





ORIGINAL PAPER

Infectious diseases

Impact of intermediate to high doses of methylprednisolone on mortality rate in patients with COVID-19 pneumonia-induced severe systemic inflammation

Mónica Climente-Martí¹  | Oreto Ruiz-Millo¹  | Ian López-Cruz²  |
Ángel Atienza-García² | Eva Martínez-Moragón³  | Emilio Garijo-Gómez⁴ |
María Luisa López-Grima⁵ | Rafael Zaragoza-Crespo⁶ | Juan Vicente Llau-Pitarch⁷ |
Daniel Bautista-Rentero⁸ | José Miguel Nogueira-Coito⁹ | Tomás Ripollés-González¹⁰ |
María Antonia Marco-Artal¹¹ | Ramón Romero-Serrano¹² | Francisco Dolz-Sinisterra¹³ |
Rosario López-Estudillo¹⁴ | for the Doctor Peset COVID-19 Working Group

¹Pharmacy Department, Doctor Peset University Hospital, Valencia, Spain

²Internal Medicine Department, Doctor Peset University Hospital, Valencia, Spain

³Pneumologia Department, Doctor Peset University Hospital, Valencia, Spain

⁴Short Stay Unit, Doctor Peset University Hospital, Valencia, Spain

⁵Emergency Department, Doctor Peset University Hospital, Valencia, Spain

⁶Critical Care Department, Doctor Peset University Hospital, Valencia, Spain

⁷Anaesthesiology and Postsurgical Critical Care Department, Doctor Peset University Hospital, Valencia, Spain

⁸Preventive Medicine Department, Doctor Peset University Hospital, Valencia, Spain

⁹Clinical Microbiology Department, Doctor Peset University Hospital, Valencia, Spain

¹⁰Radiology Department, Doctor Peset University Hospital, Valencia, Spain

¹¹Occupational Risk Prevention Department, Doctor Peset University Hospital, Valencia, Spain

¹²Health Information Management Department, Doctor Peset University Hospital, Valencia, Spain

¹³Chief Executive Officer, Doctor Peset University Hospital, Valencia, Spain

¹⁴Medical Director, Doctor Peset University Hospital, Valencia, Spain

Correspondence

Mónica Climente-Martí, Pharmacy
Department, Doctor Peset University
Hospital, Gaspar Aguilar, 90, Valencia 46017,
Spain.
Email: climente_mon@gva.es

Abstract

Introduction: In addition to respiratory support needs, patients' characteristics to guide indication or timing of corticosteroid treatment in COVID-19 patients are not completely established. This study aimed to evaluate the impact of methylprednisolone on mortality rate in patients with COVID-19 pneumonia-induced severe systemic inflammation (PI-SSI).

Methods: Between 9 March and 5 May 2020 (final follow-up on 2 July 2020), a retrospective cohort study was conducted in hospitalised patients with COVID-19 PI-SSI (≥ 2 inflammatory biomarkers [IBs]: temperature $\geq 38^\circ\text{C}$, lymphocyte ≤ 800 cell/ μL , C-reactive protein ≥ 100 mg/L, lactate dehydrogenase ≥ 300 units/L, ferritin ≥ 1000 mcg/L, D-dimer ≥ 500 ng/mL). Patients received 0.5-1.0 mg/kg of methylprednisolone for 5-10 days or standard of care. The primary outcome was 28-day

The members of the Doctor Peset COVID-19 Working Group are listed in Appendix 1.

all-cause mortality. Secondary outcomes included ≥ 2 points improvement on a 7-item WHO-scale (Day 14), transfer to intensive care unit (ICU) (Day 28) and adverse effects. Kaplan–Meier method and Cox proportional hazard regression were implemented to analyse the time to event outcomes.

Results: A total of 142 patients (corticosteroid group $n = 72$, control group $n = 70$) were included. A significant reduction in 28-day all-cause mortality was shown with methylprednisolone in patients with respiratory support (HR: 0.15; 95% CI 0.03-0.71), with ≥ 3 (HR: 0.17; 95% CI 0.05-0.61) or ≥ 4 altered IB (HR: 0.15; 95% CI 0.04-0.54) and in patients with both respiratory support and ≥ 3 (HR: 0.11; 95% CI 0.02-0.53] or ≥ 4 altered IB (HR: 0.14; 95% CI 0.04-0.51). No significant differences were found in secondary outcomes.

Conclusion: Intermediate to high doses of methylprednisolone, initiated between 5 and 12 days after symptom onset, was associated with a significant reduction in 28-day all-cause mortality in patients with COVID-19 pneumonia and ≥ 3 or ≥ 4 altered IB, independently of the need of respiratory support.

1 | INTRODUCTION

Clinical manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated disease, COVID-19, range from asymptomatic, mild pneumonia to acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome, and death.^{1,2} It is clear that the host immune response plays a key role in the pathophysiological effects of organ injury.² In severe COVID-19 pneumonia, patients' symptoms worsen and become more hypoxic 4-7 days after the onset of symptoms and can progress to ARDS between 8 and 12 days.^{3,4} A macrophage activation syndrome with hyperinflammation and cytokine storm appear to be the ultimate cause of tissue damage and organ failure in these patients.⁵⁻⁷ The similarity of SARS-CoV-2-induced hyperinflammation to hyperferritinemic syndromes supported the use of anti-inflammatory and immunomodulatory agents such as corticosteroids.^{8,9}

Initially, corticosteroids were restricted to patients with SARS-CoV-2 pneumonia and ARDS by the World Health Organization (WHO) due to their potential effects on delayed viral clearance and the increased risk of secondary infections or death.^{10,11} Later, the RECOVERY clinical trial¹² has demonstrated the benefit of low dose of dexamethasone in reducing 28-day mortality risk among patients hospitalised with SARS-CoV-2 pneumonia. This evidence has led the WHO and scientific societies to recommend the use of dexamethasone, at a dose of 6 mg orally or intravenously once daily, or 50 mg of hydrocortisone intravenously every 8 hours, for 7-10 days, in patients with severe and critical COVID-19 and in patients who require oxygen therapy with and without invasive mechanical ventilation, advising against the routine use of corticosteroids for mild clinical conditions.¹³⁻¹⁵

Data on the efficacy of other corticosteroids are limited to smaller trials, and not all of them have reproduced similar results.

