PLOS ONE

RESEARCH ARTICLE

Efficacy of corticosteroids in non-intensive care unit patients with COVID-19 pneumonia from the New York Metropolitan region

Monil Majmundar[1]*, Tikal Kansara[1], Joanna Marta Lenik[1], Hansang Park[1], Kuldeep Ghosh[1], Rajkumar Doshi[2], Palak Shah[1], Ashish Kumar[3], Hossam Amin[4], Shobhana Chaudhari[1], Imnett Habtes[4]

1 Department of Internal Medicine, Metropolitan Hospital, New York Medical College, New York, NY, United States of America, **2** Department of Internal Medicine, Reno School of Medicine, University of Nevada, Reno, NV, United States of America, **3** Department of Critical Care Medicine, St John's Medical College Hospital, Bengaluru, Karnataka, India, **4** Department of Internal Medicine, Division of Pulmonary and Critical Care, Metropolitan Hospital, New York Medical College, New York, NY, United States of America

* monilmajmundar1804@gmail.com

Citation: Majmundar M, Kansara T, Lenik JM, Park H, Ghosh K, Doshi R, et al. (2020) Efficacy of corticosteroids in non-intensive care unit patients with COVID-19 pneumonia from the New York Metropolitan region. PLoS ONE 15(9): e0238827. https://doi.org/10.1371/journal.pone.0238827

Editor: Muhammad Adrish, BronxCare Health System, Affiliated with Icahn School of Medicine at Mount Sinai, NY, USA, UNITED STATES

Received: July 14, 2020

Accepted: August 25, 2020

Published: September 9, 2020

Data Availability Statement: Data underlying the study cannot be made publicly available due to ethical restrictions imposed by the Metropolitan Hospital ethics committee (STAR). Data will be made available upon request to qualified researchers, with requests sent to Ms. Christina Pili, christina.pili@nychhc.org.

Funding: The author(s) received no specific funding for this work.

Abstract

Introduction

The role of systemic corticosteroid as a therapeutic agent for patients with COVID-19 pneumonia is controversial.

Objective

The purpose of this study was to evaluate the effect of corticosteroids in non-intensive care unit (ICU) patients with COVID-19 pneumonia complicated by acute hypoxemic respiratory failure (AHRF).

Methods

This was a single-center retrospective cohort study, from 16th March, 2020 to 30th April, 2020; final follow-up on 10th May, 2020. 265 patients consecutively admitted to the non-ICU wards with laboratory-confirmed COVID-19 pneumonia were screened for inclusion. 205 patients who developed AHRF ($SpO_2/FiO_2 \leq 440$ or $PaO_2/FiO_2 \leq 300$) were only included in the final study. Direct admission to the Intensive care unit (ICU), patients developing composite primary outcome within 24 hours of admission, and patients who never became hypoxic during their stay in the hospital were excluded. Patients were divided into two cohorts based on corticosteroid. The primary outcome was a composite of ICU transfer, intubation, or in-hospital mortality. Secondary outcomes were ICU transfer, intubation, in-hospital mortality, discharge, length of stay, and daily trend of SpO_2/FiO_2 (SF) ratio from the index date. Cox-proportional hazard regression was implemented to analyze the time to event outcomes.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: COVID-19, Coronavirus disease 2019; AHRF, Acute Hypoxemic Respiratory Failure; ICU, Intensive Care Unit; SF ratio, SpO_2/FiO_2 ratio.

Result

Among 205 patients, 60 (29.27%) were treated with corticosteroid. The mean age was ~57 years, and ~75% were men. Thirteen patients (22.41%) developed a primary composite outcome in the corticosteroid cohort vs. 54 (37.5%) patients in the non-corticosteroid cohort (P = 0.039). The adjusted hazard ratio (HR) for the development of the composite primary outcome was 0.15 (95% CI, 0.07–0.33; P <0.001). The adjusted hazard ratio for ICU transfer was 0.16 (95% CI, 0.07 to 0.34; P < 0.001), intubation was 0.31 (95% CI, 0.14 to 0.70; P– 0.005), death was 0.53 (95% CI, 0.22 to 1.31; P– 0.172), composite of death or intubation was 0.31 (95% CI, 0.15 to 0.66; P– 0.002) and discharge was 3.65 (95% CI, 2.20 to 6.06; P<0.001). The corticosteroid cohort had increasing SpO_2/FiO_2 over time compared to the non-corticosteroid cohort who experience decreasing SpO_2/FiO_2 over time.

