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ORIGINAL ARTICLE

A short course of corticosteroids reduces the risk of mechanical ventilation and death in patients with moderate to severe COVID 19 pneumonia: results of a retrospective monocentric cohort

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ABSTRACT

Background: Reduced mortality at 28 days in patients treated with corticosteroids was demonstrated, but this result was not confirmed by certain large epidemiological studies. Our aim was to determine whether corticosteroids improve the outcomes of our patients hospitalized with COVID-19 pneumonia.

Methods: Our retrospective, single centre cohort study included consecutive patients hospitalized for moderate to severe COVID-19 pneumonia between March 15 and April 15 2020. An early short course of corticosteroids was given during the second phase of the study. The primary composite endpoint was the need for mechanical ventilation or mortality within 28 days of admission. A multivariate logistic regression model was used to estimate the propensity score, i.e. the probability of each patient receiving corticosteroid therapy based on the initial variables.

Results: About 120 consecutive patients were included, 39 in the "corticosteroids group", 81 in the "no corticosteroids group"; their mean ages (±SD) were 66.4 ± 14.1 and 66.1 ± 15.2 years, respectively. Mechanical ventilation-free survival at 28 days was higher in the "corticosteroids group" than in the "no corticosteroids group" (71% and 29% of cases, respectively, $p < .0001$). The effect of corticosteroids was confirmed with HR .28 (95%CI .10–.79), $p = .02$. In older and comorbid patients who were not eligible for intensive care, the effect of corticosteroid therapy was also beneficial (HR .36 (95%CI .16–.80), $p = .01$).

Conclusion: A short course of corticosteroids reduced the risks of death or mechanical ventilation in patients with moderate to severe COVID-19 pneumonia in all patients and also in older and comorbid patients not eligible for intensive care.

KEYWORDS
COVID-19 pneumonia
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Introduction

Coronavirus disease-19 (COVID-19) is a global pandemic that causes severe acute pneumonia. Mortality rates are high in patients hospitalized for severe or critical disease, ranging from 15% to 44% [1]. Cytokine storms cause a worsening of the disease, with a risk of acute respiratory distress syndrome with high mortality [2,3]. Several immunomodulatory treatments have been proposed [2] such as corticosteroids, anti-interleukin-1 antibodies, and anti-interleukin-6 antibodies, achieving variable results. The use of corticosteroids was evaluated in early reports, but these included small numbers of patients or were not performed under controlled conditions [4–8]. Larger retrospective cohort studies indicated lower mortality or less need for mechanical ventilation in patients receiving corticosteroids than in control groups [9,10]. A large open-label controlled trial found lower mortality at 28 days in patients without mechanical ventilation who were treated with dexamethasone for moderate to severe COVID-19 pneumonia [11].

Similar results were obtained in cohort studies of severely ill patients in intensive care units (ICU) [12]. Lower mortality at 28 days in mechanically ventilated ICU patients treated with dexamethasone was confirmed by the Recovery trial [11].

However, in the largest epidemiological study, corticosteroid use was not associated with a reduction in mortality [1].

Many questions remain unresolved. In the event of organ failure, some patients are not eligible for admission to an ICU due to old age and comorbidities. The effects of corticosteroids in these patients remain unknown.

The appropriate regimen of oral or intravenous corticosteroids remains a matter of debate. Most studies evaluated dexamethasone. Oral dose-equivalent corticosteroids (prednisone or methylprednisolone) might be an option, but such regimens still need to be evaluated.

Here we report on the results of a cohort study of corticosteroids in patients with COVID-19 pneumonia in a French tertiary care hospital. Numerous studies on corticosteroid use have already been published, but detailed data on a homogeneous single centre population receiving the same standard of care may be useful to provide more detail on the patients included and the timing of corticosteroid therapy initiation. We also analyzed the use of corticosteroids in older and comorbid patients who were not eligible for ICU care. Our results include a propensity score analysis.

Methods

Study population

We retrospectively reviewed the medical records of consecutive inpatients over the age of 18 years with confirmed COVID-19 pneumonia, hospitalized between March 15 and April 15, 2020.

COVID-19 was confirmed by positive rRT-PCR on nasal or throat swabs or typical findings on chest computed tomography (multiple ground-glass opacities).

Only patients with moderate to severe COVID-19 were included, defined as having a score of more than 4 on the WHO Clinical Progression scale [13] and a nasal oxygen flow higher than 3 liters/min at any time during hospitalization. The WHO Clinical Progression scale has 10 ordinal levels [13].

Patients with severe disease admitted directly to the ICU, and those who died within 48 h of admission, were excluded from the study.

Patients treated with immunomodulating or immunosuppressive medications (e.g. anakinra, tocilizumab or others) were also excluded.

