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Systemic Corticosteroids for Covid-19: A Retrospective Comparative Cohort Study

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Abstract

Background: Hyperinflammation is key in the outcome of COVID-19. The role of corticosteroids (CT) is controversial.

Methods: We performed a retrospective study comparing patients with COVID-19 pneumonia admitted at two Spanish hospitals: one that treated patients with CT at admission (CT cohort), and another that prescribed CT only for indications other than COVID-19 (non-CT cohort). The primary endpoint was a combined outcome comprising non-invasive mechanical ventilation (NIMV), ICU admission, and mortality.

Results: The study population comprised 201 patients (102 in the non-CT and 99 in the CT cohort). The primary outcome occurred in 22.2% (95%CI, 14.0-30.4) and 13.7% (95%CI, 7.0-20.4) of the patients in the CT and non-CT cohorts, respectively (p=.16). Median hospital length of stay was 8 (P25-P75 6-13) vs 7 (P25-P75 5.2-11) days in the CT and non-CT cohorts (p=.2). Admission to the ICU was necessary in 7.0% (95%CI, 2.0-12.1) and 5.8% (95%CI, 1.3-10.4) of patients in the CT and non-CT cohorts (p=.95). NIMV was not used in the CT cohort (3.9% vs 0.0% for non-CT and CT; p=.13). Mortality was 18% (95%CI; 10.5-25.7) in the CT cohort, and 13.7% (95%CI 7.0-20.4) in the non-CT cohort (p=0.51). The lowest prevalence of the combined event was found in patients receiving an accumulated prednisone equivalent dose of CT (APEDCT) between 400 and 600 mg (5.2%; 95%CI, 0.6-17.7%; p=.013). This finding remained significant after the multivariate analysis (OR, 0.09; 95%CI, 0.01-0.43; p=.007).

Conclusion: An APEDCT of 400-600 mg seems to improve the progress of non–critically ill hospitalized patients with COVID-19.

Keywords: SARS-COV-2; COVID-19; Corticosteroids; Prednisone; Mortality

Background

SARS-CoV-2 is responsible for the most severe pandemic of this century [1]. The infection is very heterogeneous in terms of its course, with about 20% to 28% of patients requiring hospitalization [2-4] and about 5% requiring admission to the intensive care unit (ICU) [2]. In addition, there are no clear individual prognostic factors [5]. The poor course of the disease is the consequence of an uncontrolled systemic autoinflammatory "cytokine storm", characterized by high levels of IL-1β, IFN-γ, IL-10, and MCP1 that activates the T-helper 1 (Th1) cell response and causes severe lung damage [6,7]. Autopsy results reveal exudative and proliferative changes characteristic of diffuse alveolar damage, including an inflammatory infiltrate comprising macrophages and lymphocytes [8]. Because of these pathogenic mechanisms, prescribing corticosteroids (CT) for the treatment of COVID-19 seems reasonable [9,10]. However, treating COVID-19 with CT remains a controversial issue, with different and changing recommendations during the course of the pandemic [6,11-13].

In its initial recommendation in March and May 2020, the World Health Organization (WHO) contraindicated the use of CT for the management of COVID-19 because of potential adverse effects [14]. One meta-analysis drew similar conclusions [15]. After publication of the results of the randomized RECOVERY trial [16] in July 2020, WHO performed a meta-analysis of nine randomized trials, including those from a previous meta-analysis by the REACT Working Group [17] plus data from RECOVERY [16]. In September 2020, WHO published a specific updated document [18] recommending the use of CT in patients with severe and critical COVID-19 infection and contraindicating their use in patients with mild-moderate infection because of potential adverse effects and absence of clear benefits [13,18]. Similarly, the Infectious Diseases Society of America (IDSA) advised the use of CT over not using CT, in hospitalized patients with severe COVID-19 [19].

Owing to the uncertainty over the use of these drugs, centers have been prescribing them in different ways, especially in mild/moderate cases.

Given the controversy surrounding the approaches used, we retrospectively compared two CT strategies in patients with COVID-19 treated in two hospitals. The primary endpoint was a combined outcome comprising need for non-invasive mechanical ventilation (NIMV), ICU admission, and mortality. As a secondary endpoint, we performed an exploratory and stratified analysis of the combined outcome to identify how the effect of CT therapy varied across different subgroups and doses.