Conclusion

Among non-ICU patients hospitalized with COVID-19 pneumonia complicated by AHRF, treatment with corticosteroid was associated with a significantly lower risk of the primary composite outcome of ICU transfer, intubation, or in-hospital death, composite of intubation or death and individual components of the primary outcome.

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the RNA virus that causes coronavirus disease 2019 (COVID-19). This virus is responsible for a spectrum of disease presentation, which ranges from asymptomatic infection to severe pneumonia, respiratory failure, and death [1]. To date, SARS-CoV-2 has caused a significant degree of morbidity and mortality within the United States, with a large proportion of these cases concentrated in New York City [1]. Given the novelty of this virus, there is limited data on treating these patients. As a result, management protocols vary and are rapidly evolving with emerging data and clinical experiences.

The use of systemic corticosteroids in the management of COVID-19 infection is widely debated. The use of corticosteroids with influenza pneumonia has previously been associated with a higher risk of death [2,3] and delayed viral clearance during Severe Acute Respiratory Syndrome-related coronavirus (SARS) and Middle East Respiratory Syndrome (MERS) outbreaks [4–6]. Alternatively, few studies supported the use of corticosteroids at a low-to-moderate dose in patients with coronavirus and Influenza A (H1N1) and SARS pneumonia [7,8]. On the other hand, the World Health Organization has recommended against routine use of systemic corticosteroids to patients with COVID-19 [9]; nevertheless, a consensus statement by the Chinese Thoracic Society recommends judicious use of corticosteroids in these patients [10]. Recently, RECOVERY trial demonstrated the beneficial clinical effect of dexamethasone among patients with COVID-19 who required oxygen with and without invasive mechanical ventilation [11].

Although RECOVERY trial demonstrated a beneficial effect of dexamethasone on mortality, there are no other analogous studies that have reproduced similar results, and the current study is unique in terms of dose, duration, and type of corticosteroids used. We performed a retrospective cohort study on patients admitted to the general inpatient wards with a diagnosis of COVID-19 pneumonia complicated by acute hypoxemic respiratory failure. The purpose of

this study was to determine the clinical efficacy of corticosteroids on outcomes of intensive care unit (ICU) transfer, intubation, in-hospital death, discharge, and length of stay. We hypothesized that systemic corticosteroid use would be associated with a lower risk of a composite endpoint of ICU transfer, intubation, or death.

Methods

Study population

This is a retrospective cohort study of confirmed cases of COVID-19 pneumonia hospitalized at Metropolitan Hospital Center serving the East Harlem community in New York City. All patients were diagnosed with COVID-19 pneumonia as per the World Health Organization's interim guidance document [12]. We collected information on consecutive patients admitted to the general wards in Metropolitan Hospital from March 15, 2020, to April 30, 2020, as per our inclusion and exclusion criteria. The ethics committee of New York City Health and Hospital (STAR) and BRANY institution review board approved this study and permitted a waiver of informed consent from the study participant. We accessed the hospital databases from May 1st to 10th, 2020.

Patients were eligible for the study if they met the following inclusion criteria 1) Age $\geq$ 18 years old, 2) Confirmed cases of SARS-CoV-2 by PCR method, 3) Admitted in general wards, 4) PaO2/FiO2 (PF) ratio $<$300 if arterial blood gas was available or SpO_2/Fio_2 (SF) ratio $<$440, 5) Bilateral infiltrate on chest imaging validated by radiology staff. The exclusion criteria were 1) Patients with severe immunosuppression (HIV infection, long term use of immunosuppressive agents), 2) Pregnant woman or Lactating women, 3) Oral glucocorticoids were needed for other diseases, 4) Direct admission to intensive care unit (ICU), 5) if had any of primary composite outcome within first 24 hours of admission, 6) Patient who never required oxygen during the hospital course, 7) Patients who left against medical advice.

Procedure

A team of resident physicians reviewed and collected demographic, laboratory, clinical, and outcomes data from electronic medical records between March 15 and April 30, 2020. The inclusion criteria, exclusion criteria, individual components of all definitions of clinical outcomes were recorded separately and checked by two authors (M.M. and I.H.) (**S1 Table**). Two independent residents adjudicated all the outcome data, and any disparity was resolved by consulting the primary investigator. Patient confidentiality was protected by allocating a deidentified patient identification, and the electronic data was stored in a locked, password-protected computer.

