MEDICINA CLINICA

Original article

Effectiveness of glucocorticoids in patients hospitalized for severe SARS-CoV-2 pneumonia[☆]

José Francisco Pascual Pareja [a,b,∗], Rebeca García-Caballero [a], Llanos Soler Rangel [a,b], Miguel Angel Vázquez-Ronda [a,b], Silvia Roa Franco [a], Gema Navarro Jiménez [a], Miguel Angel Moreno Palanco [a,b], Patricia González-Ruano [a,b], Ramiro López-Menchaca [a], Pilar Ruíz-Seco [a,b], Bárbara Pagán Muñoz [a], Alejandro Gómez Gómez [a], Beatriz Pérez-Monte [a], Rebeca Fuerte Martínez [a], Jose Luis Valle López [a], Arturo Muñoz Blanco [a], Isabel Rábago Lorite [a], Patricia Martínez Martín [a], Gonzalo Serralta San Martín [a,b], Jorge Francisco Gómez-Cerezo [a,b], on behalf of the HUIS-COVID-19 working group[◇]

[a] Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Madrid, Spain
[b] Universidad Europea de Madrid Villaviciosa de Odón, Madrid, Spain

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ABSTRACT

Background: Several studies have reported the beneficial effect of glucocorticoids in the treatment of cytokine storm that occurs in patients with severe COVID-19. Various glucocorticoids regimens have been proposed.

Methods: Retrospective observational study that includes patients with severe SARS-CoV-2 pneumonia and compares admission to an Intensive Care Unit (ICU) or death during hospitalization in three groups of patients: no glucocorticoids treatment, use of glucocorticoids doses equivalent to less than 250 mg of prednisone daily and use of equivalent doses greater than or equal to 250 mg of prednisone daily. Multivariate analysis was performed using logistic regression, using the propensity index as a covariant.

Results: Of the 259 patients enrolled in the study, 67 (25.9%) had an unfavorable evolution, dying or requiring ICU admission. Comparative analyzes between different glucocorticoids treatments and the association with ICU admission or death were: glucocorticoids treatment (any dose) versus no glucocorticoids treatment (OR: 0.71 [0.30–1.66]), treatment with glucocorticoids (≥250 mg prednisone daily) versus no glucocorticoids treatment (OR: 0.35 [0.11–1.08]) and glucocorticoids treatment (≥250 mg prednisone daily) versus patients with glucocorticoids doses <250 mg prednisone daily or without glucocorticoids treatment (OR: 0.30 [0.10–0.88]).

Conclusion: The results of this study show that patients with severe SARS-CoV-2 pneumonia treated with glucocorticoids pulses with equivalent doses of prednisone greater than or equal to 250 mg have a more favorable evolution (less mortality and less admission to ICU).

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Efectividad de los glucocorticoides en pacientes hospitalizados por neumonía grave por SARS-CoV-2

RESUMEN

Introducción: Se han comunicado varios trabajos donde se ha demostrado un efecto beneficioso de los glucocorticoides como tratamiento de la tormenta de citocinas que se asocia a los cuadros graves por SARS-CoV-2, plateándose diferentes pautas de glucocorticoides.

Síndrome agudo respiratorio severo por
coronavirus 2 (SARS-CoV-2)
Índice de propensión

Métodos: Estudio observacional retrospectivo que incluye pacientes con neumonía grave por SARS-CoV-2 y compara el ingreso en una unidad de cuidados intensivos (UCI) o fallecimiento durante la hospitalización en 3 grupos de pacientes: sin tratamiento con glucocorticoides, uso de dosis diarias de glucocorticoides equivalentes menores a 250 mg de prednisona y dosis diarias equivalentes mayores o iguales a 250 mg de prednisona. Se realizó un análisis multivariante mediante regresión logística, utilizando el índice de propensión como covariante.

Resultados: De los 259 pacientes incorporados al estudio 67 (25,9%) tuvieron una evolución desfavorable, falleciendo o precisando ingreso en UCI. Los análisis comparativos entre diferentes tratamientos con glucocorticoides, y la asociación con ingreso en UCI o fallecimiento fueron: tratamiento con glucocorticoides (cualquier dosis) versus sin tratamiento con glucocorticoides (OR: 0,71 [0,30–1,66]), tratamiento con glucocorticoides (≥250 mg de prednisona al día) versus sin tratamiento con glucocorticoides (OR: 0,35 [0,11–1,08]) y tratamiento con glucocorticoides (≥250 mg de prednisona al día) versus pacientes con dosis de glucocorticoides < 250 mg de prednisona o sin tratamiento con glucocorticoides (OR: 0,30 [0,10–0,88]).