All patients were admitted to our tertiary hospital which includes internal medicine, pneumology, infectious diseases and rheumatology departments. All these departments had been reorganized to admit COVID-19 patients only.

Study design

This was a single centre, retrospective cohort study.

All patients received the same standard of care, without any significant modifications during the study period.

Before April 1, 2020, no patients received corticosteroid therapy.

From April 1st until the end of the inclusion period, corticosteroid therapy was discussed during multidisciplinary staff meetings for all moderate and severe cases. The criteria for the initiation of corticosteroids were a worsening COVID-19 pneumonia (O2 flow higher than 3 liters/minute and an inflammatory state characterized by two or more elevated inflammation biomarkers), and the absence of other complications (bacterial infection, pulmonary embolism, cardiac insufficiency). It was thought that the patients included would reach the inflammatory phase of the disease, assessed from elevated their inflammatory parameters and after the exclusion of bacterial infection.

Patients treated with corticosteroids were included in the "CS group". All patients not receiving corticosteroids were considered as the "no CS group".

Intervention

Standard of care

Standard treatment included oral hydroxychloroquine 400 mg/day for 7 days, oral azithromycin 500 mg/day on day 1 then 250 mg/day for 4 days, and parenteral β-lactam antibiotics (ceftriaxone 1 g per day or amoxicillin 3 g per day) for 7 days, if none of these was contraindicated.

All patients received thromboembolic prophylaxis based on body weight and renal function: enoxaparin 40 mg/day if the BMI was lower than 30 kg/m^2 without risks factor for thromboembolic disease, enoxaparin 60 mg/day if the BMI was over 30 kg/m^2 or if BMI $<$30 kg/m^2 with risk factors for thromboembolic disease, low dose calcic heparin if the renal filtration rate was less than 20 ml/min.

Early short-course corticosteroid therapy

Two corticosteroid regimens were administered at the physician's discretion: oral prednisone 2 mg/kg/day from day 1 to day 3 and 1 mg/kg/day from day 4 to day 6, or intravenous dexamethasone 20 mg/day from day 1 to day 3 and 10 mg/day from day 4 to day 6.

Data collection

Demographic and clinical features, including body mass index (BMI), were recorded at admission (baseline).

Comorbid conditions were recorded and particularly cardiovascular comorbidities including vascular diseases, cardiac insufficiency, hypertension, diabetes and obesity.

The time from the onset of symptoms to hospital admission, data at admission including severity scores, laboratory tests and chest computed tomography were recorded. Treatments at admission were registered, including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

The O2 flow (liters/min) was recorded in all patients at admission and at the time of corticosteroid initiation in the "CS group". For comparative purposes, the O2 flow at day 3 after admission was recorded in patients in the "no CS group", corresponding to the mean time elapsing from admission to initiation of corticosteroids in the "CS group". The maximum O2 flow during hospitalization was recorded. High-flow nasal oxygen (HFNO) was administered [14] in some patients if nasal O2 at a flow rate of 15 liters/minute proved insufficient. The indications for HFNO were the same in patients not eligible for the ICU.

Severity scores were calculated using the WHO Clinical Progression Scale [13] at admission and at corticosteroid initiation, and on day 3 after admission in the "no CS group".

Study definitions

Moderate to severe COVID-19 pneumonia included levels 5 and 6 on the WHO Clinical Progression Scale [13].

The severity of lung damage on chest computed tomography was scored at four levels according to the extent of the lesions: $<$10%, 10–25%, 25–50%, and $>$50% of lung involvement [15].

Decisions to withhold life-sustaining treatments (including invasive mechanical ventilation) were based on age and comorbidities and were discussed by physicians and intensivists at hospital admission. Patients with a do-not-intubate order (hereinafter referred to as "not eligible for ICU") received the same standard of care as others. These patients were not defined by an age threshold or a specific comorbidity. The decision was multidisciplinary and taken after individual evaluation.

Outcome measures

The primary composite endpoint was the requirement for mechanical ventilation or mortality, during a period of 28 days from admission, as used in previous studies [16–18]. Mechanical ventilation-free survival defined patients who were not mechanically ventilated and alive at day 28 after admission.

The secondary outcome was overall survival from admission to discharge.

Statistical analysis

The data were described using numbers and percentages (%) for qualitative variables. Median and interquartile ranges (IQR) were used for quantitative variables. The characteristics of patients as a function of intervention ("CS group" or "no CS group") were compared using the Chi-square test or Fisher's exact test for qualitative variables and the Mann-Whitney test for quantitative variables.

