IMPACT OF GLUCOCORTICOID TREATMENT IN SARS-COV-2 INFECTION MORTALITY: A RETROSPECTIVE CONTROLLED COHORT STUDY

Running title: Glucocorticoids and COVID-19.

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ABSTRACT

Background: Evidence to support the use of steroids in COVID-19 pneumonia is lacking. We aim to determine the impact of steroid use in COVID-19 pneumonia in-hospital mortality.

Patients and Methods: We performed a single-center retrospective cohort study in a University hospital in Madrid, Spain, during March 2020. To determine the role of steroids in in-hospital mortality, patients admitted with SARS-CoV-2 pneumonia and treated with steroids were compared to patients not treated with steroids, adjusting by a propensity-score for steroid treatment. Survival times were compared using log-rank test. Different steroid regimens were compared, and adjusted with a second propensity score.

Results: During the study period, 463 out of 848 hospitalized patients with COVID19 pneumonia fulfilled inclusion criteria. Among them, 396 (46.7%) patients were treated with steroids and 67 patients were not. Global mortality was 15.1%. Median time to steroid treatment from symptom onset was 10 days (IQR 8-13). In-hospital mortality was lower in patients treated with steroids than in controls (13.9% [55/396] versus 23.9% [16/67], HR 0.51 [0.27-0.96], p= 0.044). Steroid treatment reduced mortality by 41.8% relative to no steroid treatment (RRR 0,42 [0.048- 0.65). Initial treatment with 1 mg/kg/day of methylprednisolone versus steroid pulses was not associated with in-hospital mortality (13.5% [42/310] versus 15.1% [13/86], OR 0.880 [0.449-1.726], p=0.710).

Conclusions: Our results show that survival of patients with SARS-CoV2 pneumonia is higher in patients treated with glucocorticoids than in those not

85 treated. In-hospital mortality was not different between initial regimens of 1
86 mg/kg/day of methylprednisolone and glucocorticoid pulses.
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ABBREVIATIONS

SARS-CoV: severe acute respiratory syndrome coronavirus

COVID-19: coronavirus disease 2019

Steroids: glucocorticoids or corticoids

OR: Odds ratio

MERS-CoV: Middle east respiratory syndrome coronavirus

PaO2/FiO2: arterial oxygen tension/inspiratory oxygen fraction

CT: computed tomography

ARDS: acute respiratory distress syndrome

CRP: C- reactive protein

PEEP: positive end expiratory pressure

SD: standard deviation

CI: confidence interval

PSM: propensity-score matching

RRR: relative risk reduction

HR: hazard ratio

IQR: interquartile range

COPD: chronic obstructive pulmonary disease

LDH: Lactate dehydrogenase

SpO2: plasma oxygen saturation

ICU: Intensive care Unit

INTRODUCTION

Infection with SARS-CoV-2, presents mainly with respiratory involvement. Clinical presentation consists of a first viremic phase 7-10 days long, followed in some cases by a second phase of clinical manifestations driven by lung and systemic inflammation (1).During the initial viremic phase, antiviral drugs are recommended, especially in cases with pneumonia. Around 80% of cases will resolve after this first phase. However, another 20% will evolve to a severe pneumonitis, followed by acute respiratory distress syndrome (ARDS). In that second phase, an increase in acute phase reactants and macrophage activation markers has been identified. Poor outcomes have been associated with high IL6 levels, leading to the recommendation of treatment with IL6 antagonists.

Scarcity of anti-inflammatory targeted therapies such as tocilizumab during the initial period of SARS-CoV2 pandemic has driven the use of glucocorticoids in these patients, particularly in the more severe cases as a last-resort, despite the recommendation against it. Based on studies performed during the prior SARS-CoV, MERS-CoV, and H1N1 influenza epidemics, glucocorticoids were advised against in COVID-19 by the WHO, owing to a possible deleterious effect of prolongation of viral excretion and increased adverse events (2). The available studies have important methodologic limitations and, of note, glucocorticosteroids (from now on, steroids) were usually administered early after symptom onset (4 days)(3). Nevertheless, in the current pandemic, the Chinese National Commission recommended methylprednisolone 1-2 mg/kg/day during 3-5 days in cases with respiratory failure (4) and several studies suggest a possible beneficial effect of steroids administered in the

inflammatory phase of the disease, in patients with ARDS(5, 6). In this respect, the use of steroids as adjuvant therapy in moderate to severe ARDS is accepted in early stages at a dosage of 1 mg/kg/day of methylprednisolone in intubated patients(7). In severe and rapidly progressive ARDS, methylprednisolone appears to improve symptoms and pulmonary damage, but does not increase survival(8). Nevertheless, this inhibition of the inflammatory storm may allow to gain time to control the infection and prevent secondary multi-organ failure and shock (9). Recently, early administration of dexamethasone has shown a survival advantage in established moderate-to-severe ARDS(10). Moreover, the combined effect of steroids with other anti-inflammatory therapies used concomitantly is still to be determined, namely in those cases in which the targeted therapy needs some time to achieve a response (9).