Conclusión: Los resultados de este estudio muestran que los paciente con neumonía grave por SARS-CoV-2 tratados con pulsos con glucocorticoides con dosis equivalentes de prednisona mayor o igual de 250 mg tienen una evolución más favorable (menos mortalidad e ingreso en UCI).

Introduction

About 80% of patients with *coronavirus infection disease 2019* (COVID-19) have mild symptoms, but the rest may be more severely affected with the development of interstitial pneumonia that can be complicated by an acute respiratory distress syndrome, requiring admission to an intensive care unit (ICU) in up to 5% of the cases[1,2].

Two overlapping phases in the pathogenesis of the disease of uncertain duration have been defined[3,4]. The first one, in which there is a prevalence of direct damage by the virus, and the second one resulting from the host's inflammatory response. Many patients with severe COVID-19 have an excessive inflammatory response caused by an uncontrolled release of pro-inflammatory cytokines, defined as cytokine storm, causing diffuse alveolar damage[3–6].

In the absence of effective antiviral treatment, the only weapons currently available to us to control this inflammatory storm are supportive care and immunomodulatory treatment.

Glucocorticoid therapy has been a controversial issue in patients with SARS-CoV-2 infection. On the one hand, it is thought to inhibit tissue damage by reducing the inflammatory response, but on the other hand, it is feared that it may inhibit cell-mediated immunity, which could reduce viral clearance and worsen the course of the disease[7].

Several studies, including one clinical trial, have reported a beneficial effect of glucocorticoids on the outcome of patients with COVID-19[8–14], although not all studies have found the same benefit[15,16]. The doses of glucocorticoids used have varied widely, with some authors favouring high-dose boluses (prednisone > 250 mg) because it has a greater effect on the so-called non-genomic pathway of action[13,17].

The aim of the present study was to examine the progression of patients admitted with severe SARS-CoV-2 pneumonia in our hospital at the beginning of the pandemic, where various glucocorticoid treatment regimens were used, and to determine the association of glucocorticoid use with ICU admission or death.

Methodology

Study design and patients

Observational and retrospective study that examines the efficacy of glucocorticoid treatment in patients between the ages of 18 and 75 years with severe SARS-CoV-2 pneumonia in a conventional hospital ward at the Infanta Sofía University Hospital (HUIS) in San Sebastián de los Reyes (Madrid), with admission date from 28th February 2020 to 9th April 2020.

The diagnosis of SARS-CoV-2 infection was confirmed by gene amplification through a polymerase chain reaction of a nasopharyngeal sample.

Severe pneumonia was defined by the presence of:

- Consolidations in more than 2 fields on chest X-ray upon arrival at the emergency department, or radiological worsening with the onset of new infiltrates in the first 48 h after hospital admission.
- Room air oxygen saturation <93% or an equivalent oxygen saturation/fraction of inspired oxygen ratio (SO2/FiO2) < 443 in the first 48 h after hospital admission.

Patients with a hospital stay of less than 48 h with previous immunosuppressant or glucocorticoid treatment, associated comorbidity, which had a more relevant role than SARS-CoV-2 infection and which actually motivated hospital admission, and patients with other diseases that could act as a confounding factor, such as chronic lymphatic leukaemia, in which lymphopenia was not assessable as a prognostic marker were excluded.

Exposure to glucocorticoids and definition of outcome

The study compared patients who received standard treatment versus patients who received standard treatment plus glucocorticoids, and their association with the development of an unfavourable outcome.

An unfavourable outcome was defined as death or admission to the ICU during hospitalization. Hospital discharge without having been admitted to the ICU was defined as a favourable outcome.

The use of any dose of methylprednisolone or dexamethasone during admission was considered as glucocorticoid exposure. Two glucocorticoid exposure groups were defined. A group of patients who received maximum daily equivalent doses of prednisone under 250 mg and another group that received maximum daily equivalent doses of prednisone greater than or equal to 250 mg. Equivalent daily doses greater than or equal to 250 mg of prednisone were administered as intravenous boluses of dexamethasone 40 mg, or 250 or 500 mg of methylprednisolone for a period of 3–5 days.

The decision whether or not to initiate glucocorticoid treatment was made by the medical team treating each patient on a case-by-case basis. Patients were informed of their off-label use and gave their verbal consent, which was recorded in the electronic medical record.