What's known

- Systemic corticosteroids are one of the few interventions that have succeeded in demonstrating its effect in mortality risk reduction in critical and severe COVID-19 patients who require respiratory support.
- WHO and scientific societies recommend the use of dexamethasone, at a dose of 6 mg orally or intravenously once daily, or 50 mg of hydrocortisone intravenously every 8 hours, for 7-10 days, in patients with severe and critical COVID-19 and in patients who require respiratory support, and it is now recognised as standard of care for these patients. Nevertheless, some uncertainties still remain about their optimal use in COVID-19 patients.

What's new

- This study shows that intermediate to high-doses of methylprednisolone, initiated between 5-12 days after symptoms onset, decreases mortality risk in hospitalised patients with COVID-19 pneumonia-induced severe systemic inflammation.
- It suggests that the corticosteroid treatment effect in mortality risk reduction may be a function of hyperinflammation's degree, independently of the needs of respiratory support.
- Identify the profile of patients who might benefit most from corticosteroid therapy, defining inflammatory biomarkers and cut-off values that will allow clinicians to tailor treatment strategies in hospitalised COVID-19 patients, to reduce mortality.

While some failed to demonstrate efficacy,^{15,16} others showed beneficial effects over the course of the disease regarding the duration of the need of mechanical ventilation and admission to the intensive care unit (ICU).^{3,17,18} Therefore, other corticosteroids such as methylprednisolone or prednisone are reserved in case of not having dexamethasone, using them at equivalent doses.¹³⁻¹⁵

Despite the growing evidence supporting the corticosteroid use, some uncertainties still remain regarding their optimal use in SARS-CoV-2 pneumonia. It is known that, in addition to developing respiratory failure, a subgroup of patients will progress into a severe systemic inflammation (SSI) syndrome and several inflammatory biomarkers (IBs) have been associated with severity and a worse prognosis.¹⁹⁻²² Hence, in order to better define the profile of patients who might benefit most from corticosteroid therapy, we conducted this study with the aim of assessing the impact of intermediate to high doses of methylprednisolone on mortality rate in patients with COVID-19 pneumonia-induced SSI.

2 | METHODS

2.1 | Study design and participants

A single-centre, observational, longitudinal, retrospective study was conducted at a 539-bed general teaching hospital in Valencia (Spain), between 9 March 2020 and 5 May 2020. The recruitment period extended from 9 March to 17 April 2020 and final follow-up was completed on 2 July 2020.

Patients eligible were aged 18 years or older with severe COVID-19 pneumonia, confirmed by the reverse transcription polymerase chain reaction (RT-PCR) test, and had progressed into SSI, defined as at least two out of six IB raised over the predefined cut-off points¹⁹⁻²²: fever (body temperature $\geq 38^{\circ}\text{C}$), absolute lymphocyte count ≤ 800 cell/ μL , C-reactive protein (CRP) ≥ 100 mg/L, lactate dehydrogenase (LDH) ≥ 300 units/L, ferritin ≥ 1000 mcg/L and D-dimer ≥ 500 ng/mL.

Exclusion criteria were: previous long-term systemic corticosteroid therapy (more than 6 months), methylprednisolone or equivalent treatment at doses out of range 0.5-1.0 mg/kg or duration less than 5 days and sepsis or ARDS according to Berlin criteria²³ at the beginning of corticosteroid use or progression into SSI. Pregnant or breast-feeding women, patients transferred to an ICU or who died within the first 48 hours of admission were also excluded.

A sample-size calculation was performed to detect a 20% difference in 28-day all-cause mortality assuming a test power of 0.80, a 95% confidence level and no drop-out rate. Seventy patients in each group were required.

Every patient was fully informed about the off-label character of the treatment strategy and the potential side effects, and informed consent was obtained before initiating any treatment following the national protocol for treating hospitalised patients with COVID-19 developed by the Ministry of Health, Consumer Affairs and Social Welfare.²⁴ The study was conducted in accordance with

the ethical principles of the Helsinki Declaration and was approved by the local Clinical Research Ethics Committee (code 64/20) and classified by the Spanish Agency of Medicines and Medical Devices (HDP-GLU-2020-05).

2.2 | Procedures

Electronic health records, including laboratory results, prescribed medication, respiratory support received (oxygen with or without non-invasive or invasive ventilation) and information on vital status were reviewed for all admitted patients with laboratory-confirmed COVID-19 pneumonia at different time points containing the time of corticosteroid treatment beginning and progression into SSI, as appropriate.

Patients were divided into two cohorts based on whether they received systemic corticosteroids (corticosteroid group), initiated between 5 and 12 days after symptom onset at intermediate to high doses of methylprednisolone (or equivalent) 0.5-1.0 mg/kg through intravenous perfusion daily for 5-10 days, plus standard care or standard care alone (control group).

Decision to prescribe corticosteroids was at the discretion of the treating physician (based on time since symptom onset, respiratory compromise and the following IBs: fever, absolute lymphocyte count, CRP, LDH, ferritin and D-dimer) in accordance with the institutional protocol developed on 9 March 2020. This was approved by the Doctor Peset COVID-19 working group consensus and based on the available literature, experience from other centres around the world affected by COVID-19²⁵ and the clinical rationale based on immunology to explain the torpid course of the disease in some patients. Standard care included treatment with antivirals (lopinavir-ritonavir), antibiotics (azithromycin, ceftriaxone or others if needed), anti-malarials (hydroxychloroquine) and tocilizumab (if raised interleukin-6 [IL-6], when available) according to the national protocol approved for treating hospitalised patients with COVID-19.²⁴

2.3 | Outcomes

The primary outcome was 28-day all-cause mortality in overall population (≥ 2 IB altered) and subgroups of patients classified according to respiratory support needs at the progression into SSI and/or the number of altered IB (≥ 3 or ≥ 4). For a clearer understanding of risk, the outcomes were also modelled separately. A secondary outcome was ≥ 2 stages of improvement at Day 14 on a 7-item WHO-endorsed ordinal scale (ranging from 1 to 2, not hospitalised to 7, death).²⁶ The two outpatient strata (points 1 and 2) were combined into one, due to was not possible to know whether discharged patients were able to resume or not their normal activities. Other secondary outcomes were transfer to ICU, progression into ARDS and severe adverse effects (hyperglycaemia defined as glycaemia >200 mg/dL for two consecutive tests, nosocomial infection and sepsis).