To estimate the effects of corticosteroid therapy on mechanical ventilation-free survival, an inverse

probability weighted Cox model was performed. The inverse probability of treatment weighting (IPTW) was used to control for confounding parameters by balancing the differences in characteristics between the groups. A multivariate logistic regression model was used to estimate the propensity score (PS); i.e. the probability of each patient receiving corticosteroid therapy based on the initial variables: gender, age $\geq$65 years, patient eligible for ICU or not, global comorbidity, BMI, lymphocyte count and C-reactive protein $\geq$100 mg/l at admission, azithromycin treatment, O2 flow at corticosteroid initiation or on day 3 in the control group, period of admission (from April 1st, 2020), time between the onset of symptoms and admission. The threshold for an adequate balance between treatment groups after IPTW was an absolute standard difference of $<$10% [19]. The Cox model used for the primary analysis had a time-dependent propensity score (O2 flow being the only covariable varying over time). All patients had an initial score measured from the baseline covariates. A second measurement was performed at the initiation of corticosteroids, or on day 3 in the "No CS group". The secondary outcome, overall survival, was evaluated using the same approach as the primary outcome.

A multiple imputation chain equation (MICE) was performed to account for missing data among the covariates used for the propensity score. The number of multiple imputations was set at five with five iterations [20]. Seventeen covariates were used for MICE: age, gender, CS group patient eligible for the ICU, BMI, comorbidities, lymphocyte count, CRP, azithromycin treatment, hydroxychloroquine treatment, O2 flow rate at admission, HFNO, Nelson–Aalen estimator [21], primary outcome (mechanical ventilation or death), initial severity score, time between admission and the endpoint, lung involvement greater than 25%, time from the onset of symptoms and admission period (from April 1st, 2020). The propensity scores were based on five independent and complete datasets and were averaged according to a crossover approach [22].

Two sensitivity analyses were performed in patients treated at an early stage: those who received CS within the first three days and the first six days of hospitalization versus the "no CS group". Patients treated after the first three (or six) days were excluded. The propensity score was calculated using the same covariates as for the previous score. Finally, a subgroup analysis was performed in patients “not eligible for ICU”. In view of the sample size, a time-dependent covariate Cox model was used without the propensity score.

All tests were two-tailed, and results were considered to be statistically significant when $p < .05$. Statistical analyses were performed using R Project for Statistical Computing, Version 3.5.2 software (The R Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org/).

Our local Ethics Committee approved the conduct of this monocentric retrospective cohort study (IRB number: CLEA 2020-180). All patients were informed that their medical data might be used in an anonymous form for medical research.

Results

One hundred and twenty consecutive patients were included during the study period; 39 in the “CS group” and 81 in the “no CS group”. Their demographic and clinical data are shown in Table 1.

The two groups had comparable clinical characteristics, except for a higher O2 flow at admission in the “CS group”.

In the “CS group”, the median (IQR) times from the onset of disease and from hospital admission to the initiation of corticosteroids were 11 (9–15) days and 3 (2–5) days, respectively.

Other treatments did not differ between the two groups of patients, including antibiotics and hydroxychloroquine (Table 2). Azithromycin was administered more frequently in the “CS group”, the difference being just under the defined limit of significance (57% in the “No CS group” and 77% in the “CS group”, $p = .05$).

COVID-19 pneumonia was confirmed by rRT-PCR in 82% of cases; 93% of patients had typical lesions on chest computed tomography and 7% on chest X-ray. The extent of lesions on chest computed tomography was similar in the two groups.

Out of the entire cohort ($n = 120$), 39 patients (32.5%) died and 19 (15.8%) received mechanical ventilation.

Patients in the “CS group” had significantly higher mechanical ventilation-free survival at 28 days (71%) than those in the “no CS group” (29%), ($p < .0001$) under univariate analysis (Figure 1). Applying the propensity score, in the inverse probability of treatment weighting, the effect of CS was confirmed with HR 0.28 (95%CI .10–.79), $p = .02$ (Table 3). Covariate balances before and after weighting are shown in Figure 2.

Among patients treated with corticosteroids in the first three and first six days, mechanical ventilation-free survival at day 28 differed significantly between the “CS group” and “no CS group” even after weighting with HR

Table 1. Patient characteristics at admission.