Standard treatment included supportive measures with oxygen therapy and the combination of other drugs such as lopinavir-ritonavir, hydroxychloroquine, azithromycin, tocilizumab and
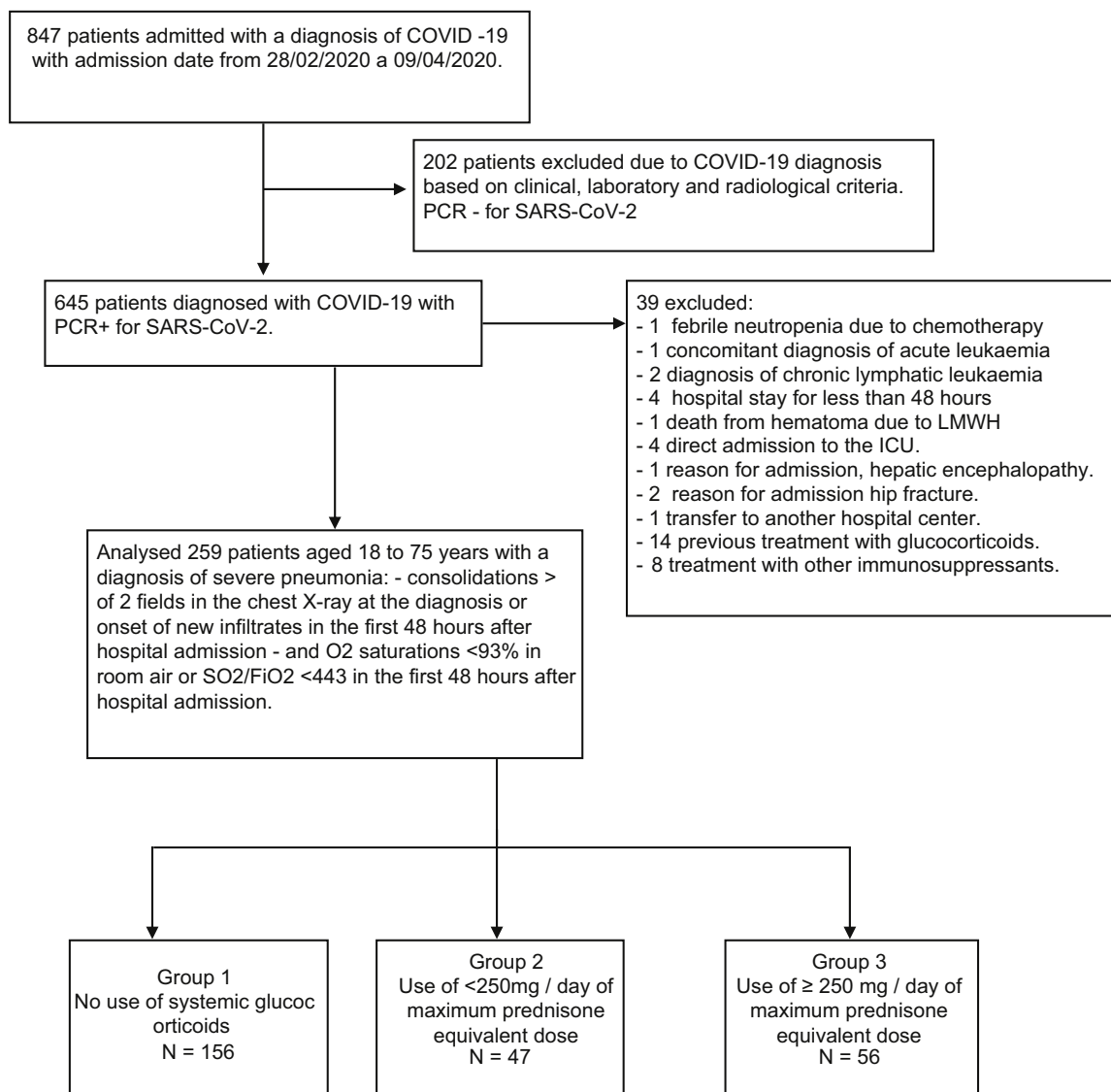
SO2/FiO2: ratio between oxygen saturation and inspiratory oxygen fraction. LMWH: Low molecular weight heparin ICU: Intensive care unit. PCR: gene amplification by polymerase chain reaction; Xr: X-ray.