2.4 | Statistical analysis

The demographic and clinical variables were described using univariate analysis. Distribution normality was assessed using the Kolmogorov–Smirnov test. Categorical variables were reported as frequencies (%); normally distributed quantitative variables, as mean and standard deviation (SD); and non-normally distributed, as median and interquartile range (IQR). Chi-square or Fisher's exact tests and *t* test for two independent samples or Mann–Whitney *U* test were used for descriptive statistics, as appropriate.

For the primary outcome of 28-day all-cause mortality, Kaplan–Meier survival plots were constructed, and survival curves for both groups were compared by use of log-rank test. Survival data were censored when the patient died or on Day 28 for survived patients. Hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained from Cox proportional hazard univariate and multivariate models to assess the relationship of corticosteroid treatment and 28-day mortality in overall population and subgroups of patients classified as previously stated. Adjusted multivariate Cox models incorporated covariates including number of comorbidities, previous neurological

antecedents, oxygen supplementation needed at the beginning of corticosteroid or progression to SSI, azithromycin therapy, lopinavir/ritonavir therapy, tocilizumab therapy and low-molecular weight heparin (LMWH) therapeutic dosage use.

Statistical analysis was performed using PASW version 19.0 for Windows (SPSS™, Inc, Chicago, IL, USA). All statistical tests were two sided, and a $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient's characteristics

During the recruitment period, a total of 327 possible candidates were admitted to the hospital (Figure 1). Of the 142 patients included, the mean (SD) age was 67.6 (13.8) years, 79 (55.6%) were men, and 63 (44.4%) were women. Distribution of age, sex, comorbidities and symptoms on admission was similar between groups, other than neurological history (13 [18.1%] vs 4 [5.7%]; $P = .045$), two or more comorbidities (50 [69.4%] vs 34 [48.6%]; $P = .018$) and

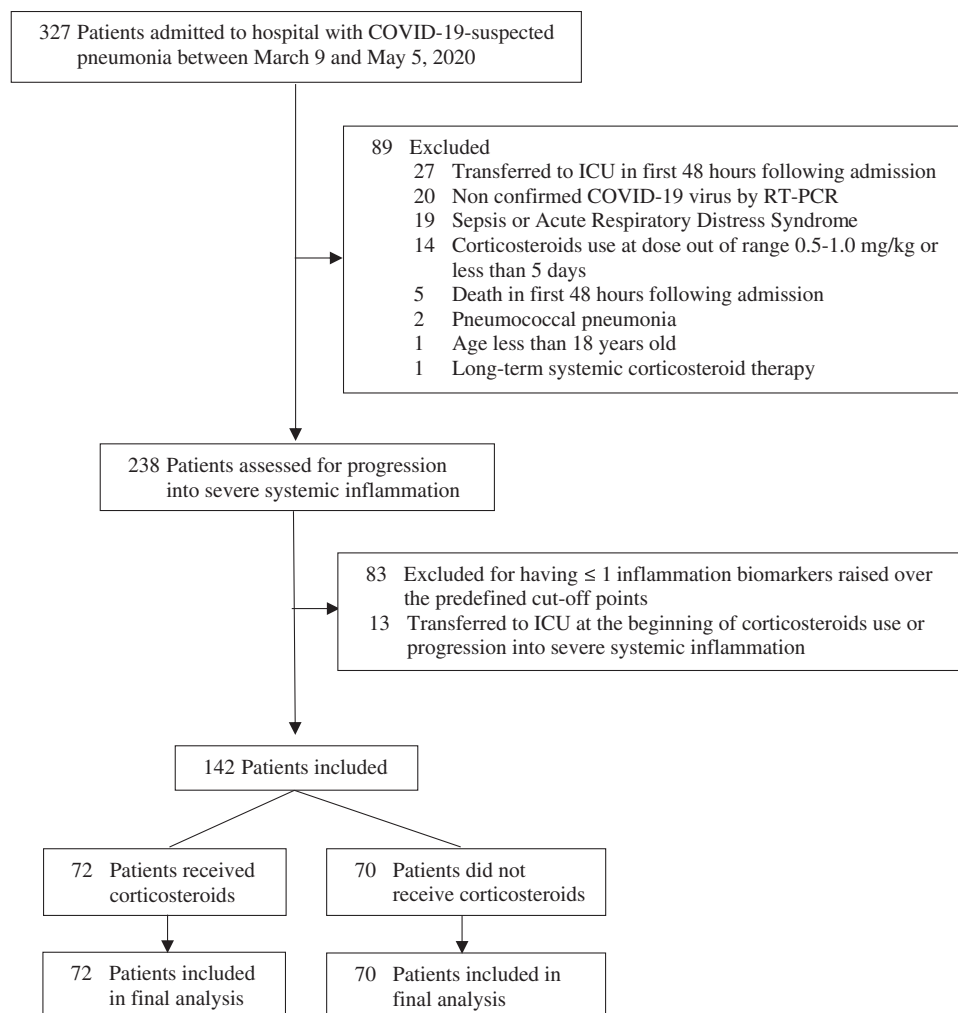


FIGURE 1 Study flow chart. ICU, intensive care unit

median time since symptom onset (6 vs 7 days; $P = .045$). The main characteristics of patients with COVID-19 pneumonia-induced SSI are presented in Table 1.