	Total $n = 120$	Group without corticosteroids $n = 81$	Group with corticosteroids $n = 39$	p
Age, median (IQR), years	67.7 (56.8–75.9)	68 (57–75.1)	67.3 (56.2–76)	.81
Female, *n* (%)	38 (31.6)	28 (34.5)	10 (25.6)	.43
Time between disease onset and admission, median (IQR) (days)	7 (4–10)	6 (4–10)	7 (6–10)	.18
SARS-CoV 2 infection conformed by rRT-PCR on nasal/throat swab, *n* (%)	98 (81.7)	67 (82.7)	31 (79.5)	.86
CT-imaging of Covid-19, *n* (%)	112 (93.3)	74 (91.4)	38 (97.4)	.27
Lung involvement $> 25\%$, *n* (%)	56 (50.5)	35 (47.9)	21 (55.3)	.59
Lung involvement $> 50\%$, *n* (%)	12 (10.8)	8 (9.9)	4 (10)	>.9
Patients not eligible for Intensive care unit, *n* (%)	41 (34.2)	27 (33.3)	14 (35.9)	.94
Body mass index, median (IQR)	28.3 (24.6–31.6)	28.3 (24.2–32)	28 (26.5–31)	>.9
Body mass index > 30, *n* (%)	47 (40.5)	33 (42.9)	14 (35.9)	.6
Global comorbidity, *n* (%)	81 (67.5)	57 (70.4)	24 (61.5)	.45
Cardiovascular comorbidity, *n* (%)	79 (65.8)	55 (67.9)	24 (61.5)	.63
Ongoing cancer, *n* (%)	7 (5.8)	3 (3.7)	4 (10.3)	.21
Diabetes, *n* (%)	15 (12.5)	11 (13.6)	4 (10.3)	.77
Immunodepression, *n* (%)	12 (10)	7 (8.6)	5 (12.8)	.52
Systolic arterial pressure, median (IQR), mmHg	127 (115–140)	128.5 (116–141)	124 (112–138)	.22
Treatment with Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers, *n* (%)	51 (42.5)	36 (44.4)	15 (38.5)	.67
WHO score 4 at admission, *n* (%)	15 (12.5)	10 (12.3)	5 (12.8)	>.9
WHO score 5 at admission, *n* (%)	105 (87.5)	71 (87.7)	34 (87.2)	>.9
O2 flow at admission, median (IQR) litre/min	3 (2–4.2)	3 (2–4)	4 (3–6)	.003
O2 flow higher than 3 litres/min at admission, *n* (%)	74 (61.7)	44 (54.3)	30 (76.9)	.03
Laboratory values, median (IQR)				
Neutrophils G/l	5.14 (3.9–7.2)	4.8 (3.6–7.2)	5.7 (4.0–7.2)	.5
Lymphocytes G/l	.89 (.70–1.28)	.91 (.70–1.27)	.86 (.71–1.31)	>.9
Platelet count G/l	215 (172.5–259.2)	213 (168–251)	232 (193–265)	.13
CRP mg/l	100.5 (58.8–175.2)	87 (51–171)	117 (74.5–180.5)	.14
Procalcitonin g/l	.2 (.1–0.4)	.18 (.0.1–0.4)	.21 (.1–0.4)	.30
ASAT IU/l	45 (31.5–73)	44 (30.3–70)	47 (32–79)	.82
ALAT IU/l	34.5 (21.8–52)	34 (21–54)	36 (23–46)	.76
GFR CKD EPI ml/min/1.73 m2	82.5 (59–99.2)	84 (59–100)	82 (64–96.5)	.84
LDH IU/l	356 (250–512)	351 (239–491)	383 (282–531)	.35
CPK IU/l	202 (92.5–426)	188 (90.3–369)	204 (99–512)	.35
Albumin g/l	27 (24.5–30.7)	27 (25–31)	28 (24–30)	.77
D dimer mcg/ml	804 (450–1296)	745 (407–1218)	931 (632–1462)	.11

Comparison of characteristics and adverse prognostic factors between the two groups with or without corticosteroid treatment.
Data are median (IQR) or *n* (%).

Table 2. Data during hospitalisation.

	Total $n = 120$	Group without corticosteroids $n = 81$	Group with corticosteroids $n = 39$	p
Azithromycin treatment, *n* (%)	76 (63.3)	46 (56.8)	30 (76.9)	.05
Other antibiotic therapy, *n* (%)	116 (96.7)	77 (95.1)	39 (100)	.30
Hydroxychloroquine, *n* (%)	65 (54.6)	46 (57.5)	19 (48.7)	.48
Max O2 flow during hospitalisation, median (IQR), L/min	8 (6–15)	6 (5–15)	12 (6–50)	.02
O2 flow at the time of CT initiation or on day 3, median (IQR), L/min	6 (3–15)	4 (2–8)	9 (6–35)	<.0001
High flow nasal oxygen, *n* (%)	18 (15)	4 (4.9)	14 (35.9)	<.0001
WHO score during hospitalisation, median (IQR)	5 (5– 6)	5 (5–5)	5 (5–6)	.65
WHO score at the time of corticosteroid initiation or on day 3, median (IQR)	5 (5–5)	5 (5–5)	5 (5– 6)	.14
Time between admission and outcome, median (IQR), days	8.5 (5–13)	6 (4–11)	13 (9.5–24)	<.0001

.1 (95%CI .02–.44), $p = .002$ and .15 (95%CI .05–.44), $p = .0005$, respectively (Table 3).