Methods

Study design

Retrospective cohort study from two Spanish hospitals, each of which applied a different therapeutic strategy for the management of patients with COVID-19 pneumonia. Hospital General Virgen de los Lirios (HGA), systematically prescribed methylprednisolone 40 mg/12 h, at admission to all patients (CT cohort), whereas Hospital Universitario San Juan de Alicante (HUSJ), reserved CT for patients with indications other than COVID-19, based on the attending physician's criteria (non-CT cohort). Both centers are in the province of Alicante, in southeastern Spain, 50 kilometers apart. The HGA has 305 beds and provides health care to 144,000 persons. The HUSJ has 396 beds and covers a population of about 220,000 inhabitants.

Study population

The study population comprised patients older than 18 years admitted with microbiologically confirmed COVID-19 pneumonia for at least 24 hours. We excluded patients admitted directly to the ICU from the emergency department, and those for whom microbiological confirmation was not available. Patients were included consecutively from the beginning of the pandemic (March 2020) until the sample size was reached at both hospitals (May 2020). Sample size was calculated using the difference in mortality observed by Wu et al. (15.8%) [2], accepting an alpha error of 0.05 and a potency of 90%, thus giving a total sample size of 90 patients per group.

Statistical analysis

The variables recorded were age, sex, treatment with ACEIs (angiotensin-converting enzyme inhibitors) or ARBs (angiotensin receptor blockers), hypertension, diabetes, dyslipidemia, heart failure, chronic pulmonary obstructive disease, asthma, chronic kidney failure (eGFR below 60 ml/min/1.73m^2), preexisting immunosuppression, HIV infection, active solid cancer, lymphoma, leukemia, Po_2/FiO_2 ratio, oxygen saturation, lymphocytes at admission, C-reactive protein (CRP) at admission, and treatment with hydroxychloroquine, chloroquine, lopinavir/ritonavir, corticosteroids, tocilizumab, and/or macrolides. We also recorded invasive mechanical ventilation (IMV) and time to IMV, NIMV and time to NIMV, ICU admission, time to ICU admission, death, date of discharge, hospital of admission, number of days hospitalized until initiation of corticosteroids, number of days of symptoms until initiation of corticosteroids, and accumulated prednisone equivalent dose of CT (APEDCT) during admission. Routine clinical data were gathered retrospectively from the medical records once the patient had been discharged. Data were entered into a password-protected electronic database and analyzed using R [20]. Missing data were imputed using the K-nearest

neighbor's algorithm. Normally distributed quantitative variables were expressed using the mean and standard deviation; non-normally distributed variables were expressed using the median and interquartile range. Proportions with 95% confidence intervals were calculated for qualitative variables. The t test was used to compare quantitative variables that followed a normal distribution. The Kolmogorov-Smirnov test was used to assess normality. The Mann-Whitney test was used to assess variables that were not normally distributed. A χ^2 test was used to compare qualitative variables. A logistic regression analysis was performed to evaluate the primary endpoint and adjust for baseline imbalances between the groups.

Ethics statement

The ethics committee at the Hospital Universitario de Elche approved the study. Given its retrospective nature, the necessity to obtain informed consent was waived. The study complies with the Declaration of Helsinki and with the Data Protection Act, and its performance followed the Standards for Good Clinical Practice and the tenets of Act 14/2007 on Biomedical Research.

Results

Study population

A total of 201 patients were included: 99 from the CT cohort and 102 from the non-CT cohort. Twelve patients in the non-CT cohort (12.7%) had received CT for indications other than COVID-19 infection according to the local protocol (11 because they developed ARDS during hospitalization, and one because he was taking prednisone as usual home treatment for reumatoid arthritis).

No significant differences were found when demographic and general baseline characteristics were taken into consideration, except for the prevalence of chronic comorbidities, with higher prevalence values recorded in the CT cohort for dyslipidemia (40.4% vs 24.5%; p=.02), use of ACEI (10.1% vs 0.0%; p=.002), and use of ARB (26.2% vs 10.7%; p=.008) (Table 1).