However, there is a lack of evidence to support steroid use, and there also is uncertainty about the most appropriate drug, dose and timing. It is unknown whether the appropriate steroid dose might be the same in different stages of the disease, and which is the therapeutic ceiling. While awaiting for results from ongoing clinical trials(11), we consider that an analysis of actual clinical practice is needed to guide the recommendations. We performed a retrospective analysis of our experience to test the hypothesis that steroid use can improve the mortality of patients with COVID-19 pneumonia.

PATIENTS AND METHODS

1. Design, study period and subjects

This single-center retrospective cohort study included patients admitted to Hospital Puerta de Hierro-Majadahonda between March 4th, 2020, and April 7th, 2020. Our institution is a 613-bed tertiary teaching hospital in Madrid, Spain.

Adult patients diagnosed with COVID-19 pneumonia according to WHO interim guidance, and complicated with ARDS and/or an hyperinflammatory syndrome, where included. Of them, patients who received corticosteroid therapy according to clinical practice were assigned to the steroid cohort, whilst patients who did not were assigned to the control cohort.

2. Data collection

Epidemiological, clinical, laboratory and radiologic data were extracted from electronic medical records (SELENE System, Cerner Iberia, S.L.U., Madrid [Spain]) using a standardized data collection form. All data were included by a primary reviewer and subsequently checked by two senior physicians.

3. Laboratory procedures

Routine blood examinations included a complete blood count, coagulation profile, serum biochemical tests (including lactate dehydrogenase), C reactive protein, D Dimer, interleukin-6 (IL-6), and serum ferritin. Chest radiographs or CT scans were also done for all inpatients.

4. Definition of the outcome

The main outcome variable was in-hospital mortality. The outcome of patients treated with steroids was compared to that of those who did not receive steroids.

5. Definition of the exposure

Exposure to corticosteroids was defined as the use of intravenous steroids at any time during the hospital admission.

Patients with steroid treatment were designated as the “treatment cohort”, and those who did not receive them as “control cohort”.

The decision to prescribe steroids was at the discretion of the treating physician as the use of corticosteroids was not included in the COVID local protocol at the time of the study. Details of corticosteroid use (including the timing of initiation, dosing, and type of medications) were recorded. Likewise, the choice of COVID treatments other than corticosteroids was at the discretion of the treating physician, although based on national and local recommendations for COVID-19 management. There were patients who were receiving prior steroid treatment due to chronic conditions (typically oral steroids). If steroid doses were modified with the aim of treating COVID, they were included as cases. If they continued with their usual steroid dose, they were included as controls.

In the treatment cohort, the first day of administration was considered as the index date (day 0). In the control cohort, the index date was selected as the date at which the patient fulfilled ARDS criteria or presented any inflammation-related parameter level over the limits of normal range. The diagnosis and grading of ARDS was determined according to modified Berlin criteria(12) (as most patients were not ventilated, the PEEP value in the modified criteria was not taken into consideration).

For the main analysis, we generated a variable with the following mutually exclusive categories: "non-use of steroids drug" (control cohort) and "use of steroids drug" (treatment cohort). Subsequently, we disaggregated the latter into two different subgroups: 1 mg/kg/day methylprednisolone or equivalent,

and steroid pulse. When a patient received different corticosteroid regimens during hospitalization, the first prescribed regimen was considered for the analysis.

6. Statistical analysis

Quantitative variables were expressed as means and standard deviations (SD) and/or medians and interquartile ranges, and qualitative variables as frequencies and percentages. The association of comorbidities among the treatment and control cohorts with mortality was assessed through univariable conditional logistic regression to compute crude odds ratios (ORs) and their 95% confidence intervals (CIs). Survival times were estimated using the Kaplan–Meier method, differences between the cohorts were compared using a log-rank test. The Mann-Whitney U test, χ^2 test, or Fisher's exact test were used to compare differences between survivors and non-survivors, where appropriate. To explore risk factors associated with in-hospital death, univariable and multivariable logistic regression models were used. Variables with a $p < 0.05$ in univariable models were selected into the multivariable.

To reduce the effect of corticosteroid treatment selection bias and potential confounding, we adjusted for differences in baseline characteristics by a propensity score, which predicts the patient's probability of being treated with steroids regardless of confounding factors, using multivariable logistic regression. Potential confounders considered in propensity score matching (PSM) analysis were those variables included in the final model by means of step-wise backward elimination procedures. The effect of corticosteroid treatment on clinical outcome was analyzed by a multivariable logistic regression, adjusted for major variables associated with mortality; the individual

propensity score was incorporated into the model as a covariate, to calculate the propensity adjusted odds ratio (OR).