On admission, there was no significant differences between groups in the proportion of patients with a pneumonia severity score CURB-65 ≥ 2 (39.4% vs 33.3%, $P = .566$). Oxygen saturation of 90%

TABLE 1 Baseline demographic, clinical characteristics and previous treatments of included patients with COVID-19 pneumonia-induced severe systemic inflammation

Patient characteristics	All patients (n = 142)	Corticosteroid group (n = 72)	Control group (n = 70)	P value
Age, years				
≥ 70	67.6 (13.8)	68.6 (14.2)	66.6 (13.4)	.406
Sex				
Male	79 (55.6)	46 (63.9)	33 (47.1)	.066
Female	63 (44.4)	26 (36.1)	37 (52.9)	
Comorbidities				
Two or more	84 (59.2)	50 (69.4)	34 (48.6)	.018
Hypertension	70 (49.3)	40 (55.6)	30 (42.9)	.179
Diabetes mellitus	26 (18.3)	14 (19.4)	12 (17.1)	.891
Dyslipidaemia	63 (44.4)	31 (43.1)	32 (45.7)	.881
Obesity (BMI ≥ 30 kg/m ²)	37/139 (26.6)	21/71 (29.6)	16/68 (23.5)	.539
Chronic pulmonary/ Respiratory disease	26 (18.3)	14 (19.4)	12 (17.1)	.891
Cardiovascular disease	17 (12.0)	9 (12.5)	8 (11.4)	1.000
Neurological history	17 (12.0)	13 (18.1)	4 (5.7)	.045
Malignancy	15 (10.6)	11 (15.3)	4 (5.7)	.114
Chronic kidney disease	11 (7.7)	8 (11.1)	3 (4.3)	.227
Liver cirrhosis or HIV	0	0	0	—
Symptoms on admission				
Time since symptom onset, median (IQR), days	7 (6)	6 (5.8)	7 (5)	.043
Three or more	107 (75.4)	56 (77.8)	51 (72.9)	.627
Fever ($\geq 38^\circ\text{C}$)	104 (73.2)	51 (70.8)	53 (75.7)	.640
Cough	103 (72.6)	54 (75.0)	49 (70.0)	.632
Dyspnoea	82 (57.7)	46 (63.9)	36 (51.4)	.183
Asthenia	64 (45.1)	37 (51.4)	27 (38.6)	.172
Muscular pain	47 (33.1)	25 (34.7)	22 (31.4)	.811
Diarrhoea	27 (19.0)	16 (22.5)	11 (15.7)	.415
Headache	17 (12.0)	11 (15.3)	6 (8.6)	.331
Vomiting	17 (12.0)	7 (9.7)	10 (14.3)	.563
Ageusia	13 (9.2)	7 (9.7)	6 (8.6)	1.000
Anosmia	9 (6.3)	4 (5.6)	5 (7.1)	.743
Syncope	5 (3.5)	1 (1.4)	4 (5.7)	.206
Sore throat	4 (2.8)	3 (4.2)	1 (1.4)	.620
CURB-65 score (0-5), median (IQR)	1 (2)	1 (2)	1 (2)	.435
≥ 2	51/140 (36.4)	28/71 (39.4)	23/69 (33.3)	.566
Previous treatments				
ACEi/ARB	48 (33.8)	28 (38.9)	20 (28.6)	.262
NSAID	7 (4.9)	3 (4.2)	4 (5.7)	.717

Note: Data are mean (SD) or n (%), unless otherwise indicated.

Abbreviations: ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; NSAID, nonsteroidal anti-inflammatory drugs.

or less and/or respiratory rate of 30 per minute or more was observed in 36.1% of patients in the corticosteroid group and 25.7% in the control group ($P = .247$). Statistical differences were not observed in CRP, LDH, D-dimer, ferritin or fever, except a lower absolute lymphocyte count (896 cell/mL [95% CI 787-1005] vs 1069 [95% CI 940-1199]; $P = .042$) in the corticosteroid group.

At the progression into SSI, in the corticosteroid group, significantly more patients were receiving supplemental oxygen with or without non-invasive ventilation (59 [81.9%] vs 41 [58.6%]; $P = .004$), presented ≥ 3 altered IB (62 [86.1%] vs 42 [60.0%]; $P = .001$) or ≥ 4 altered IB (43 [59.7%] vs 23 [32.9%]; $P = .002$). In the corticosteroid group, the proportion of patients with respiratory support needs and ≥ 3 (54 [75.0%] vs 30 [42.9%]; $P > .001$) or ≥ 4 altered IB (40 [55.6%] vs 19 [27.1%]; $P = .001$) were also higher than in the control group.

3.2 | Survival outcomes

Mortality analyses are reported in Table 2 and Figure 2. In the overall population, 28-day all-cause mortality was non-significantly lower in the corticosteroid group (5.6%), as compared with the control group (12.9%) (HR: 0.41; 95% CI 0.13-1.32; $P = .134$). Nevertheless, a significant reduction in 28-day all-cause mortality was shown in the corticosteroid group in patients with respiratory support needs (6.8% vs 22.0%; $P = .032$), with ≥ 3 altered IB (6.5% vs 19.0%; $P = .046$), with ≥ 4 altered IB (9.3% vs 30.4%; $P = .018$), and in patients showing both respiratory support needs and ≥ 3 altered IB (7.4% vs 26.7%; $P = .016$) or ≥ 4 altered IB (10.0% vs 36.8%; $P = .009$).

In both the unadjusted and the adjusted multivariate Cox models, treatment effect of corticosteroids showed a significant reduction in 28-day all-cause mortality in all the subgroups of patients analysed, being lower in patients with ≥ 3 altered IB (HR: 0.17; 95% CI 0.05-0.61; $P = .007$) and higher in patients with respiratory support needs and ≥ 3 altered IB (HR: 0.11; 95% CI 0.02-0.53; $P = .006$). Treatment effect of corticosteroids in reduction of 28-day all-cause mortality was independent of the number of comorbidities, previous

neurological antecedents, oxygen supplementation needs at the beginning of corticosteroid or progression to SSI, azithromycin therapy, lopinavir/ritonavir therapy, tocilizumab therapy and LMWH therapeutic dosage use.

3.3 | Treatment received during hospitalisation

Methylprednisolone (98.6%) or prednisone (1.4%) were initiated in the corticosteroid group at a mean (CI 95%) of 10.5 (9.4-11.6) days from symptom onset or at Day 3 (IQR: 1-6) from admission. The median dose was 1 mg/kg/day (IQR: 1-1) and the median duration of treatment 6.5 days (IQR: 5-8). Only one patient received two intravenous boluses of 250 and 500 mg of methylprednisolone. The corticosteroid group had more patients treated with azithromycin ($P = .017$), lopinavir/ritonavir ($P = .029$), tocilizumab ($P = .013$) and LMWH as therapeutic dosage use ($P = .002$). Table 3 shows therapy received during hospitalisation.

