighted model, these differences were reduced to below 10%, which removed the influence of these variables on mortality, allowing the analysis of the role of corticosteroids.
DSA: days of symptoms at admission; CRP: C-reactive protein; LDH: lactate dehydrogenase; HT: hypertension; CKD: chronic kidney disease; DM: diabetes mellitus; CDA: correlative day of admission; CHD: chronic hepatic disease

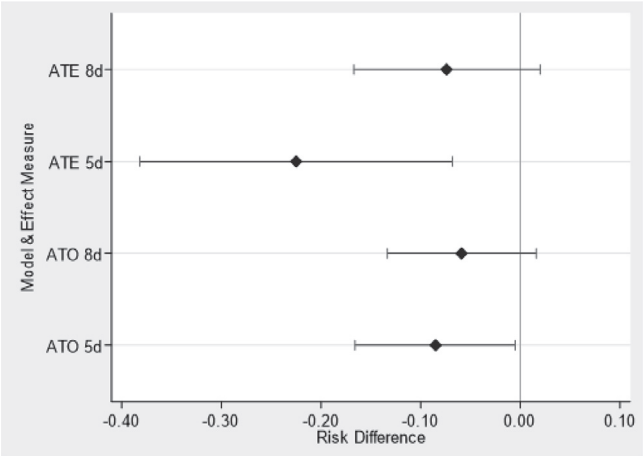
for steroid treatment — within 5 days of hospital admission and within eight days of hospital admission.

Considering the best model (overlap) for those in the group without early corticosteroid use, the probability of death was 34.1%; for those in the early corticosteroid use group, it was 25.6%. Thus, a reduction in mortality of 8.5% ($p = 0.038$) was observed.

When expanding the criteria for corticosteroid use from the first 5 days of admission to the first 8, a 5.9% ($p = 0.125$) decrease in mortality was observed, but with no significant difference between the two groups.

Discussion

The use of corticosteroids in COVID-19 is mainly supported by studies conducted with Asian and European cohorts. Our study revealed important differences between our population and those of



	Risk Difference	Std err	IC	P value
ATE 8d	-0.074	0.048	-0.167; -0.020	0.124
ATE 5d	-0.225	0.080	-0.382; -0.068	0.005
ATO 8d	-0.059	0.038	-0.134; 0.016	0.125
ATO 5d	-0.085	0.041	-0.166; -0.005	0.038

Figure 2. Average treatment in the average treatment effect (ATE) and overlap (ATO) populations for 30-day mortality with corticosteroid administration within the first 5 and 8 days of hospital admission

these other cohorts. For example, two diseases significantly influenced by the use of corticosteroids, such as diabetes and chronic lung disease, have double and half of the incidence, respectively, of those in the the RECOVERY trial population. Additionally, in patients without mechanical ventilation, the margins of benefit for corticosteroids use were narrow, and therefore differences in prevalence of comorbidities, availability of critical beds, and the use of other therapies may have reduced or reversed the reported risk–benefit relationship. This was one of the largest studied cohorts in the Latin American region with regard to evaluating the benefits of steroids in COVID-19 patients without initial mechanical ventilation.

No other antiviral therapies or immunomodulators were used for patient management; nor had vaccination been carried out. Moreover, there were no outbreaks of variants other than the one that caused the initial outbreak, allowing a pure analysis of the benefits of corticosteroids.

Our results showed that the early use of steroids during hospitalization in COVID-19 patients with supplemental oxygen requirements reduced mortality by 8.5% — a finding that supports the use of corticosteroids in COVID-19, despite the epidemiological differences observed in our population.

The differences observed between the two groups in the crude laboratory analysis reflected a more severe inflammatory profile and a higher probability of death in the early corticosteroid group. This was consistent with the 1.2% risk difference against the early use of corticosteroids observed with the crude data analysis. However, these differences were correctly compensated by the model selected.

The difference in intubation rates reflected a more severe respiratory failure in the early corticosteroids group. Since we did not have a respiratory function parameter in our model, this was not fully compensated, and therefore a bias remained in our analysis. However, this bias tended to locate the most severe patients in the early corticosteroid group, and therefore it was possible that the benefits of corticosteroids were even greater.

The results showed that as the use of corticosteroids during hospitalization was delayed, the benefit with regard to reducing mortality decreased and lost its statistical significance. This could suggest a window of opportunity for the use of corticosteroids (Siddiqi and Mehra, 2020), which would be in the period between overcoming the replicative phase of the virus and prior to the onset of the hyperinflammatory phase. Although this period is not well defined, our suggestion would be to start the treatment as soon as the patient begins to require supplementary oxygen.

The median total dose of corticosteroid used, measured in milligrams of prednisone, was equivalent to the protocol indication of 8–16 mg/day of dexamethasone for 3 days, thus demonstrating good adherence to the protocol. One day after the launch of our guidelines, the preliminary RECOVERY study was published, which caused some doctors to change the indication to 6 mg of dexamethasone for up to 10 days. However, in general, the tendency was to use therapies more aligned with the local protocol.

In our hospital, the only oral corticosteroid available is prednisone, which has traditionally been used for the management of stable patients who are chronic corticosteroid users, and not to manage acute decompensations. To evaluate the impact of its use in our patients with COVID-19, a search was conducted in pharmacy records, and statistical analysis was performed to include this third corticosteroid. Only 17 patients changed from non-users to users of early corticosteroids. Most of these were patients with a history of pharmacological immunosuppression or chronic lung disease, and the median total dose was 100 mg prednisone (25 mg/day), more consistent with maintenance doses of pharmacological immunosuppression, and far from the 320 mg suggested in our management protocol. For this reason, it was decided to keep these patients in the usual management group.

Most of the high-quality evidence demonstrating the benefits of steroid use comes from studies in which patients were categorized by level of oxygen support administered (The RECOVERY Collaborative Group et al., 2021; WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group et al., 2020). It should be considered that the severity of patients cannot be defined according to the ventilatory support received in the context of over-demand for critical beds. The same patient with the same degree of respiratory failure may receive different levels of ventilatory support, depending on the availability of this resource throughout the evolution of the pandemic. Several efforts have been made to evaluate risk-scoring systems and predictors of mortality that allow stratification of patients with COVID-19 (Knight et al., 2020; Wynants et al., 2020). It would be interesting to define the use of corticosteroids according to the category of risk or severity, rather than the ventilatory support received, since the latter is affected by the availability of the resource rather than the patient's condition.

Limitations

Adjustment for severity in our population was based primarily on the inclusion of risk factors and laboratory parameters that have been described in the literature as being related to severity or mortality (Liao et al., 2020; Wu et al., 2020; F. Zhou et al., 2020). It would have been desirable to include some parameters reflecting the level of respiratory failure, as recommended by current stratification systems (Knight et al., 2020).

The risk factor of obesity is an important factor that could not be collected for all patients because of the lack of a reliable way to calculate BMI in the context of over-demand during the first wave.

Conclusions

The use of corticosteroids in COVID-19 patients with supplementary oxygen requirements without initial invasive mechanical

ventilation reduced mortality by 8.5%. This reduction in mortality decreased with delay to the start of the treatment during hospitalization. We recommend that corticosteroid treatment be initiated as soon as possible in all patients with confirmed COVID-19 and supplementary oxygen requirements.

Competing interests

No authors have competing interests in this research.

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Ethical approval

This study was approved by the Scientific Ethics Committee of the South Metropolitan Health Service of the Health Ministry of Chile.

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