Fig. 1. Flow chart of patients included and excluded in the study.
LMWH: low molecular weight heparin; PCR: gene amplification by polymerase chain reaction; Xr: X-ray; SO2/FiO2: ratio between oxygen saturation and inspiratory oxygen fraction; ICU: intensive care unit.

anakinra, according to local, dynamic, guiding, and consensual hospital guidelines, which was updated according to the publications that became available during the inclusion period. Tocilizumab and anakinra were administered at the discretion of the treating medical team; interleukin 6 values had to be greater than 40 pg/mL in order to administer tocilizumab.

Working method and variables

Patients who met all the inclusion criteria and none of the exclusion criteria were selected from a database (HUIS-COVID) that was created to register the clinical data of patients hospitalized for COVID-19.

The variables analysed were: demographic characteristics (age, sex and race), previous medical history, medication prior to admission, date of onset of symptoms, date of hospital admission, date

of the outcome, oxygen saturation and inspiratory fraction of oxygen ratio (SO2/FiO2) on arrival at the emergency department and at 48 h, laboratory data upon arrival at the emergency department and at 48 h (percentage of lymphocytes, C-reactive protein [CRP], lactate dehydrogenase [LDH] and D-dimer), radiological findings on arrival at the emergency department and at 48 h and treatments during admission.

Statistical analysis

For descriptive purposes, the qualitative variables were expressed as absolute frequency and percentage, the quantitative variables as medians and interquartile ranges (IQR).

First, a univariate analysis of the variables recorded in the different glucocorticoid exposure groups was performed. Qualitative variables were analysed using the Chi square test and quantitative

variables using the U-Mann–Whitney test. Variables that showed statistically significant differences in univariate analysis (p < 0.05) were used through logistic regression to calculate the index of propensity to receive treatment with glucocorticoids (any dose) and equivalent doses of prednisone greater than or equal to 250 mg.

Subsequently, a univariate analysis was performed to describe the variables that were associated with the development of an unfavourable outcome. Finally, a multivariate analysis was performed using logistic regression to study the association of the use of glucocorticoids (any dose) and the use of equivalent doses of prednisone greater than or equal to 250 mg with the development of an unfavourable outcome. The multivariate analysis was adjusted to the variables that had shown an association in the univariate analysis. The same analysis was repeated incorporating the propensity indices with the use of glucocorticoids (any dose) or the exposure group with an equivalent dose of prednisone ≥ 250 mg. Statistical analysis was performed with the SPSS version 19.0 software.

Ethical aspects

The hospital's research committee approved the conduct of the study. The study complies with the ethical guidelines and standards for research as reflected in the World Medical Association's Declaration of Helsinki and the Oviedo Convention on Human Rights and Biomedicine. All data was treated with the utmost confidentiality, in accordance with current legislation.

Results

Of the 847 patients who were admitted to our hospital from 28th February to 9th April 2020 with a diagnosis of coronavirus infection (Fig. 1), 202 patients were initially excluded in whom the diagnosis was based on clinical, laboratory and radiological criteria.

Of the 645 patients in whom the diagnosis of SARS-CoV-2 was confirmed with a gene amplification study by polymerase chain reaction of a nasopharyngeal sample, 39 patients were excluded: one due to admission coinciding with febrile neutropenia due to chemotherapy, another for concomitant diagnosis of acute leukaemia, 2 with a diagnosis of chronic lymphatic leukaemia, 4 for hospital stays shorter than 48 h, one death from hematoma secondary to treatment with low molecular weight heparin (LMWH), 4 direct admissions to the ICU, one admission for hepatic encephalopathy as the main cause, 2 for admission of hip fracture, another for transfer to another center, 14 due to previous glucocorticoid use and 8 due to use of other immunosuppressive treatments.

Finally, 259 patients aged 18–75 years with a diagnosis of severe SARS-CoV-2 pneumonia were included, of which 156 did not receive glucocorticoid treatment (group 1), 47 received maximum daily glucocorticoid equivalent doses of less than 250 mg of prednisone (group 2) and 56 received maximum daily glucocorticoid equivalent doses greater than or equal to 250 mg of prednisone (group 3). The characteristics of the patients stratified in different groups are detailed in Table 1. The patients who received glucocorticoids were older, with group 3 being the oldest. There were no differences regarding sex and race in the different groups. Comorbidity was similar, varying only the percentage of asthmatics, which was higher in group 2.