3.4 | Secondary clinical outcomes

Despite the median (IQR) WHO scale scores at the progression into SSI were similar in both groups (4 [4-4] vs 4 [3-4]; $P = .006$), scores 4 (hospitalised, requiring additional oxygen therapy) and 5 (hospitalised, requiring high-flow nasal oxygen therapy, non-invasive mechanical ventilation or both) were significantly higher in the corticosteroid group (59 [81.9%] vs 41 [58.6%]; $P = .004$). Improvement in two or more points in the 7-point WHO scale at Day 14 was statistically non-significant higher in the corticosteroid group than in the control group in overall population (36 [50.0%] vs 31 [44.3%]; $P = .607$).

No differences in the proportion of patients with progression in respiratory support (4 [5.6%] vs 8 [11.4%]; $P = .339$) or in patients transferred to the ICU at Day 28 from admission were found (4 [5.6%] vs 1 [1.4%]; $P = .366$). Despite not significant, more patients

TABLE 2 Effect of corticosteroids (vs control) on mortality at 28 days: Univariate and multivariate analysis

28-day mortality	No. of deaths/total no. of patients (%)		Univariate analysis		Multivariate analysis ^a	
	Corticosteroids group	Control group	HR (95% CI)	P value	HR (95% CI)	P value
<i>Subgroups</i>						
Respiratory support needed	4/59 (6.8)	9/41 (22.0)	0.28 (0.08-0.89)	.032	0.15 (0.03-0.71)	.016
Three or more altered IB	4/62 (6.5)	8/42 (19.0)	0.30 (0.09-0.98)	.046	0.17 (0.05-0.61)	.007
Four or more altered IB	4/43 (9.3)	7/23 (30.4)	0.24 (0.07-0.78)	.018	0.15 (0.04-0.54)	.004
Respiratory support and ≥ 3 altered IB	4/54 (7.4)	8/30 (26.7)	0.23 (0.07-0.77)	.016	0.11 (0.02-0.53)	.006
Respiratory support and ≥ 4 altered IB	4/40 (10.0)	7/19 (36.8)	0.20 (0.06-0.67)	.009	0.14 (0.04-0.51)	.002

Note: Results from Cox proportional hazards univariate and multivariate models.

Abbreviation: IB, inflammatory biomarker.

^aAdjusted for number of comorbidities, previous neurological antecedents, oxygen supplementation needed at the beginning of corticosteroid or progression to SSI, azithromycin therapy, lopinavir/ritonavir therapy, tocilizumab therapy and LMWH therapeutic dosage use.

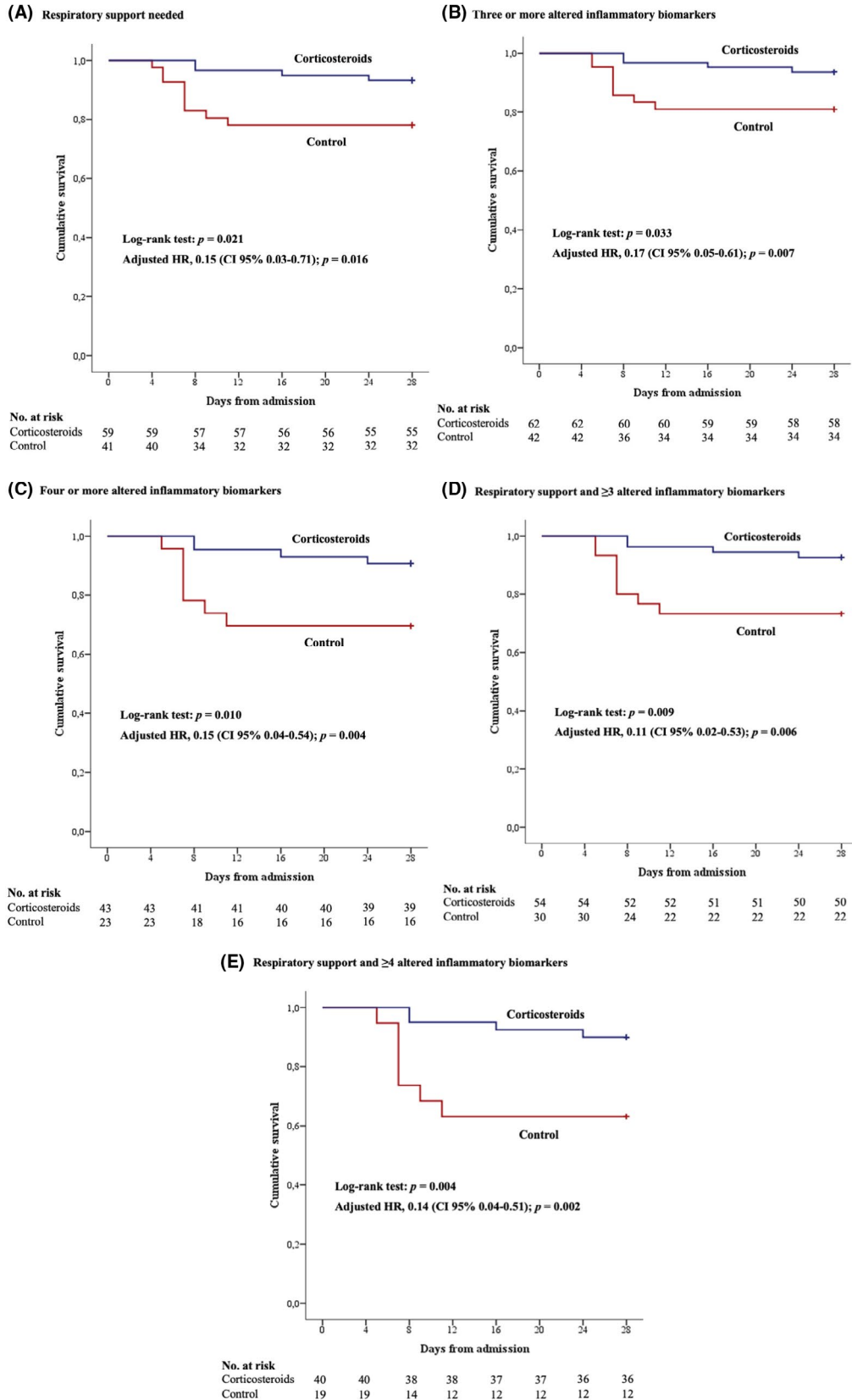


FIGURE 2 Kaplan–Meier survival curves for 28-day all-cause mortality in patients with COVID-19 pneumonia-induced severe systemic inflammation stratified for treatment (corticosteroids vs control group). Panels (A)–(E) show 28-day all-cause mortality by subgroups: patients with respiratory support needs (A), ≥ 3 (B) or ≥ 4 (C) altered inflammatory biomarkers and patients with both respiratory support and ≥ 3 (D) or ≥ 4 (E) altered inflammatory biomarkers. Survival curves were compared by use of log-rank test. Estimates of hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained from adjusted multivariate Cox models