Likewise, a second propensity score was developed to adjust for the choice of initial steroid regimen.

All statistical analyses were performed using SPSS system (version 26.0 for Windows, SPSS Inc., Chicago, IL, USA). The statistical significance level was set at a two-sided p value of < 0.05. A hazard ratio (HR) or an odds ratio (OR) was reported along with 95% confidence interval (CI).

7. Ethics

The study was approved by the Institutional Review Board (CEIm) at Hospital Universitario Puerta de Hierro-Majadahonda (BRA-COR-2020–03), and a waiver for the informed consent was granted. The study complied with the provisions in EU and Spanish legislation on data protection and the Declaration of Helsinki 2013.

8. Registration: The protocol of the study was registered in EU PAS Register #EUPAS34753 on 15th April 2020 and publicly available at:

http://www.encepp.eu/encepp/studySearch.htm

9. Data sharing: After publication, the data will be made available to others on reasonable requests to the corresponding authors. A proposal with a detailed description of study objectives and statistical analysis plan will be needed for evaluation of the reasonability of requests. Additional materials might also be required during the process of evaluation. De-identified participant data will be provided after approval from the principal researchers of the Hospital Puerta de Hierro-Majadahonda.

RESULTS

During the study period, 848 patients with COVID-19 and pneumonia were admitted to the hospital. 463 out of 848 patients (55%) were included. Among them, 396 were treated with steroids, whilst 67 were assigned to the control cohort. A total of 385 patients that were excluded from participation were hospitalized with COVID-19, but did not develop ARDS or increase in inflammatory markers.

Clinical characteristics

Clinical characteristics of the cases and controls are displayed in Table 1. Median time to steroid treatment from the onset of symptoms was 10 days (IQR 8-13). Among patients treated with steroids, 310 (78.3 %) patients were initially treated with 1 mg/kg/day methylprednisolone or equivalent (22.5% of them received steroid pulses later-on) and 86 (21.7%) received pulses from the beginning.

Patients treated with steroid pulses received a median of 3 pulses (IQR 2-4), followed by tapering in 25% of cases. Pulses of methylprednisolone were classified in the following groups: <250 mg/d (20.1%), 250 mg/d (62.5%), and 500 mg/d (17.1%).

Forty-one patients (8.9%) in our series were considered immunosuppressed including patients that were receiving prior steroid treatment. Of these, 10 (24.4%) had underlying rheumatologic conditions, 16 (39.0%) had underlying onco-hematologic conditions and the remaining patients presented other conditions that involved the administration of immunosuppressive treatment.

The percentage of immunosuppressed patients in both cohorts was similar (9.3% steroids cohort vs. 6.0% control cohort, p 0.369).

In-hospital mortality of patients treated with steroids compared to patients not treated with steroids

Global in-hospital mortality was 15.3%. Characteristics of survivors and non-survivors are shown in Appendix Table 1.

In-hospital mortality was lower in patients treated with steroids than in controls (13.9% versus 23.9%, HR 0.51 [0.27-0.96], p= 0.044) (Table 2). Steroid treatment reduced mortality by 41.8% relative to no steroid treatment (RRR 0.42 [0.048-0. 65]). We calculated a number necessary to treat of 10. A propensity score to reduce the effect of steroid treatment selection bias was developed. Significant differences in baseline characteristics between steroid-treated and non-treated patients, such as onco-hematologic underlying conditions, peptic ulcer disease, LDH and SpO2, were considered for the propensity score. Peptic ulcer disease, is considered a relative contraindication for steroid use, and this may have influenced an inferior steroid use in patients with a history of this condition. The difference in mortality persisted after applying the propensity score adjusted for steroid treatment (Table 2). Figure 1 demonstrates differences in the probability for survival at day 30 for patients with SARS-CoV2 infection, according to steroid treatment (log-rank p <0.001).

Among patients with moderate or severe ARDS, in-hospital mortality was lower in patients treated with steroids than in the controls (26.2% versus 60%, OR 0.23 [0.08-0.71], p=0.014). Appendix Figures 1 and 2 show differences in probability of survival at day 30 according to steroid treatment, stratified according to ARDS severity.

The effect of steroid treatment on mortality in different subsets of patients was consistent with a protective effect (Figure 2).

Table 3 shows the risk factors for mortality in both univariable and multivariable analyses, including those adjusted by the propensity score for steroid treatment. Older age, chronic kidney disease, more severe ARDS and elevated lactate dehydrogenase (LDH) levels were independent risk factors for mortality, whereas steroid treatment was an independent protective factor. Except for ARDS severity, these results were confirmed when adjusted by propensity score for steroid treatment.