Group 2 and 3 patients had lower SO2/FiO2 and lymphocyte percentages compared to group 1, with higher LDH, CRP and D-dimer values. There were no significant differences in the values of these variables between patients in groups 2 and 3. There were differences regarding the various treatments used during admission in each of the groups, being statistically significant in the treatments with LMWH, azithromycin, tocilizumab, interferon beta-1B and anakinra, and in the use of non-invasive mechanical ventilation (Table 1). Regarding glucocorticoid treatment, it was longer in group 2 patients. The median and IQR of the total treatment time with glucocorticoids in group 3 was 3 (3–6) days. A total of 21 patients (37.5%) in group 3 received other glucocorticoid regimens apart from glucocorticoid boluses. The median and IQR of equivalent dose of maximum daily prednisone administered in group 3 was 312.5 mg (312.5–312.5), vs 133.8 mg (100-133.8) from group 2 (Table 1).

Of the 259 patients enrolled in the study, 67 (25.9%) had a course defined as unfavourable. They had lower SO2/FiO2 and lymphocyte percentages and higher D-dimer, LDH and CRP values (Table 2). In addition, these patients received more treatment with lopinavir-ritonavir, interferon beta 1-B, and tocilizumab than patients with a favourable outcome. On the other hand, patients with an unfavourable course were prescribed LMWH less often.

Regarding the use of glucocorticoids and the association with an unfavourable course, the crude analysis did not find significant differences between the use of high doses of glucocorticoids and not receiving glucocorticoids, although there were significant differences with respect to the group of patients treated with lower glucocorticoids doses, the latter group showing an unfavourable course of up to 42.6% (Table 1).

The multivariate analysis (Table 3) demonstrated a beneficial effect of the use of high doses of glucocorticoids (group 3) compared to patients not treated with glucocorticoids and patients treated with lower doses of corticosteroids (group 2). This association was statistically significant, although statistical significance was lost when only compared with the group that had not received corticosteroid treatment and adjusted with the propensity index as a covariate.

Six patients were not included in the multivariate analysis because they did not have LDH values. There were 6 patients who had not received glucocorticoids and who had a favourable course. The D-dimer variable was also not included, as it had not been collected in 14 patients. There was a correlation between D-dimer values and the percentage of lymphocytes (Pearson's correlation index of –0.130, with a p = 0.042) and CRP values (Pearson's correlation index of 0.200, with a value of p = 0.002).

Discussion

The results of this study suggest that patients with severe SARS-CoV-2 pneumonia treated with glucocorticoid pulses, with prednisone equivalent doses greater than or equal to 250 mg, have a more favourable course than patients treated with lower doses of glucocorticoids, or than those who did not receive glucocorticoid treatment (Table 3). This favourable course was not observed in the crude analysis but was observed when adjusted for other variables such as those associated with more severity such as age, SO2/FiO2, lymphocyte percentage, D-dimer, LDH and CRP. In the same vein as the results of our study are those reported by Calleja et al.[13], who analysed the course of patients treated with high doses of glucocorticoids (>250 mg of methylprednisolone) associated or not with tocilizumab, finding a trend towards a decrease in deaths and intubation when both drugs were combined.

We have not found this favourable course with lower glucocorticoid doses, as has been shown in other studies. The results of the RECOVERY clinical trial have recently been reported[14], which compared treatment with dexamethasone doses of 6 mg per day, for 10 days, to the standard treatment, showing a decrease in mortality at 28 days (21.5% vs. 25%). This was more evident in patients undergoing invasive mechanical ventilation (29% vs. 40.7%).

Table 1
Patient characteristics.