In 41 patients (16 female, 25 male) with a median age of 76.2 (IQR 71.5–82.2) years, a decision was taken to withhold life-sustaining treatments, including invasive mechanical ventilation. Fourteen were in the "CS group" and 27 in the "no CS group". Among these patients, a significantly lower risk of mechanical ventilation or death was observed in the "CS group" than in the "no CS group" (9 (64.3%) and 22 (81.5%) patients, respectively): HR .36 (95%CI .16–.80), $p = .01$ (Table 3, Figure 3).

Out of the 39 patients treated with corticosteroids, 27 received oral prednisone and 12 received intravenous dexamethasone. The characteristics of these patients differed: patients treated with oral prednisone were younger (65.6 ± 13.6 years, vs 72.2 ± 10.2 years), but their severity assessed at admission and at the initiation of corticosteroids did not differ. Four of the 27 patients

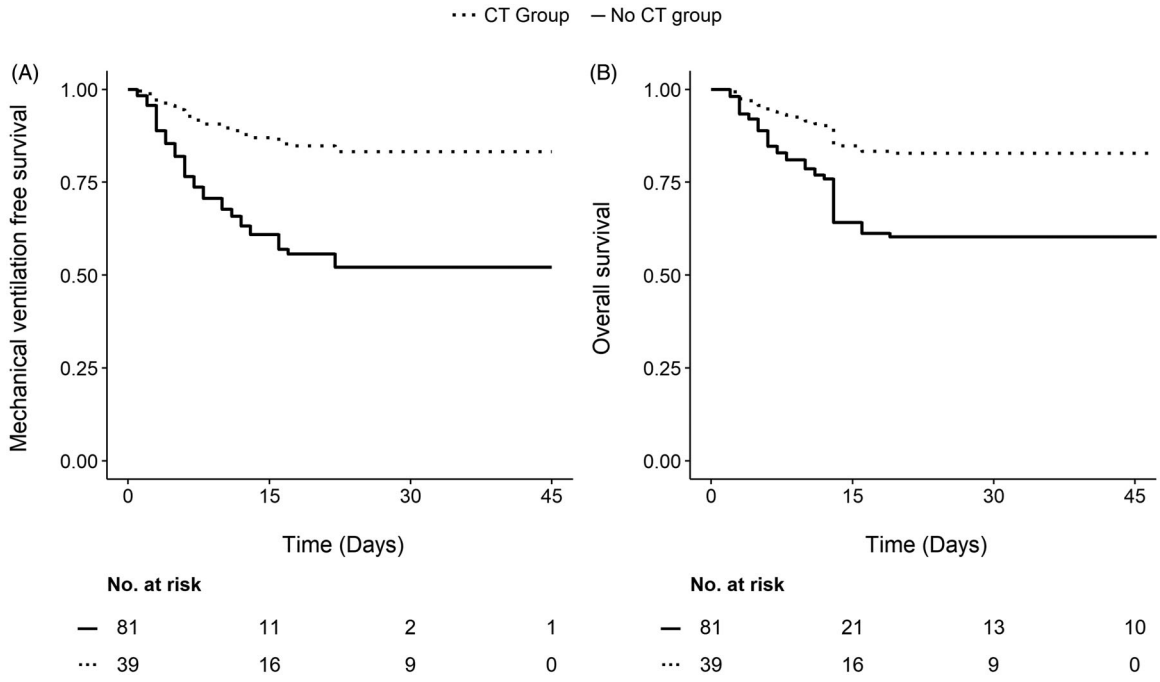

Figure 1. Kaplan-Meier curves for mechanical ventilation-free survival (A) and overall survival (B) in the weighted sample (IPWT). Mechanical ventilation-free survival defined patients who were not mechanically ventilated and alive at day 28 after admission.

Table 3. Primary and secondary outcomes at 28 days.

		No. of events		Unadjusted		IPTW	
Population	Outcome	Group without corticosteroids	Group with corticosteroids	HR (95%CI)	*p*	HR (95%CI)	*p*
Total cohort $n = 120$	Mechanical ventilation-free survival	42/81	9/39	.43 (.21–.85)	.02	.28 (.10–.79)	.02
Total cohort $n = 120$	Overall survival	30/81	9/39	.74 (.37–1.49)	.405	.37 (.13–1.11)	.076
Patients not eligible for ICU $N = 41$	Mechanical ventilation-free survival	22/27	9/14	.36 (.16–.80)	.01	–	–
CT in 3 first days ($n = 102$)	Mechanical ventilation-free survival	42/81	7/21	.41 (.19–.86)	.019	.10 (.02–.44)	.002
CT in 6 first days ($n = 114$)	Mechanical ventilation-free survival	42/81	9/33	.32 (.16–.63)	.0009	.15 (.05–.44)	.0005

receiving oral prednisolone and 5 of the 12 on intravenous dexamethasone had died or were on mechanical ventilation on day 28.