Nasopharyngeal swab samples were obtained from all patients at admission and tested using real-time reverse transcriptase-polymerase chain reaction assays at LabCorp laboratory to identify SARS-CoV-2 infected patients. The decision to give corticosteroids was at the discretion of the treating physician. All corticosteroid dosages were converted to the equivalent dose of methylprednisolone [13,14]. The calculation of the SF ratio and PF ratio has been elaborated in the **S1 File**. In the study, the index date was not taken as the date of admission. In the non-corticosteroid cohort, the index date was taken as the date when the patient's SF ratio went below 440, or the PF ratio went below 300. For the corticosteroid cohort, the date when corticosteroid was started was taken as the index date.

Outcomes

Our primary outcome was the composite outcome of intensive care unit (ICU) transfer, intubation, or death. Secondary outcomes were discharge, intensive care unit transfer, intubation,

death, composite of intubation or death, length of stay, and a daily trend of SF ratio since the index date.

Statistical analysis

Baseline characteristics of both cohorts were expressed using descriptive statistics. The continuous variables were exhibited as a mean ± standard deviation or a median with interquartile range (IQR) for normal and non-normal distribution, respectively. Categorical variables were extrapolated in frequency and proportions. The t-test and Mann-Whitney-Wilcoxon tests were applied for normal and non-normal distribution, respectively, to compare continuous variables between two cohorts. Fisher's exact test or Pearson's chi^2 tests were implemented to compare categorical variables.

Time to event (composite primary outcome and secondary outcomes) was defined as the time from the index date of the study to the specified events. We used the cox-proportional hazard model to determine univariable and multivariable hazard ratio (HR) and 95% confidence interval (CI) for the corticosteroid group compared with non-corticosteroid group on the development of composite primary outcome, ICU transfer, intubation, death, composite of intubation or death, and discharge. The multivariable cox-proportional model included SF ratio, age, gender, chronic lung disease, white blood cell count, platelet count, tocilizumab, and therapeutic dose of Enoxaparin (for the construction of multivariate model–**S2 File**). We applied the test for proportionality assumption based on the Schoenfeld Residuals. For the primary outcome and other secondary outcomes, we constructed Kaplan-Meier curves and used the log-rank test to compare. Censoring was applied on the day of discharge. Linear regression was used to show the difference between the length of stay between two cohorts. Mixed-effects linear regression with restricted maximum likelihood was used to perform a longitudinal analysis to assess the trend of SF ratio over time between two cohorts. The fixed-effect constant was suppressed, and unstructured residual errors were generated. A likelihood ratio test vs. linear model chi-square test was used to assess the appropriateness of using a multilevel model. Margins were calculated to display predicted probabilities. Missing data were not imputed. All tests were 2-sided, and a P-value less than 0.05 was considered statistically significant. All analyses were performed with STATA software, version 16.0 (StataCorp LLC).

Result

Study population

We screened 265 consecutive patients admitted to the Metropolitan Hospital, New York Medical College, from March 15 to April 30, 2020, and included 205 patients in the final analysis of the study. The date of the final follow-up was May 10, 2020. The mean age of the entire cohort was 57.61±15.86 years, 153 (74.63%) patients were male, and 149 (73.04%) patients were of Hispanic ethnicity/race. The common comorbidities were hypertension (103, 50.24%), obesity (84, 42%), and diabetes (83, 40.49%) (**Table 1**). At the time of analysis, a total of 14 patients (out of 205) were still admitted to the hospital. Of 205 patients, 60 (29.27%) patients received systemic corticosteroids, and 145 (70.73%) patients did not receive it.

Corticosteroid cohort

Patients in the corticosteroid cohort received systemic corticosteroids in the form of methylprednisolone (n = 29, 48.33%), prednisone (n = 10, 16.67%), hydrocortisone (n = 1, 1.67%), and dexamethasone (n = 20, 33.33%). Corticosteroid was commenced at a median of 2 days (IQR, 1–5) following admission, on a median or equivalent dose of 80 mg per day (IQR, 60–

Table 1. Demographic, laboratory characteristics, and outcomes by corticosteroids.