	Total cohort n 201	CT cohort n 99	Non-CT cohort n 102	p
Age (years)	64.1±14.3	65.3±13.6	63.0±15.0	.24
Older than 69 years (n/%)	69/34.3	38/38.3	31/30.3	>.99
Males (n/%)	104/51.7	49/49.5	55/53.9	.62
Diabetes (n/%)	34/16.9	16/16.2	18/17.6	.92
Hypertension (n/%)	80/39.8	44/44.4	36/35.3	.23
Dyslipidemia (n/%)	65/32.3	40/40.4	25/24.5	.02
Chronic heart failure (n/%)	10/4.9	5/5.0	5/4.9	>0.99
COPD (n/%)	11/5.4	5/5.0	6/5.8	>0.99
Asthma (n/%)	13/6.4	3/3.0	10/9.8	.09
Cancer (n/%)	12/5.9	9/14.1	3/2.9	.009
ACE inhibitor use (n/%)	10/4.9	10/10.1	0/0	.002
ARB blockers use (n/%)	37/18.4	26/26.2	11/10.7	.008
C-reactive protein (mg/dL)	68.5±74.4	83.0±77.2	46.8±66.8	<.001
Lymphocytes (cells/mL)	980±475	960±469	1018±484	.52
D dimer (ng/mL)	1294±2480	900±771	552±2076	<.001
Lactate dehydrogenase (U/L)	288 (208-370)	303 (242-416)	251 (179-357)	.001
Baseline oxygen saturation (%)	94 (91-96)	93 (88-96)	95 (93-97)	<.001
Baseline oxygen saturation ≤93% n (%)	75 (39.2)	48 (52.7)	27 (27.0)	<.001
p02 (mmHg)	76.3±25.1	57.4±12.9	83.4±31.0	.09

CURB65 >2 n (%)	52 (26)	33 (33)	19 (18)	.02
CALL score >9 n (%)	87 (43.2)	51 (49)	36 (35)	.06
Pharmacological treatments				
Lopinavir/ritonavir (n/%)	128/63.6	78/78.8	50/49.0	<.001
Hydroxychloroquine (n/%)	168/83.5	99/100.0	69/67.7	<.001
Chloroquine (n/%)	17/8.4	0	17/16.6	<.001
Azithromycin (n/%)	172/85.5	84/84.8	88/86.3	.93
Tocilizumab (n/%)	5/2.4	1/1	4/3.9	.38
Corticosteroids (n/%)	110/54.7	98/97.9	12/12.7	<.001
Cumulative prednisone equivalent dose (mg)	599±277	603.1±279	470.6±206	.38
Time to start CT (days)				
Since initial symptoms	11.5±4.2	8.5±4.6	9.8±7.8	.54
Since admission	0.7±1.7	0.5±1.3	2.23±1.9	.01
Outcomes				
Composite outcome (n/%)	36/17.9	22/22.2	14/13.7	.16
Length of stay (days)	8 (6-12)	8 (6-13)	7 (5-11)	.2
NIMV (n/%)	4/1.9	0	4/3.9	.13
ICU admission (n/%)	13/6.4	7/7.?	6/5.8	.95
Time to ICU admission (days)	3.0 (2.0-4.0)	4.0 (2.5-5.0)	2.5 (1.2-3.0)	.2
Death (n/%)	32.0/15.9	18/18.0	14.0/13.7	.5

Table 1: Demographics baseline clinical characteristics of the patients, COVID-19 severity related variables, pharmacological treatments for COVID-19 and outcomes. CT: Systematic use of corticosteroids. Non-CT: Use of corticosteroids in indications other than COVID-19 pneumonia. COPD: Chronic obstructive pulmonary disease. ACE: Angiotensin-converting enzyme. ARB: Angiotensin II receptor blockers. ICU: Intensive care unit. NIMV: Non-invasive mechanical ventilation.

According to the CURB65 and CALL scales, 26.0% and 43.2% of patients had severe COVID-19 pneumonia (Table 1). Severity was greater in the CT cohort, as shown by higher values for CRP (83.0±77.2mg/dL vs 46.8±66.8mg/dL; p<.001), plasma D-dimer (900±771ng/mL vs 552±2076ng/mL; p<.001), and lactate dehydrogenase (303 [242-416]U/L vs 251 [179-357]U/L; p=.001). In line with higher severity, again in the CT cohort, oxygen saturation on ambient air was lower (93[88-96] % vs 95[93-97] %; p<0.001) and oxygen saturation on ambient air lower than 93% was more frequent (48%vs27%; p<.001). More patients in the CT cohort had a CURB65 score higher than 2 (33%vs18%; p=.02). However, the difference was not significant when the proportion of patients with a CALL score higher than 9 was taken into consideration (49%vs35 %; p=.06).

Pharmacological management of COVID-19

The most frequently used drugs other than CT corticosteroids were azithromycin (85.5% of patients), hydroxychloroquine (83.5%), and the combination of lopinavir/ritonavir (63.6%) (Table 1). Comparison of CT groups by therapy revealed differences, with patients in the CT cohort being treated more frequently with lopinavir/ritonavir (78.0% vs 49.0%; p<.001) and hydroxychloroquine (100% vs 67.7%; p<.001) and less frequently with chloroquine (0.0% vs 16.6%; p<.001).