TABLE 3 Therapy received during hospitalisation

Therapy received during hospitalisation	All patients (n = 142)	Corticosteroid group (n = 72)	Control group (n = 70)	P value
Corticosteroids				
Time since symptom onset, mean (95% CI), days	NA	10.5 (9.4-11.6)	NA	—
Drug: Intravenous methylprednisolone	71 (50.0)	71 (98.6)	0 (0)	—
Daily dose, mg/kg	NA	1 (1-1)	NA	—
Duration, days	NA	6.5 (5-8)	NA	—
De-escalation regimen	23 (16.2)	23 (31.9)	NA	—
Second treatment with corticosteroids	5 (3.5)	5 (6.9)	0 (0)	—
Concomitant therapy				
Hydroxychloroquine	139 (97.9)	71 (98.6)	68 (97.1)	.617
Azithromycin	133 (93.7)	71 (98.6)	62 (88.6)	.017
Ceftriaxone	127 (89.4)	63 (87.5)	64 (91.4)	.625
Lopinavir/ritonavir	71 (50.0)	29 (40.3)	42 (60.0)	.029
Tocilizumab	7 (4.9)	7 (9.7)	0 (0)	.013
Interferon beta-1b	3 (2.1)	1 (1.4)	3 (4.3)	.363
Anakinra	2 (1.4)	2 (2.8)	0 (0)	.066
Human immunoglobulin	1 (0.7)	1 (1.4)	0 (0)	1.000
Remdesivir	0 (0)	0 (0)	0 (0)	—
Vasopressors	0 (0)	0 (0)	0 (0)	—
LMWH	126 (88.7)	71 (98.6)	55 (78.6)	<.001
LMWH therapeutic dosage use	33 (23.2)	25 (34.7)	8 (11.4)	.002

Note: Data are median (IQR) or n (%), unless otherwise indicated.

Abbreviation: LMWH, low-molecular weight heparin.

progressed into ARDS in the corticosteroid group (19 [26.4%] vs 9 [12.9%]; $P = .069$). Both groups had a similar proportion of severe adverse events such as hyperglycaemia (8 [11.1%] vs 4 [4.3%]; $P = .208$), nosocomial infections (3 [4.2%] vs 2 [2.9%]; $P = 1.000$) and sepsis (0 [0.0%] vs 1 [1.4%]; $P = .493$).

4 | DISCUSSION

In this study, including 142 patients with COVID-19 pneumonia-induced SSI, we found that intermediate to high-dose (0.5-1.0 mg/kg/day) methylprednisolone therapy, initiated between 5 and 12 days after symptom onset, was associated with a significant reduction in the risk of 28-day all-cause mortality in patients with ≥ 3 or ≥ 4 altered IB, independently of the need of respiratory support. A lower non-significant 28-day mortality was also observed in the overall population with ≥ 2 IB.

Despite higher comorbidity and more SSI observed in the corticosteroid group, the effect of methylprednisolone in reduction of 28-day all-cause mortality was demonstrated. In fact, significantly more patients were receiving respiratory support or presented ≥ 3 or ≥ 4 altered IB in this group. Improvement on ≥ 2 points in the 7-point

WHO scale at Day 14 was non-significantly higher in the corticosteroid group, and no differences in the proportion of patients with progression in respiratory support or transferred to ICU at Day 28 from admission were found, showing that corticosteroid treatment not only reduced the risk of death but also may attenuate progression to the hyperinflammation phase that requires escalation of care in patients with COVID-19 pneumonia. Also, there was no evidence of an increased risk of severe adverse events, like hyperglycaemia, nosocomial infections and sepsis in patients treated with methylprednisolone as previously reported.¹⁴

Although seven patients in the corticosteroid group received tocilizumab and none in the control group ($P = .013$), a recent systematic review,²⁷ including COVID-19 patients with similar characteristics of our study population, has shown inconsistent results regarding the efficacy of tocilizumab from retrospective studies with low-moderate methodological biases. Even so, REMAP-CAP study²⁸ has reported IL-6 receptor antagonists such as tocilizumab seem to improve survival outcomes in critically ill patients with COVID-19.

In our study population, 28-day all-cause mortality was up to four times lower than previous published studies.^{12,29} However, mortality in the control group for patients with ≥ 3 or ≥ 4 altered IB, alone or combined with respiratory support, was similar (between 20% and

30%) to other studies.^{12,29} Also, as can be seen in Table 2, the mortality rate in each subgroup of patients increases according to the number of IB altered (≥ 2 , ≥ 3 or ≥ 4). In the control group, mortality rate increases around 10% by each altered IB added (from 12.9% to 30.4%), while in the corticosteroid group, only an absolute increase from 5.6% to 9.3% is shown between groups, demonstrating that the treatment effect of corticosteroids in our population may be until three times higher than previously reported in patients with severe and critical COVID-19.^{11,14,17}

The clinical benefit of dexamethasone,^{11,12,17} hydrocortisone^{3,16} or methylprednisolone^{18,30} has been evaluated in previous studies. In different trials, the corticosteroid dosing extended from low to high doses^{3,11,12,16-18,30} and total duration of treatment varied between 3 and 14 days.^{3,11,12,16-18,30} Studies comparing the efficacy of methylprednisolone and dexamethasone have obtained heterogeneous results.³¹⁻³³ Clinical outcomes have also been very unequal between studies, and it is uncertain whether these apparent differences are related to the corticosteroid formulation and dose, the severity of illness or issues related to statistical power.^{3,11,12,14,16-18,30}

Trials evaluating methylprednisolone have not demonstrated a clear benefit. In a randomised trial that included 393 patients with severe COVID-19,³⁰ similar 28-day mortality rates with 1 mg/kg/day methylprednisolone for 5 days compared to placebo were obtained (37.1% vs 38.2%, $P = .629$). In another trial conducted in 85 patients with moderate to severe disease with abnormal gas exchange and laboratory parameters suggesting a hyperinflammatory state,¹⁸ methylprednisolone (40 mg/12 hour for 3 days, then 20 mg/12 hour for 3 days) reduced the risk of the composite endpoint of admission to ICU, non-invasive ventilation or death, without showing significant differences in mortality (20% vs 18%, $P > .05$).