The maximum O_2 nasal flow differed significantly between the two groups, with a median of 6 (IQR 5–15) liters/min in the "no CS group" and 12 (IQR 6-50) liters/min in the "CS group", $p = .02$ (Table 2).

HNFO was used more frequently in the "CS group" than in the "no CS group" (Table 2).

Overall survival did not differ significantly between the "CS group" and "no CS group", with HR .74 (95%CI .37–1.49), $p = .41$ and HR .37 (95%CI .13–1.11), $p = .076$, respectively, before and after weighting.

Discussion

In a single-centre, real-life population receiving the same standard of care, our findings confirmed the efficacy of corticosteroids in reducing the risk of mechanical ventilation or death in patients with moderate to severe COVID-19 pneumonia. These results were in line with those of previous cohort studies [9,10,17,18] and a large randomized trial [11] where corticosteroids were included in the standard of care for COVID-19 pneumonia. Corticosteroid therapy was also beneficial in older and comorbid patients who were not eligible for intensive care.

The characteristics of our population were comparable to those of most previous studies [9–11], with a median age of 67.7 years, a majority of men (68%), a high rate of comorbidities (67.5%) and the same level of disease severity (hospitalized patients requiring oxygen therapy with a flow higher than 3 liters/min at admission or during hospitalization (levels 5 or 6 on the WHO score).

The effects of corticosteroids remain a matter of debate [1,16,23]. During a clinical trial in Brazil [16], no difference was observed between patients treated with

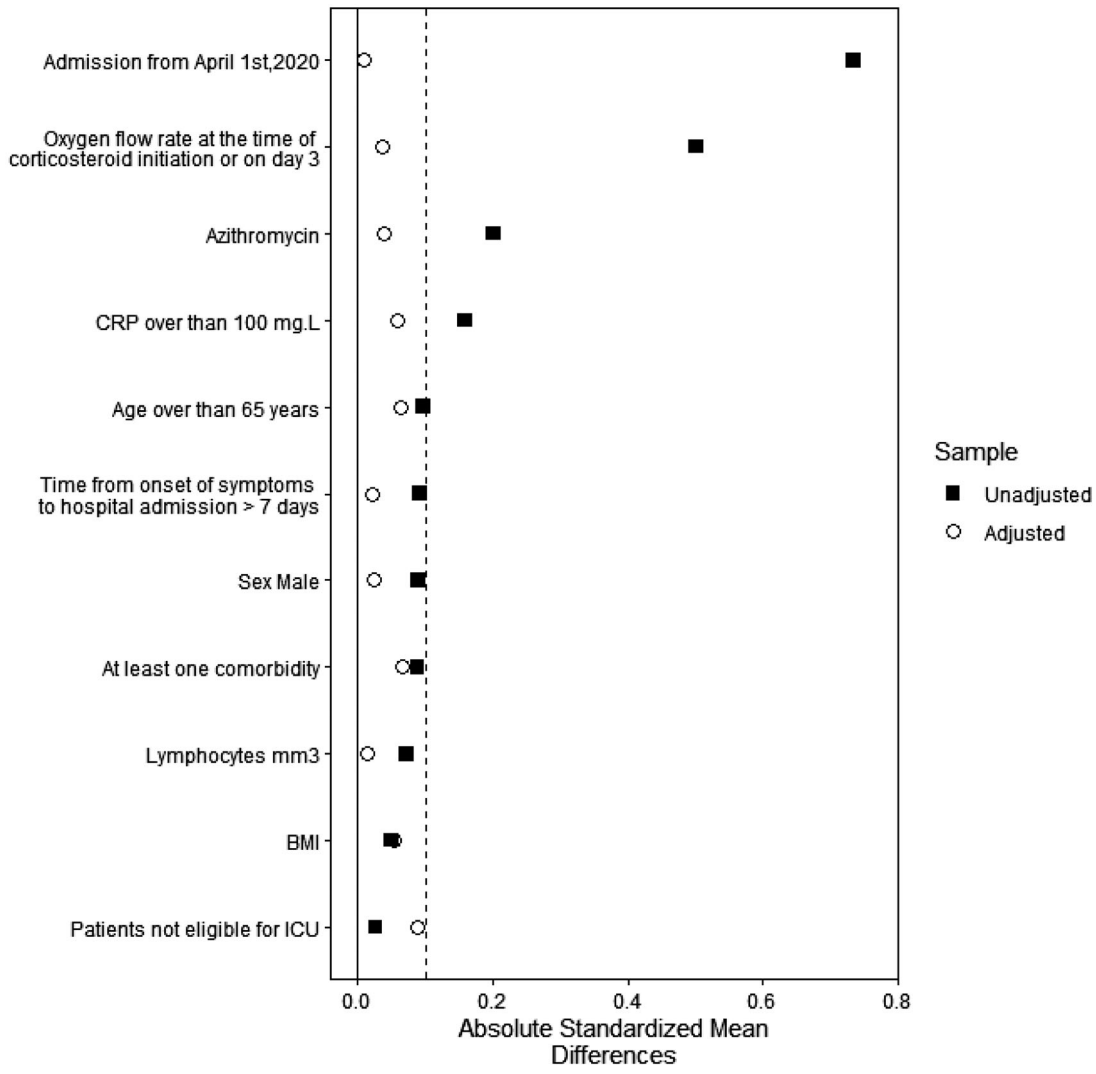

Figure 2. Mean differences in covariate balances before and after weighting.