	Total (N = 205)	Corticosteroids (N = 60)	Without corticosteroids (N = 145)	P-value
Demographic Characteristics				
Age, mean (SD)	57.61 (15.86)	58.67 (13.35)	57.18 (16.81)	0.543
Sex, n (%)				**0.011**
Male	153 (74.63)	52 (86.67)	101 (69.67)	
Female	52 (25.37)	8 (13.33)	44 (30.34)	
Ethnicity/Race, n (%)				0.476
Hispanic	149 (73.04)	46 (77.97)	103 (71.03)	
Non-Hispanic African American	29 (14.22)	5 (8.47)	24 (16.55)	
Non-Hispanic White	8 (3.92)	3 (5.08)	5 (3.45)	
Others	18 (8.82)	5 (8.47)	13 (8.97)	
Comorbidities				
Obesity, n (%)	84 (42)	18/59 (30.51)	66/141 (46.81)	**0.033**
BMI (kg/m^2), median (IQR)	28.7 (25–33.47)	26.7 (23.1–31.8)	29.34 (25–34.64)	**0.035**
Hypertension, n (%)	103 (50.24)	35 (58.33)	68 (46.90)	0.136
Diabetes Mellitus, n (%)	83 (40.49)	23 (38.33)	60 (41.38)	0.686
Chronic Lung disease, n (%)	32 (15.61)	11 (18.33)	21 (14.48)	0.489
Cancer, n (%)	10 (4.88)	1 (1.67)	9 (6.21)	0.170
Coronary Disease, n (%)	23 (11.22)	5 (8.33)	18 (12.41)	0.40
Heart Failure, n (%)	7 (3.41)	2 (3.33)	5 (3.45)	0.967
Clinical Parameters				
PaO2/FiO2, median (IQR)[$]	239.29 (152–277.78)	136.36 (65.13–218.97)	261.91 (219.04–280.95)	<**0.001**
SpO2/FiO2, median (IQR)	328.57 (213.64–409.52))	190 (92.5–298.44)	339.29 (278.13–419.05)	<**0.001**
SOFA score < 5, n (%)		53 (88.33)	120 (82.76)	0.40
SOFA score ≥ 5, n (%)		7 (11.67)	25 (17.24)	
Medications				
Corticosteroid[#], median (IQR)				-
Initiation from admission (Days)		2 (1–5)	-	
Dose (mg/day)		80 (60–107)	-	
Duration (Days)		5 (4–7)	-	
Total Dose (mg)		400 (240–642)	-	
Hydroxychloroquine, n (%)	201 (98.05)	57 (95)	144 (99.31)	**0.076**
Tocilizumab, n (%)	18 (8.78)	11 (18.33)	7 (4.83)	**0.002**
Enoxaparin therapeutic dose, n (%)	76 (37.07)	40 (66.67)	36 (24.83)	<**0.001**
Laboratory Parameters				
Hb (g/dL), mean (SD)	12.84 (2.10)	13 (1.77)	12.78 (2.23)	0.492
WBC (x10^3/ μL), median (IQR)	7.92 (5.97–10.8)	8.61 (6.42–12.03)	7.68 (5.8–10.48)	0.107
Absolute Lymphocyte Count (x10^3/ μL), median (IQR)	0.89 (0.64–1.25)	0.84 (0.63–1.24)	0.92 (0.65–1.31)	0.427
Platelets (x10^9/L), median (IQR)	211 (163–301)	278.5 (185–338.50)	200 (157–260)	<**0.001**
GFR (ml/min/1.73m^2), median (IQR)	77.3 (50–112.5)	70.10 (60–105.60)	79 (41–113.90)	0.939
AST (units/L), median (IQR)	46.50 (34–65)	55 (36–72)	44 (33–61)	**0.048**
ALT (units/L), median (IQR)	33 (21–64)	42 (23–95)	32 (21–54)	0.058
Inflammatory Markers				
Procalcitonin (ng/mL), median (IQR), (N = 160)	0.33 (0.17–0.73)	0.42 (0.17–0.89)	0.29 (0.16–0.60)	0.301
Ferritin (ng/mL), median (IQR), (N = 150)	987 (529–1685)	1002 (652–1774)	982 (457–1631)	0.291
LDH (U/L), median (IQR), (N = 148)	404 (300.47–485.5)	449 (325–540)	386 (297–475)	0.068
D-Dimer (ng/dL), median (IQR), (N = 164)	443 (261–1196)	653.5 (347.5–2065.5)	377 (235.50–1015)	**0.004**
C-Reactive Protein (mg/dL), median (IQR), (N = 135)	16.24 (7.36–24.38)	21 (9.76–29.34)	12.1 (6.65–22.19)	**0.005**