Corticosteroids were administered to 54.7% of all the participants 11.5±4.2 (mean±sd) days after the initial COVID-19 symptoms, with a median APEDCT of 599±277 mg. Although the patients in the CT cohort received a higher APEDCT (603.1±279

mg vs 470.6±206), the difference was not significant (p=.38). Mean time to initiation of CT after onset of the initial COVID-19 related symptoms was similar for both groups (8.5±4.6 days for the CT cohort, and 9.8±7.8 days for the non-CT cohort; p=.54).

Outcomes

The main composite outcome was recorded in 17.9% of patients, with no significant differences between the cohorts (22.2% [95%CI 14.0-30.4] in the CT cohort and 13.7% [95%CI 7.0-20.4] in the non-CT cohort; p=.16). Similarly, there were no significant differences when each of the components of the main composite outcome was taken into consideration (Table 1). Data were similar in both cohorts for the proportion of patients requiring admission to the ICU (7% [95%CI, 2.0-12.1] in the CT cohort, and 5.8% [95%CI, 1.3-10.4] in the non-CT cohort; p=.95) and mortality (18% [95%CI, 10.5-25.7] in the CT cohort and 13.7% [95%CI, 7.0-20.4] in the non-CT cohort; p=.51). Length of stay was similar (8 days [P25-P75 6.0-13.0] in the CT cohort vs 7 days [P25-P75 5.2-11.0] in the non-CT cohort; p=.2), and NIMV was used more frequently in the non-CT cohort, although the difference was not statistically significant.

We performed an exploratory stratified analysis of the main combined outcome based on sex, age, CRP, baseline oxygen saturation, lymphocytes, D-dimer, ACEI use, ARB use, days with COVID-19 symptoms before initiation of CT use, and APEDCT (Figures 1 and 2). The lowest prevalence of the combined event was found in patients who received an APEDCT of between 400 and 600 mg (5.2%; 95%CI, 0.6-17.7%; p=.013). Logistic regression showed that the association remained significant (OR, 0.09 [95%CI, 0.01-0.43]; p=.007). Other variables associated with the combined outcome were age above 70 years (OR, 11.13[95%CI, 4.2-33.6]; p<.001), lymphocytes below 901 cells/mL (OR, 3.52[95%CI, 1.37-9.7]; p=.01), and baseline oxygen saturation below 91% (OR, 6.44[95%CI, 2.57-17.11]; p<.001) (Table 2).

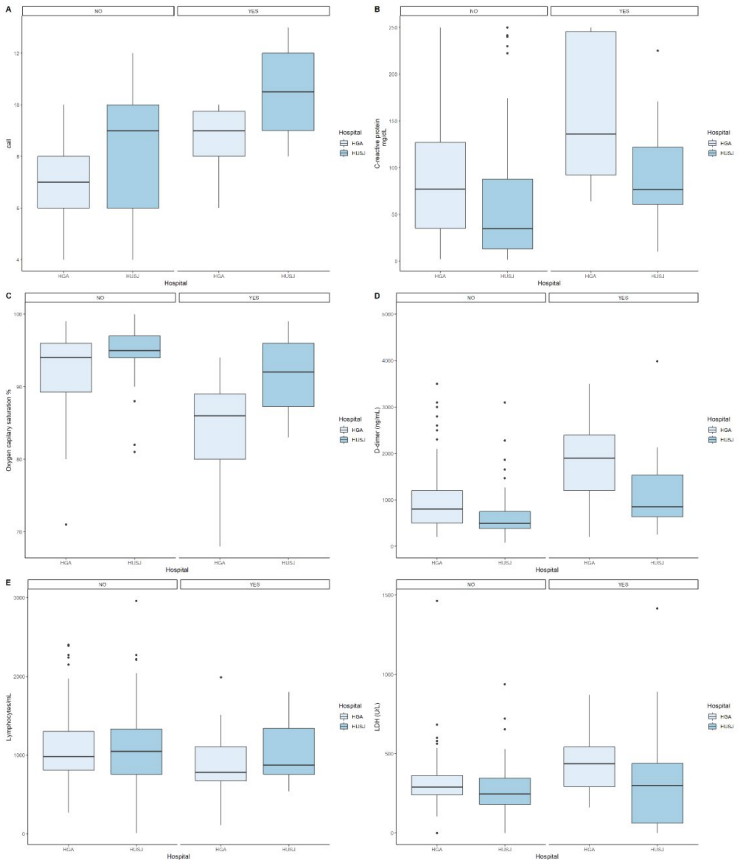

Figure 1: Exploratory analysis. A) CALL score of patients with and without the combined outcome in both groups. B) C-reactive protein at admission in patients with and without the combined outcome in both groups. C) Oxygen saturation at admission in patients with and without the combined event. D) D dimer levels in patients with and without the combined event. E) Lymphocytes on admission in patients with and without the combined event.