methylprednisolone and those receiving placebo. In Chinese cohorts [1,23,24], corticosteroids were not associated with lower mortality. In the study by Liu et al. [23], 24.5% of patients were treated with low to moderate doses of corticosteroids, mostly methylprednisolone. The median initial daily methylprednisolone-equivalent dose was 80 mg (IQR 40–80 mg). In the entire cohort, patients who received corticosteroids had a higher mortality rate than those who had not (72/158, 45.6% vs. 56/488, 11.5%; $p < .0001$). Indeed, in a large Chinese cohort [1], corticosteroid use increased mortality in patients with severe disease and in those on mechanical ventilation. As in the Brazilian study, the patients had more severe disease than in our study since more were admitted to the ICU: 27.8% of patients on corticosteroids were in the ICU in the study by Wu et al. [1] and 36% in the study by Jeronimo [16].

Conversely, several cohort studies and the Recovery clinical trial indicated lower mortality rates at 28 days in patients treated with corticosteroids [8–11,18,25]. Our data confirmed the efficacy of corticosteroids in patients with moderate to severe pneumonia, not including patients initially admitted to the ICU.

In elderly and comorbid patients who were not deemed eligible for intensive care, we found that corticosteroids resulted in a significantly reduced risk of death or mechanical ventilation. In another French study [26], a high percentage of patients were considered not to be eligible for transfer to the ICU (48%). However detailed data on this specific group (elderly and comorbid patients) were not provided as only data on pooled patients were reported. In another study that included elderly patients, the mean age was 71.8 years [25], but data on patients not eligible for the ICU were not supplied. In other cohort studies, the mean age did not differ from that in our population [9,10], but no data were provided regarding outcomes in the elderly population.