Nevertheless, in a quasi-experimental study⁴ which used an early short course of methylprednisolone 0.5-1 mg/kg/day for 3 days in patients with moderate to severe COVID-19 reported a significantly lower rate of the primary composite endpoint of death, ICU transfer and, mechanical ventilation, as well as a significantly lower mortality rate (21.7% vs 26.3%, $P = .024$). It was advocated by corticosteroid timing as key factor and corticosteroid therapy at dyspnoea onset. These measures seemed to prevent from disease progression associated with the proinflammatory host response. On the contrary, in a retrospective cohort study³⁴ including 205 patients with COVID-19 pneumonia-induced acute hypoxemic respiratory failure treated with methylprednisolone at a median or equivalent dose of 80 mg/day (IQR: 60-107), a lower but non-significant difference in mortality was found (14.5% vs 25.0%, $P = .114$), despite demonstrating a significantly lower risk of the primary composite outcome of ICU transfer, intubation or in-hospital death.

Although data from observational and randomised trials overall support the role of corticosteroids for severe COVID-19,^{29,35} most of the studies associate this benefit with the need for respiratory support. In addition, the variability in the clinical course of the disease, the evidence from different observational studies suggesting association of some IB with worse outcomes¹⁹⁻²² and the different clinical response to corticosteroids confirmed by clinical observation

in daily practice led us to hypothesise that the benefits of corticosteroid therapy could also depend on the degree of hyperinflammation.

Hence, in order to identify which patients benefit the most from corticosteroid therapy, we conducted this study focusing on a subgroup of patients with COVID-19 pneumonia-induced SSI and analysed the effect of methylprednisolone depending on respiratory support needs and the number of altered IB.¹⁹⁻²²

Interestingly, we found significant benefit in 28-day all-cause mortality among patients receiving methylprednisolone who had ≥ 3 and ≥ 4 altered IB, suggesting that the magnitude of the benefit seems to be closely related to the degree of hyperinflammation (see Table 2, Figure 2). In these patients, benefit was even higher if, in addition to the elevation in IB, they also needed respiratory support. Nevertheless, the results of this post hoc subgroup analysis should be confirmed in a randomised clinical trial with risk stratification based on the level of hyperinflammation.

Our study has other limitations as it is a single-centre study with an observational and retrospective nature. Prognostic similarity at baseline cannot be assumed. Despite being included in the institutional protocol from 29 March 2020, the prescription of corticosteroids was at the discretion of the treating physician and variability cannot be completely ruled out. Lastly, the selection of the IB to determine the progression into SSI was based on the outcomes from different observational studies, but the prognostic value and optimal clinical use of some of them are still uncertain.¹⁹⁻²²

This study is unique in terms of the subset of patients included, since it focuses on a subgroup of patients progressing into a severe inflammatory syndrome. To our knowledge, there are no studies comparing the effect of corticosteroid therapy according to the inflammation degree, and our findings suggest that in this subgroup of patients, corticosteroids may be even more beneficial than shown in the RECOVERY trial.¹²

5 | CONCLUSION

Intermediate or high dose (0.5-1.0 mg/kg/day) of methylprednisolone was associated with a significant reduction in the risk of 28-day all-cause mortality in hospitalised patients with COVID-19 pneumonia-induced SSI, independently of the need of respiratory support. Benefits in mortality were higher in patients with both respiratory support and ≥ 3 or ≥ 4 altered IB.

ACKNOWLEDGEMENTS

We are grateful to Prof. Alberto Ferrer-Riquelme, Multivariate Statistical Engineering, from the Department of Applied Statistics, OR and Quality at Universitat Politècnica de Valencia, Spain, for his critical review of the statistical analyses. We also thank Veronica Chorro-Mari, PharmD, PhD, at Barts Health NHS Trust for her English language review.

We declare a different version of this paper is available as preprint publication at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3756801.

DISCLOSURES

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Mónica Climente-Martí  <https://orcid.org/0000-0002-4387-1987>
Oreto Ruiz-Millo  <https://orcid.org/0000-0001-5829-6957>
Ian López-Cruz  <https://orcid.org/0000-0001-7252-8961>
Eva Martínez-Moragón  <https://orcid.org/0000-0001-8986-9463>