(*Continued*)

Table 1. (Continued)

	Total (N = 205)	Corticosteroids (N = 60)	Without corticosteroids (N = 145)	P-value
IL-6 (pg/ml), median (IQR), (N = 36)	87.25 (28.90–146.25)	65 (25.80–104)	116 (89.30–182.10)	0.084
Outcomes, n (%)				
ICU transfer/Intubation /Death, (N = 202)	67 (33.17)	13 (22.41)	54 (37.50)	**0.039**
Intubation/Death, (N = 202)	59 (29.21)	13 (22.41)	46 (31.94)	0.178
ICU Transfer, (N = 202)	59 (29.21)	12 (20.69)	47 (32.64)	0.091
Intubation, (N = 200)	47 (23.50)	11 (18.97)	36 (25.35)	0.334
Death, (N = 191)	42 (21.99)	8 (14.55)	34 (25)	0.114
Discharge, (N = 191)	149 (78.01)	47 (85.45)	102 (75)	0.114
Length of stay (days), median (IQR), (N = 191)	8 (5–15)	9 (6–17)	7 (5–13.50)	**0.025**

Abbreviations: BMI–Body Mass Index, Hb–Hemoglobin, WBC–white blood cell, PaO2 –Partial Pressure of Arterial Oxygen, SpO2 = Saturation of oxygen from Pulse oximeter, AST–Aspartate Transferase, ALT–Alanine Transferase, LDH–Lactate Dehydrogenase, IL-6 –Interleukin-6, ICU–Intensive Care Unit, SOFA–Sequential organ failure assessment, IQR–Interquartile range

$—calculated by converting SpO_2 to PaO_2, then diving by FiO_2

#—includes Hydrocortisone, Prednisone, Methylprednisolone, Dexamethasone

https://doi.org/10.1371/journal.pone.0238827.t001

107) of Methylprednisolone (equivalent to 12 (IQR, 9–16) mg of dexamethasone) for a median duration of 5 days (IQR, 4–7) (Table 1).

Comparison of the cohort with and without corticosteroid

Table 1 demonstrates the baseline characteristics and outcomes of the study population separated by corticosteroid treatment. Mean patient age was similar in both the cohorts (corticosteroids, 58.67±13.35 years; non-corticosteroid, 57.18±16.81 years, [P = 0.543]). The corticosteroid cohort had more male patients as compared with the non-corticosteroid cohort (NCC) (86.67% vs. 69.97%, P = 0.011). There was no difference in the distribution of Hispanics race/ethnicity between two cohorts (corticosteroid, 77.97% vs. non-corticosteroid, 71.03%; P = 0.48). Patients among the NCC were more obese than the corticosteroid cohort (46.81% vs. 30.51%, P = 0.033). The prevalence of other comorbidities was similar across both cohorts. Patients in the corticosteroid cohort had a low median SpO_2/FiO_2 (SF ratio) of 190 (IQR, 92.5–298.44) compared with the median SF ratio of 339.29 (IQR, 278.13–419.05) in the non-corticosteroid cohort ($P < 0.001$). More percentage of patients in the corticosteroid cohort received Tocilizumab and therapeutic dose of enoxaparin compared with the non-corticosteroid cohort (18.33% vs. 4.83%, P = 0.002; 66.67% vs. 24.83%, P = <0.001, respectively). Among the laboratory parameters, median platelet counts (278.5 vs. 200, P = <0.001), and median AST (55 vs. 44, P = 0.048) were higher in corticosteroid cohort compared to non-corticosteroid cohort. Among inflammatory markers, a median D-Dimer (653.5 vs. 377, P = 0.004) and C-reactive protein (21 vs. 12.1, P = 0.005) were higher in corticosteroid cohort compared to NCC.