In-hospital mortality of patients treated with different steroid regimens: pulses versus 1 mg/kg/day

Characteristics of patients initially treated with 1 mg/kg/day of methylprednisolone (or equivalent) versus those initially treated with steroid pulses are displayed in Appendix Table 2**.** Being treated with either regimen was not associated with in-hospital mortality (13.5% versus 15.1%, OR 0.880 [0.449-1.726], p=0.710; RRR 0.10 [-0.59-0.50]).

A propensity score for the choice of initial steroid regimen was developed. After adjusting by this propensity score, there were still no differences in mortality.

Characteristics of patients initially treated with 1 mg/kg/day that eventually required salvage steroid pulses

A subset of patients initially treated with 1 mg/kg/d of methylprednisolone received subsequent steroid pulses, in a median of 3-days-time (IQR 2-7). Baseline characteristics of these patients, as opposed to those who did not, are presented in Appendix Table 3. Diabetic patients, those with underlying

neurologic disease or higher levels of LDH at steroid initiation were more prone to require subsequent pulses, according to the multivariable analysis.

DISCUSSION

Our results show that survival of patients with SARS-CoV2 pneumonia is higher in patients treated with steroids than in those not treated. These results support the use of steroids in SARS-CoV2 infection. In-hospital mortality was not different between initial regimens of 1 mg/kg/day of methylprednisolone and steroid pulses.

The timing of the steroid administration might be decisive. In the present study, patients received steroid treatment in a median of 10 days after onset of symptoms, presumably during the inflammatory phase of the disease. Three distinct stages of COVID-19 illness have been suggested(1). Siddiqi et al(1) suggested that from stage IIB-on, starting when hypoxia develops, anti-inflammatory therapies such as steroids could be beneficial, due to the predominant role of inflammation in its pathophysiology.

The warning against the use of steroids in COVID19 is based on studies that administered this therapy earlier-on during the course of the disease, and relies on the experience from different viruses(13). Moreover, it has been speculated that steroid administration in patients with SARS-CoV2 infection could be deleterious due to an increase of viral shedding or a delay in viral clearance. Although this theory was not confirmed in a recent work by Fang(14), it is worth considering if steroids are to be administered early-on in the course of the

disease. As referred by Shang et al(15), the evidence about the use of steroids is inconclusive and randomised controlled trials are needed.

In the present series, steroids were used in patients with hypoxemia that were not at an early phase of the disease, as stated by the median time from the onset of symptoms to steroid administration. As many as 64% of the cases fulfilled ARDS criteria at the time of steroid administration. At this stage, as suggested by the lower rates of mortality seen in the treatment cohort when compared to the control group, steroid treatment was beneficial. In general, guidelines recommend not using corticosteroids in patients with COVID-19, or using them only in intubated patients(16) or in the setting of randomized clinical trials(17). In our series, steroid treatment was beneficial in patients with moderate to severe ARDS, but a trend to a better survival was also seen in cases with mild ARDS, though it did not reach statistical significance, possibly due to a small sample size. When steroids are delayed to more advanced stages, we might be missing a therapeutic window to prevent the evolution to severe ARDS and the need for mechanical ventilation. Nevertheless, the optimal stage for steroid treatment remains to be elucidated.

Patients with higher LDH levels responded better to steroid treatment in the present series. As LDH can be considered a surrogate marker for the extent of lung involvement, these results would indicate that patients with more extensive lung damage might benefit more from steroid treatment. In this respect, our results are in line with those reported by others(5) .

A pattern of cytokines resembling that of secondary hemophagocytic lymphohistiocytosis has been associated with SARS-CoV2 infection(18). Mehta et al(19) suggested a role for corticosteroid in patients with severe COVID-19

and hyperinflammation diagnosed based on cytokine elevation profile. In our series, steroid protective effect was more intense in cases with higher D-dimer and C-reactive protein levels.

Optimal steroid dosing also needs clarification. Most patients treated with steroids in the present series received a weight-adjusted dose, but a significant proportion of patients (39.4%) received higher doses in pulses, either from the start or as salvage therapy, after a weight-adjusted course. In our series, we were not able to demonstrate a difference in mortality between these two regimens, even after adjusting by a propensity score taking into consideration the regimen choice and disease severity. An analysis of secondary adverse effects, which are usually dose-related, would help decide between regimens, if both dosing regimens were confirmed to be associated with equivalent outcomes.

Our results are in line with a more preliminary work by Wang(20), who reported a shorter duration of fever and a faster improvement of SpO2 in cases of severe SARS-CoV2 pneumonia treated with 1-2 mg/kg/day of methylprednisolone during a period of 5-7 days. The present study has a considerably larger sample size, a more diverse population, and the added value of a propensity score to adjust for steroid treatment. Moreover, we report an impact on in-hospital mortality.