	Group 1 No use of systemic glucocorticoids n = 156	Group 2 Use of <250 mg/day of prednisone maximum equivalent dose n = 47	Group 3 Use of ≥250 mg/day of prednisone maximum equivalent dose n = 56	p*	p**
Median age (IQR)	60 (50–68.8)	61 (52–70)	65 (56.3–71)	0.034	0.01
Females, n (%)	47 (30.1)	17 (36.2)	16 (28.6)	0.671	0.827
Race, n (%)				0.406	0.714
Caucasian	130 (83.3)	34 (72.3)	44 (78.6)		
Latin American	21 (13.5)	12 (25.5)	10 (17.9)		
Other	5 (3.2)	1 (2.1)	2 (3.6)		
Previous diagnoses, n (%)					
Arterial hypertension	68 (43.6)	25 (53.2)	25 (44.6)	0.505	0.892
Diabetes	28 (17.9)	6 (12.8)	13 (23.2)	0.389	0.392
Obesity	26 (16.7)	8 (17)	12 (21.4)	0.718	0.425
Cardiovascular disease	16 (10.3)	2 (4.3)	4 (7.1)	0.398	0.494
COPD/asthma	15 (9.6)	10 (21.3)	4 (7.1)	0.047	0.578
Hypoventilation syndrome	19 (12.2)	4 (8.5)	9 (16.1)	0.507	0.461
Solid and/or hematologic malignancy	7 (4.5)	1 (2.1)	2 (3.6)	0.757	0.771
Previous Treatments, n (%)					
Statins	40 (25.6)	15 (31.9)	20 (35.7)	0.320	0.151
ACEI/ARB	58 (37.2)	20 (42.6)	22 (39.3)	0.797	0.780
Days from symptom onset to hospitalization-median (IQR)	7 (5–9.3)	6 (5–7)	6.5 (4–8)	0.168	0.288
Days from symptom onset to glucocorticoid treatment-median (IQR)		11 (8–13)	10 (7.3–15)	0.637	
Prednisone equivalent maximum daily dose (mg) administered-median (IQR)		133.8 (100–133.8)	312.5 (312.5–312.5)	<0.001	
Total days or time in days of glucocorticoid treatment-median (IQR)		5 (3.8–8.3)	3 (3–6)	0.008	
SO2/FiO2[a]-medium (IQR)	310 (219–373.1)	280 (107–342)	284 (186.5–341.3)	0.131	0.094
Median laboratory analysis (IQR)					
Lymphocyte percentage[a]	11.1 (8.3–16.6)	9 (6.2–12.9)	10.1 (6.6–14.5)	0.015	0.081
Lactate dehydrogenase count[b] U/l	343.5 (282–420)	467 (341–533)	420 (320.8–555.3)	<0.001	0.002
C-reactive protein[b] (mg/l)	116.9 (69.2–182.2)	171 (106.8–245)	141.7 (88.8–241.3)	0.003	0.031
D-dimer[b] (ng/mL)	780 (475–1,550)	1035 (610–1757.5)	960 (592.5–1745)	0.173	0.119
Treatment during admission, n (%)					
Hydroxychloroquine/Chloroquine	153 (98.1)	47 (100)	54 (96.4)	0.423	0.486
Azithromycin	91 (58.3)	37 (78.7)	43 (76.8)	0.006	0.014
Lopinavir/Ritonavir	28 (17.8)	9 (19.1)	8 (14.3)	0.774	0.531
Interferon beta-1B	5 (3.2)	6 (12.8)	1 (1.8)	0.012	0.583
Tocilizumab	20 (12.8)	19 (40.4)	21 (37.5)	<0.001	0.004
Anakinra	0	0	3 (5.4)	0.004	<0.001
Low molecular weight heparin (LMWH)	81 (51.9)	29 (61.7)	49 (87.5)	<0.001	<0.001
Non-invasive mechanical ventilation	8 (5.1)	7 (14.9)	14 (25)	<0.001	<0.001
Outcomes n (%)					
Favourable: discharge from hospital	120 (76.9)	27 (57.4)	45 (80.4)	0.014	0.596
Unfavourable: intubation or death	36 (23.1)	20 (42.6)	11 (19.6)		
Days of hospitalization to outcome-median (IQR)	8 (6-10)	12 (6-17)	12.5 (8–17.8)	<0.001	<0.001
Diagnosed with venous thromboembolic disease, n (%)	6 (3.8)	6 (12.8)	11 (19.6)	0.001	<0.001
Unfavourable outcomes in a patient without LMWH, n (%)	20/75 (26.7)	14/18 (77.8)	2/7 (28.6)	<0.001	0.913
Unfavourable outcomes in a patient with LMWH, n (%)	16/81 (19.8)	6/29 (20.7)	9/49 (18.4)	0.966	0.846

IQR: interquartile range; cardiovascular disease: chronic atrial fibrillation and/or ischemic heart disease and/or heart failure; SO2/FiO2: ratio between oxygen saturation and inspiratory oxygen fraction.

* Comparison between groups 1, 2 and 3.

** Comparison between groups 1 and 3.

[a] Lowest value in the first 48 h.

[b] Highest value in the first 48 h.

A possible explanation for the lack of benefit derived from the use of glucocorticoids with lower doses in our study could be due to the characteristics of these patients, as this group had a lower percentage of LMWH use (Table 1), especially considering that up to almost 78% of the patients without LMWH in this group had an unfavourable course (Table 1). This fact could mean an important role for undiagnosed or untreated thromboembolic disease as a cause of unfavourable course in this group [18–22]. In this sense, it is worth wondering whether using lower doses of glucocorticoids could have a lower anti-inflammatory effect and therefore, further

Table 2
Factors associated with unfavourable course (admission to ICU or death).