Comparison of patients with and without composite primary outcome

A comparison of demographic, clinical, and laboratory parameters of patients with and without the composite primary outcome is demonstrated in Table 2. Patients with the primary outcome were older (64.52±15.46 vs. 53.78±14.78; OR = 1.62 per 10 years of age; 95% CI, 1.30–2.01; P <0.001), more hypertensive (67.16% vs. 40.74%; OR = 2.98; 95% CI, 1.61–5.5; P = 0.001) and had more coronary artery disease (20.9% vs. 5.19%; OR = 4.83; 95% CI, 1.85–12.64; P = 0.001). Patients with the primary outcome were more hypoxemic as indicated by

Table 2. Clinical and laboratory indices of patients with and without composite primary outcome (ICU transfer or intubation or death).

	Primary Outcome (N = 67)	Without Primary Outcome (N = 135)	Odds Ratio (95% CI)	P-value
Demographic Characteristics				
Age, mean (SD)	64.52 (15.46)	53.78 (14.78)	**1.62 (1.30–2.01)***	**<0.001**
Sex, n (%)				0.348
Male	47 (70.15)	103 (76.30)	0.73 (0.38–1.41)	
Female	20 (29.85)	32 (23.70)	Reference	
Ethnicity/Race, n (%)				
Hispanic	51 (76.12)	96 (71.64)	1.29 (0.66–2.54)	0.452
Comorbidities				
Obesity, n (%)	26 (39.39)	57 (43.51)	0.84 (0.46–1.54)	0.581
BMI (kg/m^2), median (IQR)	28.88 (25–31.39)	28.64 (24.86–34.83)	0.99 (0.95–1.04)	0.740
Hypertension, n (%)	45 (67.16)	55 (40.74)	**2.98 (1.61–5.5)**	**0.001**
Diabetes Mellitus, n (%)	30 (44.78)	51 (37.78)	1.34 (0.74–2.42)	0.34
COPD/Asthma, n (%)	14 (20.9)	18 (13.33)	1.71 (0.8–3.71)	0.169
Cancer, n (%)	5 (7.46)	4(2.96)	2.64 (0.69–10.18)	0.158
CAD, n (%)	14 (20.9)	7 (5.19)	**4.83 (1.85–12.64)**	**0.001**
HF, n (%)	2 (2.99)	5 (3.70)	0.8 (0.15–4.24)	0.793
Clinical Parameters				
PaO2/FiO2, median$ (IQR)	192.86 (71.72–253.57)	256.25 (197.22–280.95)	**0.93 (0.89–0.96)***	**<0.001**
SpO2/FiO2, median (IQR)	240 (104.44–361.91)	339.29 (266.67–419.05)	**0.96 (0.93–0.98)***	**0.001**
SOFA score < 5, n (%)	50 (74.63)	120 (88.89)	Reference	**0.011**
SOFA score ≥ 5, n (%)	17 (25.37)	15 (11.11)	**2.72 (1.26–5.87)**	
Medications				
Corticosteroid#, median (IQR)				
Initiation from admission (Days)	3 (1–4)	2 (1–5)		
Number of patients, n(%)	13 (19.40)	45 (33.33)	**0.48 (0.24–0.97)**	**0.042**
Dose, (mg/day)	60 (53.5–80)	80 (60–107)		
Duration (Days)	6 (4–9)	5 (5–6)		
Total Dose (mg)	320 (192–642)	400 (240–640)		
Hydroxychloroquine, n (%)	67 (100)	131 (97.04)	NA	NA
Tocilizumab, n (%)	8 (11.94)	9 (6.67)	1.89 (0.70–5.17)	0.21
Enoxaparin therapeutic dose, n (%)	37 (55.22)	37 (27.41)	**3.27 (1.7–6.03)**	**<0.001**
Laboratory Parameters				
Hb (g/dL), mean (SD)	12.62 (2.33)	12.97 (1.96)	0.92 (0.8–1.06)	0.269
WBC (x10^3/ μL), median (IQR)	9.54 (6.16–12.99)	7.65 (5.8–9.76)	**1.12 (1.04–1.21)**	**0.003**
Absolute Lymphocyte Count (x10^3/ μL), median (IQR)	0.80 (0.58–1.12)	0.96 (0.69–1.36)	1.02 (0.78–1.32)	0.892
Platelets (x10^9/L), median (IQR)	194 (152–260)	229 (176–323)	**0.96 (0.93–0.99)***	**0.011**
GFR (ml/min/1.73m^2), median (IQR)	60 (34.6–85.5)	88.6 (60–120.4)	**0.87 (0.81–0.94)***	**<0.001**
AST (units/L), median (IQR)	47.5 (37.5–66)	45 (32–66)	1.03 (0.96–1.10)*	0.428
ALT (units/L), median (IQR)	30.5 (23.5–52)	34 (21–70)	0.94 (0.88–1.02)*	0.173
Inflammatory Markers				