REFERENCES

- Barlow A, Landolf KM, Barlow B, et al. Review of emerging pharmacotherapy for the treatment of coronavirus disease 2019. *Pharmacotherapy*. 2020;40(5):416-437.
- Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J Hear Lung Transplant*. 2020;39(5):405-407.
- Angus DC, Derde L, Al-Beidh F, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *J Am Med Assoc*. 2020;324(13):1317-1329.
- Fadel R, Morrison AR, Vahia A, et al. Early short-course corticosteroids in hospitalized patients with COVID-19. *Clin Infect Dis*. 2020;71(16):2114-2120.
- Liu Q, Zhou YH, Yang ZQ. The cytokine storm of severe influenza and development of immunomodulatory therapy. *Cell Mol Immunol*. 2016;13(1):3-10.
- Chen TL, Wong WW, Chiou TJ. Hemophagocytic syndrome: an unusual manifestation of acute human immunodeficiency virus infection. *Int J Hematol*. 2003;78(5):450-452.
- Gao YM, Xu G, Wang B, et al. Cytokine storm syndrome in coronavirus disease 2019: a narrative review. *J Intern Med*. 2021;289(2):147-161.
- Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-1034.
- Colafrancesco S, Alessandri C, Conti F, et al. COVID-19 gone bad: a new character in the spectrum of the hyperferritinemic syndrome? *Autoimmun Rev*. 2020;19(7):102573.
- Zha L, Li S, Pan L, et al. Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19). *Med J Aust*. 2020;212:416-420.
- Villar J, Añón JM, Ferrando C, et al. Efficacy of dexamethasone treatment for patients with the acute respiratory distress syndrome caused by COVID-19: study protocol for a randomized controlled superiority trial. *Trials*. 2020;21(1):717.
- RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704.
- National Institutes of Health (NIH). COVID-19 Treatment Guidelines [NIH web site]. 2020. <https://www.covid19treatmentguidelines.nih.gov>. Accessed April 22, 2021.
- World Health Organization (WHO). Corticosteroids for COVID-19. Living Guidance—2 Sept 2020. WHO. 2020. <https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1>. Accessed April 22, 2021.
- Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clin Infect Dis*. 2020:ciaa478. <https://doi.org/10.1093/cid/ciaa478>
- Dequin P-F, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *J Am Med Assoc*. 2020;324(13):1298-1306.
- Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *J Am Med Assoc*. 2020;324(13):1307-1316.
- Corral L, Bahamonde A, Arnaiz delas Revillas F, et al. GLUCOCOVID investigators. Methylprednisolone in adults hospitalized with COVID-19 pneumonia: an open-label randomized trial (GLUCOCOVID). *Wien Klin Wochenschr*. 2021;3:1-9.
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
- Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934-943.
- Liao D, Zhou F, Luo L, et al. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. *Lancet Haematol*. 2020;7(9):e671-e678.
- Wang D, Hu BO, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *J Am Med Assoc*. 2020;323(11):1061-1069.
- Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin definition. *J Am Med Assoc*. 2012;307(23):2526-2533.
- Moraleda L, Escosa T, Sainz D, et al. [Technical document. Clinical management of COVID-19: hospital care]. Spain: Ministry of Health, Consumer Affairs and Social Welfare. 2020. https://www.msbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Protocolo_manejo_clinico_ah_COVID-19.pdf. Accessed April 22, 2021.
- Gil-Navarro MV, Luque-Márquez R. Hospital pharmacy in the multidisciplinary team of COVID inpatient units. *Farm Hosp*. 2020;44(7):40-42.
- World Health Organization. WHO R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial Synopsis. *World Heal Organ*. 2020:1-9. <https://www.who.int/publications/i/item/covid-19-therapeutic-trial-synopsis>. Accessed April 22, 2021.
- Cortegiani A, Ippolito M, Greco M, et al. Rationale and evidence on the use of tocilizumab in COVID-19: a systematic review. *Pulmonology*. 2021;27(1):52-66.
- REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med*. 2021;384(16):1491-1502.
- Sterne JAC, Murthy S, Diaz JV, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *J Am Med Assoc*. 2020;324(13):1330-1341.
- Jeronimo CMP, Farias MEL, Val FFA, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with coronavirus disease 2019 (COVID-19; Metcovid): a randomized, double-blind, phase IIb, placebo-controlled Trial. *Clin Infect Dis*. 2021;72(9):e373-e381.
- Fatima SA, Asif M, Khan KA, et al. Comparison of efficacy of dexamethasone and methylprednisolone in moderate to severe COVID 19 disease. *Ann Med Surg*. 2020;60:413-416.
- Ko JJ, Wu C, Mehta N, et al. A comparison of methylprednisolone and dexamethasone in intensive care patients with

- COVID-19. *J Intensive Care Med.* 2021;36(6):673-680. <https://doi.org/10.1177/0885066621994057>
33. Raju R, Prajith V, Biatrix PS, Chander SJUJ. Therapeutic role of corticosteroids in COVID-19: a systematic review of registered clinical trials. *Futur J Pharm Sci.* 2021;7(1):67.
34. Majmundar M, Kansara T, Lenik JM, et al. Efficacy of corticosteroids in non-intensive care unit patients with COVID-19 pneumonia from the New York Metropolitan region. *PLoS One.* 2020;15:e0238827.
35. Siemieniuk RAC, Bartoszko JJ, Ge L, et al. Drug treatments for COVID-19: Living systematic review and network meta-Analysis. *BMJ.* 2020;371:m4852.

How to cite this article: Climente-Martí M, Ruiz-Millo O, López-Cruz I, et al. Impact of intermediate to high doses of methylprednisolone on mortality rate in patients with COVID-19 pneumonia-induced severe systemic inflammation. *Int J Clin Pract.* 2021;75:e14479. <https://doi.org/10.1111/ijcp.14479>

APPENDIX 1

The Doctor Peset COVID-19 Working Group members (alphabetical order): Marta Acosta-Dávila, Juan Alberola-Enguítanos, Ulises Alfredo-López, Cristina Álvarez-Herreros, Rocío Armero-Ibáñez, Ángel Atienza-García, Daniel Bautista-Rentero, Alberto Berenguer-Muncharaz, Carmen Borraz-Ordás, Sergio Calvache-Castillo, Juan José Camarena-Miñana, Mar Carmona-Martín, Daniel Castelló-García, Mónica Climente-Martí, Francisco Dolz-Sinisterra, María José Fabiá-Valls, Emilio Garijo-Gómez, Cristina Pilar Giménez-Lozano, Rosa González-Pellicer, Héctor Hernández-Garcés, Ignacio Inchaurreaga-Álvarez, María Ángeles Juan-Gómez, Juan Vicente Llau-Pitarch, Ian López-Cruz, Rosario López-Estudillo, María Luisa López-Grima, María Antonia Marco-Artal, Ángel Marcos-Fendián, Eva Martínez-Moragón, Ana Míguez-Santiyán, José Miguel Nogueira-Coito, Martín Parejo-Montell, Tomás Ripollés-González, Ramón Romero-Serrano, Oreto Ruiz-Millo, Belén Salvador-Montero, Cyntia Sánchez-Martín, Azahar Sancho-Artés, Amparo Valero-Doménech, Josefina Zaballos-Bon, Rafael Zaragoza-Crespo.

Affiliations of the COVID-19 Working Group: Doctor Peset University Hospital. Gaspar Aguilar, 90, Valencia 46017, Spain.