	Hospital discharge n = 192 (74.1%)	Unfavourable course Intubation or death n = 67 (25.9%)	p
Median age (IQR)	60 (50–69)	65 (56–70)	0.043
Females, n (%)	60 (31.3)	20 (29.9)	0.831
Race, n (%)			0.552
Caucasian	155 (80.7)	53 (79.1)	
Latin American	30 (15.6)	13 (19.4)	
Other	7 (3.6)	1 (1.5)	
Previous diagnoses, n (%)			
Arterial hypertension	83 (43.2)	35 (52.2)	0.202
Diabetes	35 (18.2)	12 (17.9)	0.954
Obesity	30 (15.6)	16 (23.9)	0.128
Cardiovascular disease	16 (8.3)	6 (9)	0.875
COPD/asthma	21 (10.9)	8 (11.9)	0.823
Hypoventilation syndrome	22 (11.5)	10 (14.9)	0.458
Solid and/or hematologic malignancy	8 (4.2)	2. 3)	0.666
Previous treatments, n (%)			
Statins	57 (29.7)	18 (26.9)	0.661
ACEI/ARB	70 (36.5)	30 (44.8)	0.229
Days from symptom onset to hospitalization-median (IQR)	7 (5–8)	6.5 (4.8–8)	0.270
Days from symptom onset to glucocorticoid treatment-median (IQR)	11 (7.3–15)	11 (9–15)	0.464
SO2/FiO2 worse in the first 48 h-median (IQR)	316.1 (257.3–373)	190 (95–303.2)	<0.001
Median laboratory analysis (IQR)			
Lymphocyte percentage[a] count	11.3 (8.5–16.4)	8.3 (5.1–11.4)	<0.001
Lactate dehydrogenase[b] U/l	348 (284.8–438.8)	478 (349–571)	<0.001
C-reactive protein[b] (mg/l)	114.1 (69–171.8)	196 (139–253)	<0.001
D-Dimer[b] (ng/mL)	770 (480–1315)	1170 (815–2260)	<0.001
Treatment during admission, n (%)			
Hydroxychloroquine/chloroquine	188 (97.9)	66 (98.5)	0.762
Azithromycin	127 (66.1)	44 (65.7)	0.944
Lopinavir/Ritonavir	24 (12.5)	21 (31.3)	<0.001
Interferon beta-1B	6 (3.1)	6 (9)	0.051
Tocilizumab	29 (15.1)	31 (46.3)	<0.001
Anakinra	2 (1)	1 (1.5)	0.766
Low molecular weight heparin	128 (66.7)	31 (46.3)	0.003
Non-invasive mechanical ventilation	22 (11.5)	7 (10.4)	0.821

Cardiovascular disease: chronic atrial fibrillation and/or ischemic heart disease and/or heart failure; IQR: interquartile range; SO2/FiO2: ratio between oxygen saturation and inspiratory oxygen fraction.

[a] Lowest value in the first 48 h.

[b] Highest value in the first 48 h.

favour the development of thromboembolic disease, especially in this group of patients who had worse severity markers (SO2/FiO2 and percentage of lower lymphocytes and higher D-dimer, CRP and LDH values). One hypothesis is that prednisone doses lower than 250 mg would not fully activate the non-genomic[17] pathway of glucocorticoid action, acting only on the genomic pathway, and may diminish its effect on the cytokine storm. On the other hand, it should be taken into account that the non-genomic mechanism of action is faster and could have other effects, such as inhibition of platelet aggregation[23], which could influence the course of patients with severe SARS-CoV-2 pneumonia.

Group 1 (patients not treated with glucocorticoids) had the lowest percentage of treatment with LMWH, although these patients were less severe (higher SO2/FiO2 and percentage of lymphocytes and lower D-dimer, CRP and LDH values). The absence of LMWH treatment is probably less relevant in this group, since 26.7% of the patients without LMWH treatment in this group had an unfavourable course, compared to 77.8% of group 2 and 28, 6% of group 3 (Table 1). The fact that the first patients treated for COVID-19 in our hospital were included in the study could explain the high percentage of patients without LMWH treatment, since

LMWH treatment in these patients was not standardised at that time.

On the other hand, it should be noted that the patients treated with glucocorticoids in our study had a longer hospital stay than the patients not treated with them, a result that differs from other publications, which demonstrated benefits with these drugs. We interpret this as a marker of higher severity in these patients, as well as the lower SO2/FiO2 value and percentage of lymphocytes or higher values of D-dimer, LDH and CRP, and even the higher use of non-invasive mechanical ventilation in these patients. One hypothesis would be that, as the use of glucocorticoids was not standardised, the most severe patients received glucocorticoid treatment even later than many authors recommend. Fadel et al. demonstrated a reduction in hospital stay in patients treated with glucocorticoids when they were administered early[8].