A study by Zhou(9), including only critical patients and without a control group, suggested that steroid treatment could enhance oxygen saturation and arterial PaO2/ FiO2 ratio, although mortality remained similar to that reported in the literature. Our study suggests that besides ICU patients with severe ARDS,

other subsets of patients in an earlier phase of the disease could benefit from steroid therapy, and possibly avoid ICU admission.

Other treatment-related factors that could influence mortality and were not evenly distributed regarding to exposure to steroids, such as hydroxychloroquine or tocilizumab use, were not independent predictors for mortality in the multivariable analysis.

The present study is a retrospective study that analyses real-life data, and as such, treated and untreated patients are not comparable according to all baseline characteristics. To overcome this limitation, we applied two propensity scores to the analysis, one for steroid treatment versus no steroid treatment and the second one, for the initial steroid regimen choice. Results were confirmed when including the propensity scores. As a single center study, the results need external validation. The only outcome that was evaluated in the study was mortality. We consider that ICU admission during the study period is not a reliable marker of poor outcome, given the scarcity of available ICU beds during that critical moments of the pandemic, which forced to apply strict restrictions for ICU admission.

The potential impact of steroids in the mortality of COVID-19 pneumonia suggested by this study supports the need to carry out randomized clinical trials with the aim to establish their role. The optimal timing for administration, the subset of patients with the best risk/benefit ratio and the appropriate dosing and duration remain to be elucidated.

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Conceptualization and study design: AFC, BRA

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Data collection: AMG, ASL, GCS, PMS, LGG, SBA, AGG, AVA, JGI, IMT, ESC, CPH, LDTC

Data interpretation: BRA, AFC, EMR, ARM, ACD

Writing first draft: AFC, BRA

Critical revision for important intellectual content, all authors; final approval, all authors;

Revision and English proofreading: CPH

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

AFC and BRA had full access to all the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. **Hasan K. Siddiqi M, MSCR, and Mandeep R. Mehra, MD, MSc.** 2020. COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal. Journal of Heart and Lung Transplantation doi:10.1016/j.healun.2020.03.012.
2. **Organization WH.** 2020. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance. 13rd March.
3. **Ho JC, Ooi GC, Mok TY, Chan JW, Hung I, Lam B, Wong PC, Li PC, Ho PL, Lam WK, Ng CK, Ip MS, Lai KN, Chan-Yeung M, Tsang KW.** 2003. High-dose pulse versus nonpulse corticosteroid regimens in severe acute respiratory syndrome. Am J Respir Crit Care Med **168:**1449-1456.
4. **Medicine NHCSAoTC.** 2020. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7).
5. **Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y.** 2020. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med doi:10.1001/jamainternmed.2020.0994.
6. **Villar J, Confalonieri M, Pastores SM, Meduri GU.** 2020. Rationale for Prolonged Corticosteroid Treatment in the Acute Respiratory Distress

Syndrome Caused by Coronavirus Disease 2019. Crit Care Explor **2:**e0111.

7. **Pastores SM, Annane D, Rochwerg B, Corticosteroid Guideline Task Force of S, Esicm.** 2018. Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part II): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Crit Care Med **46:**146-148.

8. **Sarzi-Puttini P, Giorgi V, Sirotti S, Marotto D, Ardizzone S, Rizzardini G, Antinori S, Galli M.** 2020. COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? Clin Exp Rheumatol **38:**337-342.

9. **Zhou W, Liu Y, Tian D, Wang C, Wang S, Cheng J, Hu M, Fang M, Gao Y.** 2020. Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia. Signal Transduct Target Ther **5:**18.

10. **Villar J, Ferrando C, Martinez D, Ambros A, Munoz T, Soler JA, Aguilar G, Alba F, Gonzalez-Higueras E, Conesa LA, Martin-Rodriguez C, Diaz-Dominguez FJ, Serna-Grande P, Rivas R, Ferreres J, Belda J, Capilla L, Tallet A, Anon JM, Fernandez RL, Gonzalez-Martin JM, dexamethasone in An.** 2020. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med **8:**267-276.

11. **Zhou YH, Qin YY, Lu YQ, Sun F, Yang S, Harypursat V, Tang SQ, Huang YQ, He XQ, Zeng YM, Li Y, Xu XL, Zhao T, Chen YK.** 2020. Effectiveness of glucocorticoid therapy in patients with severe novel

coronavirus pneumonia: protocol of a randomized controlled trial. Chin Med J (Engl) doi:10.1097/CM9.0000000000000791.

12. **Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS.** 2012. Acute respiratory distress syndrome: the Berlin Definition. JAMA **307:**2526-2533.

13. **Russell CD, Millar JE, Baillie JK.** 2020. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet **395:**473-475.

14. **Fang X, Mei Q, Yang T, Li L, Wang Y, Tong F, Geng S, Pan A.** 2020. Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-19. J Infect doi:10.1016/j.jinf.2020.03.039.