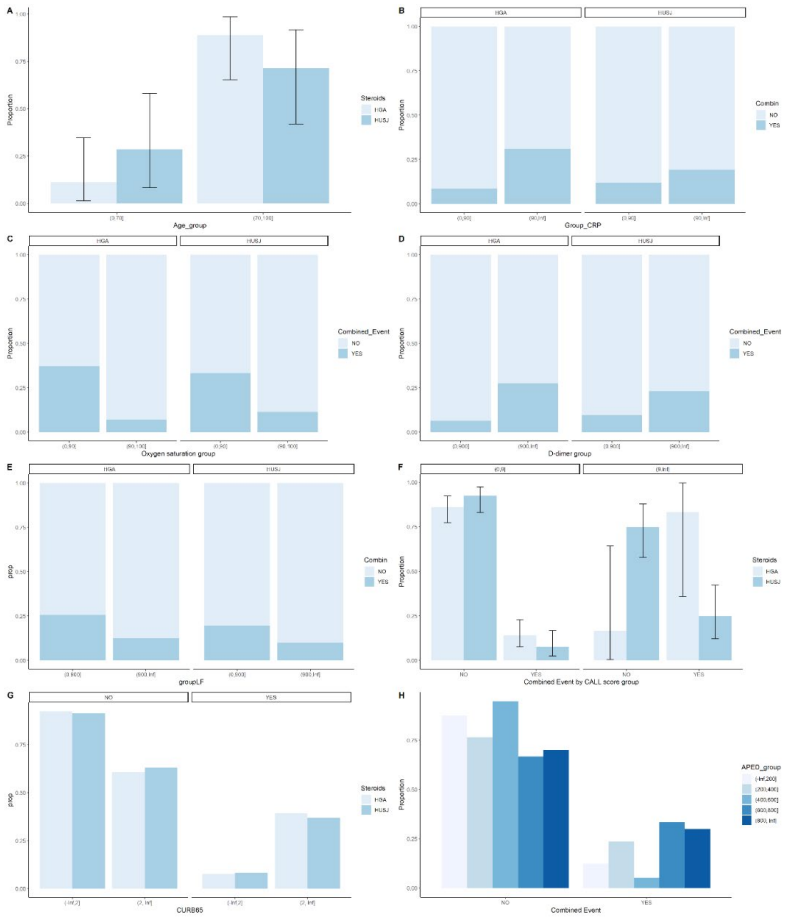

Figure 2: Stratified analysis by: A) age group, B) PCR group, C) Oxygen saturation group, D) D-dimer group, E) Lymphocyte group, F) Steroid reception, G) CURB 65 score, H) Accumulated equivalents of prednisone received.

Variable	Odds ratio (95%CI)	p-value
Age 71-100 years	11.1 (4.2-33.6)	<.001
Baseline oxygen saturation <91%	6.4 (2.6-17.1)	<.001
CT 400-600 eq prednisone	0.1 (0.01-0.4)	<.001
Lymphocytes <901/mL	3.5 (1.34-9.7)	.01
Female sex	2.1 (0.8-5.7)	.13

Table 2: Logistic regression model. CT: Corticosteroids.

Discussion

The present study did not show a significant impact of CT therapy on the progress of patients hospitalized in a conventional ward with COVD-19. The second main finding, although exploratory, is that in contrast with findings from previous studies, it seems that prognosis might depend on the total dose of corticosteroids administered, with a better prognosis when a APEDCT of between 400 and 600 mg is administered during admission.

Although COVID-19 is essentially considered a hyper inflammatory disease with an exaggerated immune response against the virus, none of the anti-inflammatory strategies considered demonstrated a beneficial effect, except when CT were administered in severe and critical cases [9,10,21], as shown in a recent update by the WHO [18]. This update (7,184 patients) concluded that administering corticosteroids in COVID-19 reduces mortality at 28 days by 6.7% and 8.7% in severe and critical cases. When non-severe cases are taken into consideration there is even less evidence, with some studies estimating an increase of 3.9% (95%CI, 1.2% reduction vs 10.7% increase) in mortality at 30 days [18]. These results show that the effect of corticosteroids is different between patients, with no precise individual markers of a potential benefit. In the present study, we did not observe a poorer clinical course in patients whose condition was severe enough to require hospitalization according to the attending physician.