The limitations of our work, apart from being a single-center study, are those inherent in retrospective cohort studies, when comparing groups that are not totally homogeneous. To try to minimize these biases, the model was adjusted to the indices of propensity to receive glucocorticoid treatment. As previously mentioned, patients treated with glucocorticoids had higher severity

Table 3

Comparative analyses between different treatments with or without glucocorticoids and the association with unfavourable outcomes (admission to the ICU or death).

Analysis type		Number of unfavourable outcomes by number of patients	Crude analysis OR (95% CI)	Multivariate analysis[*] OR (95% CI)	Multivariate analysis adjusted for propensity index[**] OR (95% CI)
1	Glucocorticoid therapy (any dose) versus no glucocorticoid therapy	31/103 (30.1%)	1.44 (0.82–2.52)	0.69 (0.30–1.59)	0.71 (0.30–1.66)
		36/156 (23.1%)	p = 0.207	p = 0.380	p = 0.432
2	Glucocorticoid treatment≥ 250 mg prednisone per day) versus no glucocorticoid treatment	11/56 (19.6%)	0.82 (0.38–1.74)	0.31 (0.10–0.97)	0.35 (0.11–1.08)
		36/156 (23.1%)	p = 0.596	p = 0.044	p = 0.067
3	Glucocorticoid treatment (≥ 250 mg prednisone per day) versus other patients[a]	11/56 (19.6%)	0.64 (0.31–1.33)	0.30 (0.11–0.87)	0.30 (0.10–0.88)
		56/203 (27.6%)	p = 0.229	p = 0.026	p = 0.028

[*] Adjusted for age, ratio between oxygen saturation and inspiratory oxygen fraction (SO2/FiO2) worse in the first 48 h, percentage of lymphocytes lower in the first 48 h, highest CRP in the first 48 h, highest LDH in first 48 h, lopinavir/ritonavir treatment, tocilizumab treatment and low molecular weight heparin treatment.

[**] Multivariate analysis adjusted to the same variables described above plus the propensity index of each glucocorticoid regimen specified in each type of analysis. The analysis to calculate the propensity index included the variables: age, lowest SO2/FiO2 in the first 48 h, lower percentage of lymphocytes in the first 48 h, highest CRP values in the first 48 h, highest LDH values in the first 48 h, azithromycin treatment, interferon beta 1B treatment (except in Test 2), tocilizumab treatment, anakinra treatment, low molecular weight heparin treatment, use of non-invasive ventilation and history of asthma (except in analysis 2).

[a] The rest of the patients would be those who have received doses of corticosteroids < 250 mg of prednisone per day and those who had not received treatment with corticosteroids.

markers. The adjustment was carried out using the propensity index as a covariate in the logistic regression model for the development of unfavourable outcomes. We did not use other methods such as matching or stratification for the small sample size of our study. However, the key limitation of the propensity index adjustment is that it only adjusts for recorded variables. In this sense, there are variables not recorded in our data that could influence the time of prescribing glucocorticoids, such as the course of dyspnoea during admission or of SO2/FiO2 or chest X-ray 48 h after admission, or other variables that are difficult to record, such as the subjective assessment of the doctor.

This study points to a beneficial effect of glucocorticoids at equivalent doses of prednisone > 250 mg in patients with severe SARS-CoV-2 pneumonia, but more clinical trials are needed to study the effect of glucocorticoids in these patients, determining both the ideal glucocorticoid dose and the most appropriate starting time. At the time of writing, many clinical trials are underway to assess the effect of other immunomodulators in patients with severe COVID-19, but it should not be forgotten that these drugs are more expensive than glucocorticoids and may even face supply problems in the event of increased demand in further waves of the current pandemic.

Conflict of interests

The authors declare that they have no conflict of interest directly or indirectly related to the contents of the manuscript.

Appendix A. Members of the HUIS-COVID-19 Working Group

D. Arranz, R. Beltrán, R. Cadenas, C. Casanova, J.A. de Boer, R. del Valle, G. García, B. Iglesias, A. Lung, O. Madridano, M. Martín, M. Merino, M. Moral, S. Muñoz, M. Neira, B. Núñez, I. Perales, A. Pérez, M. Reche, T. Reinoso, J.M. Rizo, C. Sánchez, M. Sereno and T. Valbuena.

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