15. **Shang L, Zhao J, Hu Y, Du R, Cao B.** 2020. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet **395:**683-684.

16. **Alhazzani W, Moller MH, Arabi YM, Loeb M, Gong MN, Fan E, Oczkowski S, Levy MM, Derde L, Dzierba A, Du B, Aboodi M, Wunsch H, Cecconi M, Koh Y, Chertow DS, Maitland K, Alshamsi F, Belley-Cote E, Greco M, Laundy M, Morgan JS, Kesecioglu J, McGeer A, Mermel L, Mammen MJ, Alexander PE, Arrington A, Centofanti JE, Citerio G, Baw B, Memish ZA, Hammond N, Hayden FG, Evans L, Rhodes A.** 2020. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Crit Care Med doi:10.1097/CCM.0000000000004363.

17. **Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, Edwards KM, Gandhi R, Muller WJ, O'Horo JC, Shoham S, Murad MH, Mustafa RA, Sultan S, Falck-Ytter Y.** 2020. Infectious

Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Clin Infect Dis doi:10.1093/cid/ciaa478.

18. **Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B.** 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet **395:**497-506.

19. **Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, Hlh Across Speciality Collaboration UK.** 2020. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet **395:**1033-1034.

20. **Wang Y, Jiang W, He Q, Wang C, Wang B, Zhou P, Dong N, Tong Q.** 2020. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia. Signal Transduct Target Ther **5:**57.

589 **Table 1. Baseline demographic and clinical characteristics of the patients**

590 **in both cohorts**

N=463	STEROIDS Cohort (N=396)	CONTROL Cohort (N=67)	p value
Gender (Men), n (%)	276 (69.7)	41 (61.2)	0.200
Age, Mean (SD)	65.4 (12.9)	68.1 (15.7)	0.132
Charlson score, Mean (SD)	2.0 (2.3)	2.3 (2.6)	0.389
Underlying Medical Conditions, n (%)	306 (77.3)	53 (79.1)	0.874
High Blood pressure	182 (46.0)	32 (47.8)	0.793
Ischemic heart disease	72 (18.2)	12 (17.9)	0.957
Diabetes	84 (21.2)	13 (19.4)	0.871
Obesity	29 (7.3)	6 (9.0)	0.619
Dyslipidemia	113 (28.5)	22 (32.8)	0.471
Cardiovascular risk factors	249 (63.2)	48 (71.6)	0.215
Chronic kidney disease	24 (6.1)	4 (6.0)	0.977
Onco-hematologic	49 (12.4)	16 (23.9)	***0.021***
COPD	71 (17.9)	10 (14.9)	0.607
Transplant (SOT/SCT)	9 (2.3)	1 (1.5)	0.685
Neurologic	35 (8.8)	11 (16.4)	0.074
Rheumatologic	14 (3.5)	1 (1.5)	0.707
Hepatic	10 (2.5)	5 (7.5)	0.051
Peptic Ulcer disease	3 (0.8)	3 (4.5)	***0.013***
Thromboembolic disease	5 (1.3)	3 (4.5)	0.062
Thyroid disorders	15 (3.8)	5 (7.5)	0.189

Immunosuppression	37 (9.4)	4 (6.0)	0.171
Clinical symptoms at admission, n (%)			
Cough	312 (79.6)	44 (65.7)	***0.017***
Fever	353 (90.3)	56 (83.6)	0.131
Dyspnea	272 (69.2)	42 (62.7)	0.321
Gastrointestinal	92 (23.2)	13 (19.4)	0.532
Sore throat	22 (5.6)	4 (6.0)	0.780
Anosmia/ageusia	28 (7.1)	5 (7.5)	0.802
Myalgia	82 (20.7)	12 (17.9)	0.743
Headache	29 (7.3)	4 (6.0)	0.691
Fatigue	63 (15.9)	15 (22.4)	0.216
Chest pain	23 (5.8)	3 (4.5)	0.662
Rash	2 (0.5)	0	0.560
Increased sputum production	6 (1.5)	5 (7.5)	***0.013***
Confusion	18 (4.7)	10 (15.4)	***0.003***
Days from onset of symptoms to diagnosis, Mean (SD)	8.5 (5.1)	6.9 (3.9)	***0.021***
Days from onset of symptoms to hospital admission, Mean (SD)	7.6 (4.2)	7.0 (3.7)	0.231
Days from onset of symptoms to therapy, Mean (SD)	7.4 (4.1)	7.1 (3.6)	0.506
Days from onset of symptoms to inclusion, Mean (SD)	10.8 (4.8)	8.7 (4.4)	***0.002***
Treatment, n (%)			
Hydroxychloroquine	393 (99.5)	62 (92.5)	***0.001***