At the beginning of the pandemic, CT were even contraindicated because of absence of benefit, increased risk of adverse effects, and concerns about prolonged viral clearance [22]. However, given recent evidence of a beneficial effect in severe and critical cases, some international authorities have changed their recommendations. [18,19] Nonetheless, the controversy has not yet been resolved, especially in non-severe cases of COVID-19.

From approximately the seventh to tenth day of symptoms onward, increasing autoinflammatory activity is noted in COVID-19 in severe and critical cases [21,23]. Information about the time-dependent effect of corticosteroids on the course of COVID-19 is not clear, with timing data not reported in most studies or extrapolated from viral infections other than SARS-Cov-2. [6,11–13] Despite concern regarding potential prolonged viral clearance, this has not been found to be related to corticosteroids in COVID-19, but rather to severity and old age [24]. The results from an Italian observational study showed that even when used early in moderate and severe cases, corticosteroids are not associated with longer viral clearance [25]. Today, we do not have specific markers that distinguish the phases of the disease. A sub-analysis of the RECOVERY [16], trial suggested a greater benefit when dexamethasone is initiated seven days after onset of the initial symptoms; however, the low quality of the evidence and the difficulty in establishing the individual timing of the disease leads WHO experts to recommend against basing initiation of therapy on a specific threshold of days with symptoms [18].

The intensity of the anti-inflammatory effect, which depends mainly on the specific molecule and dose, must also be taken into consideration when prescribing corticosteroids in COVID-19 [26]. Dexamethasone, hydrocortisone, and methylprednisolone are the three drugs used in the main recent randomized trials [18]. In order to analyze the intensity of the anti-inflammatory effect of the regimens used in the various studies, we estimated the APEDCT and found that an APEDCT of between 400 mg and 600 mg is associated with a better outcome in patients hospitalized in a conventional ward with COVID-19. Given that the high-dose cut-off values reported in most publications differ from author to author, and that the WHO review [18] and our results indicate that the lower effective APEDCT is 400 mg, it seems reasonable to classify the intensity of anti-inflammatory treatment using this cut-off value. When an APEDCT of 400 mg is considered the cut-off for high and low intensity of corticosteroid therapy, we can suggest that early therapy is beneficial in patients severe enough to be hospitalized with COVID-19, irrespective of the specific drug used, with a beneficial APEDCT of 400-600 mg. This range is consistent with the cumulative dose used in MetCOVID [27], GLUCOCOVID [28], and Steroid-SARI [17], and similar to that applied in RECOVERY [16], albeit with the difference that the benefit obtained in these randomized trials was limited to critical cases. Our study adds evidence of a benefit in non-critical hospitalized cases.

On the other hand, published data on the adverse effects of high doses of CT in COVID-19 are scarce. However, superinfection with several pathogens has been described in immunosuppressed COVID-19 patients [29,30]. Nevertheless, although corticosteroids have been proposed as a risk factor for COVID-19–associated pulmonary aspergillosis [31], and concerns over Strongyloides hyperinfection syndrome have also been raised [32], it seems that the incidence is very low [29,33], and the main scientific societies do consider that the benefits outweigh the risks, at least for severely and critically ill patients [18,19]. They also recommend special consideration of preventive measures, such as treatment with ivermectin, which has added antiviral effects [34], in regions with high prevalence of strongyloidiasis or in migrants from those areas [35].

Our study has limitations, which are mainly associated with its retrospective observational design. Firstly, patients were treated at two hospitals with different management protocols. In addition, the ICU admission criteria were not standardized for both centers. Similarly, use of drugs other than CT for the treatment of COVID-19 and disease severity differed between the two centers. The question of severity is probably the most important limitation of the study since it makes comparison between the cohorts difficult. Consequently, the benefit of corticosteroids might have been masked. The strength of our study is that data were obtained from daily clinical practice.

In summary, we did not find differences in the short-term progress of hospitalized COVID-19 patients treated early with corticosteroids. Analysis of secondary endpoints suggested that the effect of CT depends on the accumulated dose, with an APEDCT of 400-600 mg as the dose with the best prognosis.

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