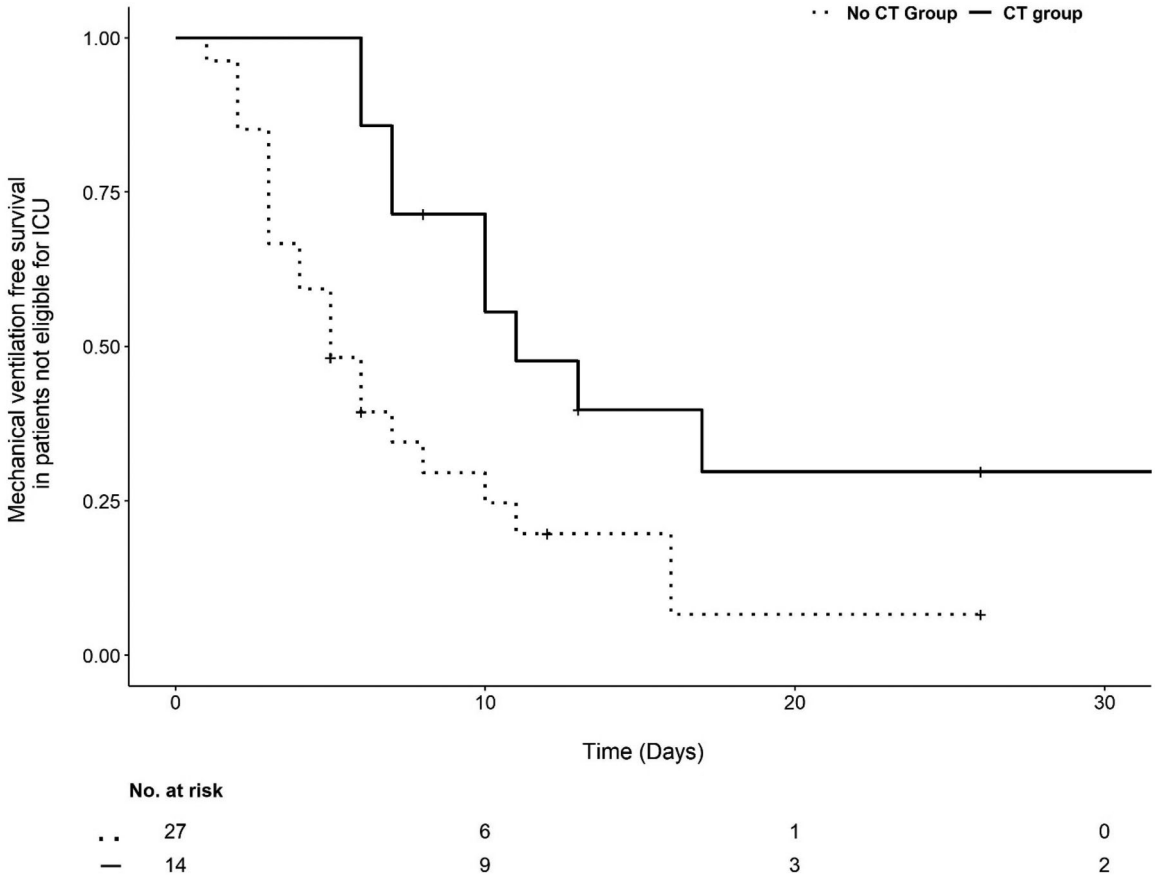

Figure 3. Kaplan–Meier curves for mechanical ventilation-free survival in patients not eligible for ICU care ($n = 41$).

To our knowledge, only one previous study has found lower mortality at 28 days in patients over 60 years of age treated with CS [16], but most of them were in the ICU at inclusion.

The specific corticosteroid regimen does not appear to influence efficacy. In the study by Fernandez-Cruz et al., no difference in mortality at 28 days was observed between methylprednisolone and glucocorticoid pulse therapies [10]. However, in a retrospective study comparing high dose versus standard dose corticosteroids, the high dose regimen was associated with increased mortality and a greater risk of mechanical ventilation [27]. A short course of low dose CS is now recommended for severe COVID-19 pneumonia; in the Recovery study, dexamethasone 6 mg/day was proposed [11].

In our study, higher doses of corticosteroids were employed, as proposed at the start of the pandemic when studies comparing different regimens were not available [17].

We propose that oral prednisone be given whenever possible. Although we cannot draw any firm conclusions, the two regimens appeared not to differ in terms of their efficacy. In the study by Fadel et al., some patients were switched to oral prednisolone [9].

In our study, corticosteroids were initiated at a median 11 days after disease onset. A similar delay (10 days) was observed in a previous study [10]. This timing corresponds to the inflammatory phase of the disease characterized by a cytokine storm [3].

Our retrospective study had several limitations. It only included a small cohort at a single centre, and was therefore biased in several ways. The principal bias was due to the chronological design of the study, as corticosteroids were mainly used during the second study period and comparisons were made between before and after the introduction of corticosteroids as a therapeutic option.

Although the standard of care was the same during both parts of the study, after April 1, 2020 it is possible that better care influenced prognosis. This period effect was therefore included in the multivariate analysis.

To control selection bias due to baseline covariate values induced by the retrospective nature of this study, we chose to use a propensity score. Propensity-matched cohort studies in the context of COVID-19 have rarely

been reported [1,10,12,17,23]. Nelson et al. [12] analyzed responses to methylprednisolone in a cohort of mechanically ventilated patients and found a higher number of mechanical ventilation-free days and a higher probability of extubation in patients receiving methylprednisolone. The median time from admission to the initiation of methylprednisolone was four days [12].

Another study compared mortality rates in 396 patients treated with corticosteroids and 67 controls. The analysis included propensity score adjustment for corticosteroid treatment [10] and produced a 41% reduction in mortality [10]. The study population was comparable to ours: the median time to the initiation of corticosteroids was 10 days after disease onset, and the mean age of patients was 65 years in the CS group and 68 years in the control group.

Another limitation was the small number of patients included.

We found no significant difference in mortality rates between the two groups, but the p value was close to significance ($p = .07$), and HR was low (.37). This non-significance was probably due to a lack of statistical power, with fewer events than for the main outcome.

Conclusion

A short course of corticosteroids reduced the risk of death or mechanical ventilation in patients with moderate to severe COVID-19 pneumonia. This result was also confirmed in old and comorbid patients who were not eligible for admission to the ICU. Propensity score analysis confirmed this result in our cohort study comparing outcomes before and after corticosteroid treatment was introduced.

Author contributions

Substantial contributions to the conception or design of the work: CC, MB, NS, ND, CBQ, VL, RD.

Acquisition, analysis, or interpretation of data for the work: CC, MB, NS, ND, BD, RD,

Drafting the work or revising it critically for important intellectual content: CC, MB, NS, ND, BD, ST, MLS, MM, FC, HB, SLJ, SA, RD.

Final approval of the version submitted for publication: All authors.

Ethics approval

The study was approved by our local Ethics Committee: IRB CLEA-2020-180.

Disclosure statement

The authors have no conflicts of interest to declare.

Availability of data and material

(Data transparency): all data are available on request to Prof. Robin DHOTE (corresponding author).

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