Lopinavir/Ritonavir	287 (73.0)	42 (62.7)	0.106
Azithromycin	208 (53.9)	29 (43.9)	0.144
Interferon	186 (47.6)	28 (41.8)	0.427
Tocilizumab	177 (44.9)	12 (18,5)	***< 0.001***
Anakinra	8 (2.0)	0	0.241
Other treatments*	65 (16.4)	20 (29.9)	***0.009***
PaO2/FiO2, Mean (SD)	263 (112.1)	267 (78.9)	0.878
SatO2/FiO2, Mean (SD)	286 (123.0)	244 (91.9)	***0.021***
Brescia-COVID19 ≥2, n (%)	77 (17.4)	16 (23.9)	0.411
ARDS, n (%)			
No	156 (39.4)	9 (13.4)	***< 0.001***
Mild	96 (24.2)	43 (64.2)	
Moderate	116 (29.3)	15 (22.4)	
Severe	28 (7.1)	0	
Admitted to ICU at D0	30 (7.6%)	0	***0.013***
Laboratory (day 0), Mean (SD)			
Lymphocyte counts	1,004 (1,354)	1,190 (1,042)	0.342
Lactate dehydrogenase	396 (154)	338 (117)	***0.018***
D- Dimer	2.5 (7.6)	2.1 (4.6)	0.741
C-reactive protein	141 (85)	122 (76)	0.157
Ferritin	1,353 (2.220)	763 (1.008)	0.347
Interleukin 6 (IL-6)	196 (228)	62 (62)	***0.039***
Chest CT (at hospital admission), n (%)			
Normal imaging	16 (4.1)	2 (3.1)	***0.033***
Unilateral pneumonia	29 (7.5)	12 (18.5)	

Bilateral interstitial pneumonia	217 (55.8)	27 (41.5)
Patchy bilateral pneumonia	93 (23.9)	16 (24.6)
Confluent bilateral pneumonia	34 (8.7)	8 (12.3)

*Including DRVr/ doxycycline/ clarithromycin and other antibiotics

COPD: chronic obstructive pulmonary disease; SOT: solid organ transplantation; SCT: stem cell transplantation; D0: day 0; SD: standard deviation; N/A: non-applicable; PaO2/FiO2: arterial oxygen tension/inspiratory oxygen fraction; SatO2/FiO2: oxygen saturation /inspiratory oxygen fraction; ARDS: acute respiratory distress syndrome; ICU: intensive care unit; Brescia-COVID19: respiratory severity scale Brescia-COVID-19; CT: computed tomography scan; IL-6: Interleukin 6; DRVr: ritonavir-boosted darunavir.

592 **Table 2. Association between steroid treatment and mortality in patients**
593 **with SARS-COV-2 Infection, according to steroid exposure and steroid**
594 **regimen**

Steroid Exposure	Survivors (N = 392)	Non-survivors (N = 71)	HR (95% CI)	*p* value
No corticosteroid treatment	51 (76.1%)	16 (23.9%)	0.514 (0.274-0.965)	***0.038****
Steroid treatment	341 (86.1%)	55 (13.9%)		
Steroid treatment (adjusted by PSM)			0.360 (0.139-0.932)	***0.035****
Steroid Regimen				
1 mg/kg/day	268 (86.5%)	42 (13.5%)	0.880 (0.449-1.726)	0.710**
Pulses	73 (84.9%)	13 (15.1%)		

595 *No steroids compared to steroid treatment (any regimen); **Initial 1mg/kg/day compared to
596 initial steroid pulses
597 PSM: propensity score matching

598 **Table 3. Univariable and multivariable analyses of factors associated with hospital mortality in patients with SARS-**

599 **COV-2 Infection.**

Variables	Univariable analysis		Multivariable analysis		Multivariable adjusted according to propensity score	
	OR (95% CI)	p value	OR (95% CI)	p-value	OR (95% CI)	p value
Age	1.12 (1.08-1.15)	***<0.001***	1.13 (1.08-1.18)	***0.048***	1.11 (1.05-1.18)	**<0.001**
Age-adjusted Charlson score	1.34 (1.21-1.49)	***<0.001***				
Underlying medical conditions	3.6 (1.5-8.6)	***0.002***				
High Blood pressure	3.1 (1.8-5.3)	***<0.001***				
Ischemic heart disease	3.1 (1.7-5.4)	***<0.001***				
Diabetes	2.8 (1.6-4.9)	***<0.001***				
Dyslipidemia	2.0 (1.2-3.4)	***0.011***				
Cardiovascular risk factors	2.5 (1.4-5.7)	***0.003***				
Chronic kidney disease	9.2 (4.1-20.5)	***<0.001***	29.13 (7.93-107.03)	***<0.001***	43.28 (6.90-273.87)	***<0.001***
Onco-hematologic	2.5 (1.3-4.6)	***0.005***				
Transplant (SOT/SCT)	8.9 (2.5-32.6)	***0.001***				
Neurologic	3.1 (1.6-6-1)	***0.002***				