(*Continued*)

Table 2. (Continued)

	Primary Outcome (N = 67)	Without Primary Outcome (N = 135)	Odds Ratio (95% CI)	P-value
Procalcitonin (ng/mL), median (IQR), (N = 157)	0.56 (0.25–1.36)	0.23 (0.13–0.56)	0.99 (0.94–1.07)	0.964
Ferritin (ng/mL), median (IQR), (N = 147)	1037 (821–1685)	918.5 (427–1690)	0.98 (0.85–1.12)***	0.731
LDH (U/L), median (IQR), (N = 145)	433.5 (347.5–532)	383 (289–471)	1.10 (0.94–1.30)**	0.212
D-Dimer (ng/dL), median (IQR), (N = 161)	878.5 (336–3372)	389 (238–798)	**1.05 (1.001–1.100)*** **	**0.045**
C-Reactive Protein (mg/dL), median (IQR), (N = 132)	21.53 (12.95–29.78)	11.2 (6.69–22.14)	**1.06 (1.02–1.1)**	**0.003**
IL-6 (pg/ml), median (IQR), (N = 35)	90.5 (32–161)	85.2 (25.8–131.5)	1.03 (0.97–1.08)*	0.385

Abbreviations: BMI–Body Mass Index, CAD–coronary artery disease, HF–Heart failure, Hb–Hemoglobin, WBC–white blood cell, PaO2 –Partial Pressure of Arterial Oxygen, SpO2 = Saturation of oxygen from Pulse oximeter, AST–Aspartate Transferase, ALT–Alanine Transferase, LDH–Lactate Dehydrogenase, IL-6 –Interleukin-6, ICU–Intensive Care Unit, SOFA–Sequential organ failure assessment, IQR–Interquartile range

*Per 10 unit Increase

**per 100 unit increase

***per 1000 unit increase

$—calculated by converting SpO_2 to PaO_2, then diving by FiO_2

#—includes Hydrocortisone, Prednisone, Methylprednisolone, Dexamethasone

https://doi.org/10.1371/journal.pone.0238827.t002

lower median SF ratio (240, IQR (104.44–361.91) vs. 339.29, IQR (266.67–419.05); OR = 0.96 per 10 unit increase; 95% CI, 0.93–0.98; P = 0.001), and more critically ill as indicated by more patient with ≥5 Sequential Organ Failure Assessment Score (SOFA) (25.37% vs. 11.11%; OR = 2.72, 95% CI, 1.26–5.87; P = 0.011). Amon primary outcome group, more patients received a therapeutic dose of Enoxaparin (55.22% vs. 27.41%; OR = 3.27; 95% CI 1.7–6.03; P <0.001). Patients with primary outcome had elevated median value of all inflammatory markers such as D-dimer (878.5, IQR (336–3372) vs. 389, IQR (238–798); OR = 1.05 per 1000 unit increase; 95% CI, 1.001–1.10; P = 0.045), and C-reactive protein (21.53, IQR (12.95–29.78) vs. 11.2, IQR (6.69–22.14); OR = 1.06; 95% CI, 1.02–1.10; P = 0.003).

Primary outcome (composite of ICU transfer, intubation or death)

Out of 202 eligible patients, 13 (22.41%) patients developed primary outcome in the corticosteroid cohort compared with 54 (37.5%) patients in the non-corticosteroid cohort (P = 0.039). In both unadjusted and adjusted analysis, patients who received corticosteroids were less likely to have had a primary outcome [(unadjusted hazard ratio, 0.45; 95% CI, 0.24 to 0.82; P—0.009), (Table 3, Fig 1, **Panel A**), (adjusted hazard ratio, 0.15; 95% CI, 0.07 to 0.33; P < 0.001) (Table 3)]. Proportionality assumption was not violated (global test P = 0.153).