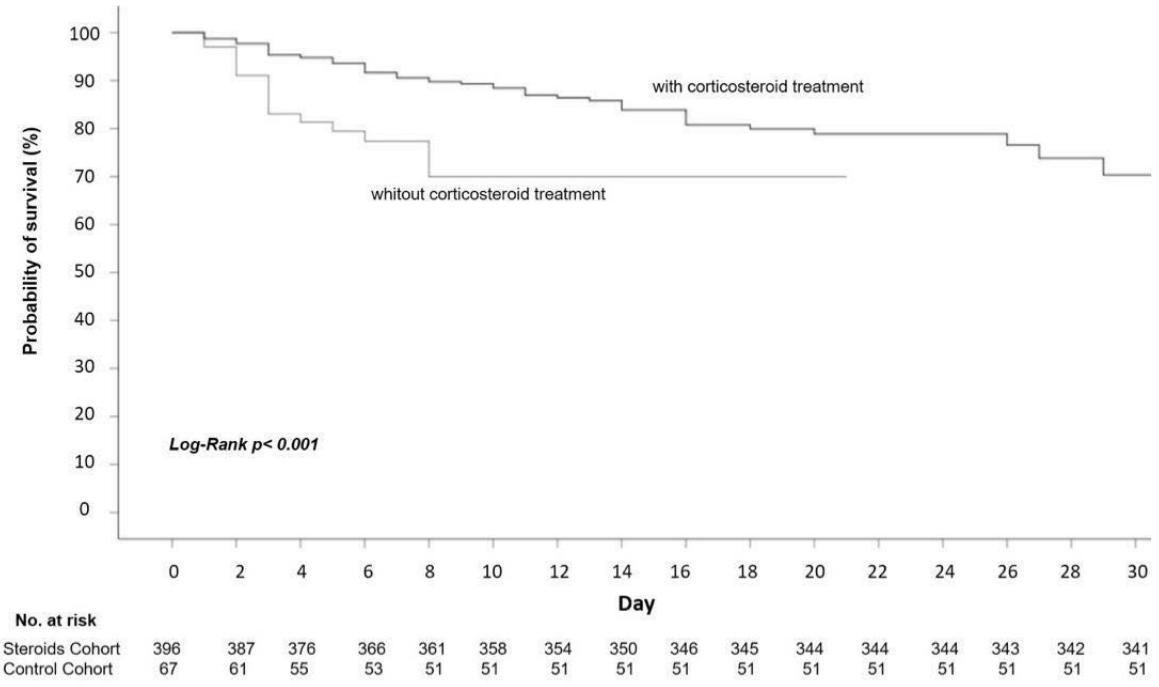
Hydroxychloroquine	0.13 (0.28-0.59)	***0.013***				
Lopinavir/Ritonavir	0.42 (0.25-0.70)	***0.001***				
PaO2/FiO2 (on D0)	0.99 (0.98-0.99)	***<0.001***				
SatO2/FiO2 (on D0)	0.99 (0.991-0.998)	***<0.001***				
ARDS	1.77 (1.01-3.09)	***0.046***	2.00 (1.14-3.51)	***0.015***	1.17 (0.51-2.67)	0.714
Lactate dehydrogenase (on D0)	1.003 (1.001-1.005)	***0.001***	1.004 (1.00-1.01)	***0.002***	1.001 (1.00-1.01)	***0.012***
D Dimer (on D0)	1.04 (1.00-1.07)	***0.036***				
C-reactive protein (on D0)	1.004 (1.001-1.008)	***0.011***				
Steroid treatment	0.51 (0.27-0.96)	***0.044***	0.34 (0.12-0.99)	***0.048***	0.19 (0.05-0.74)	***0.016***

SOT: solid organ transplantation; SCT: stem cell transplantation; D0: day 0; PaO2/FiO2: arterial oxygen tension/inspiratory oxygen fraction; SatO2/FiO2: oxygen saturation /inspiratory oxygen fraction; ARDS: acute respiratory distress syndrome

603 **Figure legends.**

604 Figure 1. Probability of survival from D0 to hospital discharge of patients with
605 SARS-COV-2 infection, according to steroid exposure.

606 Figure 2. Forest plot of stratified analyses for in-hospital mortality showing the
607 adjusted odds ratio of corticosteroid treatment. The subgroups were classified
608 by demographic and disease characteristics.



No. at risk																
Steroids Cohort	396	387	376	366	361	358	354	350	346	345	344	344	344	343	342	341
Control Cohort	67	61	55	53	51	51	51	51	51	51	51	51	51	51	51	51