Secondary outcomes

In the corticosteroid cohort, 12 (20.69%) patients were transferred to ICU as compared with 47 (32.64%) patients in the non-corticosteroid cohort (P = 0.09). In the unadjusted and adjusted Cox-analysis, patients who received corticosteroid were less likely to require ICU transfer [(unadjusted hazard ratio, 0.49; 95% CI, 0.26 to 0.93; P– 0.029), (adjusted hazard ratio, 0.16; 95% CI, 0.07 to 0.34; P < 0.001)] (Table 3, S1 Fig). In the corticosteroid cohort, 11 (18.97%) patients were intubated compared with 36 (25.35%) patients in the non-

Table 3. Unadjusted and model-adjusted risk of primary and secondary outcomes.

Outcomes	Model Type*	Univariable Estimate (95% CI)	P-Value	Multivariable Estimate (95% CI)	P-Value
		Steroid vs. Non-Steroid		Steroid vs. Non-Steroid	
Primary Outcome	Cox-proportional hazard	**0.45 (0.24–0.82)**	**0.009**	**0.15 (0.07–0.33)**	**<0.001**
Secondary Outcomes					
ICU transfer	Cox-proportional hazard	**0.49 (0.26–0.93)**	**0.029**	**0.16 (0.07–0.34)**	**<0.001**
Intubation	Cox-proportional hazard	0.66 (0.33–1.29)	0.221	**0.31 (0.14–0.70)**	**0.005**
Death	Cox-proportional hazard	0.62 (0.29–1.35)	0.228	**0.53 (0.22–1.31)**	**0.172**
Intubation/death	Cox-proportional hazard	0.60 (0.33–1.12)	0.108	**0.31 (0.15–0.66)**	**0.002**
Discharge	Cox-proportional hazard	1.17 (0.83–1.65)	0.380	**3.65 (2.20–6.06)**	**<0.001**
Length of stay (Days)	Linear regression	1.15 (-1.61 - +3.92)	0.41	-1.06 (-4.26 - +2.14)	0.515

Primary outcome is a composite of ICU transfer, intubation or death

*Models adjusted for SF ratio, age, gender, COPD, WBC, platelet count, tocilizumab and therapeutic dose of Enoxaparin

https://doi.org/10.1371/journal.pone.0238827.t003

corticosteroid cohort (P = 0.33). In the unadjusted and adjusted Cox-analysis, patients who received corticosteroid were less likely to require intubation [(unadjusted hazard ratio, 0.66; 95% CI, 0.33 to 1.29; P– 0.221), (adjusted hazard ratio, 0.31; 95% CI, 0.14 to 0.70; P– 0.005)] (**Table 3**, **S2 Fig**). In the corticosteroid cohort, 8 (14.55%) patients died compared with 34 (25%) patients in the non-corticosteroid cohort (P = 0.09). In the unadjusted and adjusted Cox-analysis, patients who received corticosteroid were less likely to die [(unadjusted hazard ratio, 0.62; 95% CI, 0.29 to 1.35; P– 0.228), (adjusted hazard ratio, 0.53; 95% CI, 0.22 to 1.31; P– 0.172)]; however, it was statistically non-significant (**Table 3**, **Fig 1**, **Panel B)**. In the corticosteroid cohort, 13 (22.41%) patients intubated or died compared with 46 (31.94%) patients in the non-corticosteroid cohort (P = 0.178). In the unadjusted and adjusted Cox-analysis, patients who received corticosteroid were less likely to have a composite of intubation or death events [(unadjusted hazard ratio, 0.60; 95% CI, 0.33 to 1.12; P– 0.108), (adjusted hazard ratio, 0.31; 95% CI, 0.15 to 0.66; P– 0.002)] (**Table 3**, **Fig 1**, **Panel C)**. In the corticosteroid cohort, 47 (85.45%) patients were discharged compared with 102 (75%) patients in non-corticosteroid cohort (P = 0.11). In the unadjusted and adjusted Cox-analysis, patients who had received corticosteroid had more likely to be discharged [(unadjusted hazard ratio, 1.17; 95% CI, 0.83 to 1.65; P– 0.380), (adjusted hazard ratio, 3.65; 95% CI, 2.20 to 6.06; P < 0.001)] (**Table 3**, **S3 Fig**). Proportionality assumptions were not violated for any of the secondary outcomes tested by Cox-regression. The median length of stay was higher in the corticosteroid cohort (9 days,

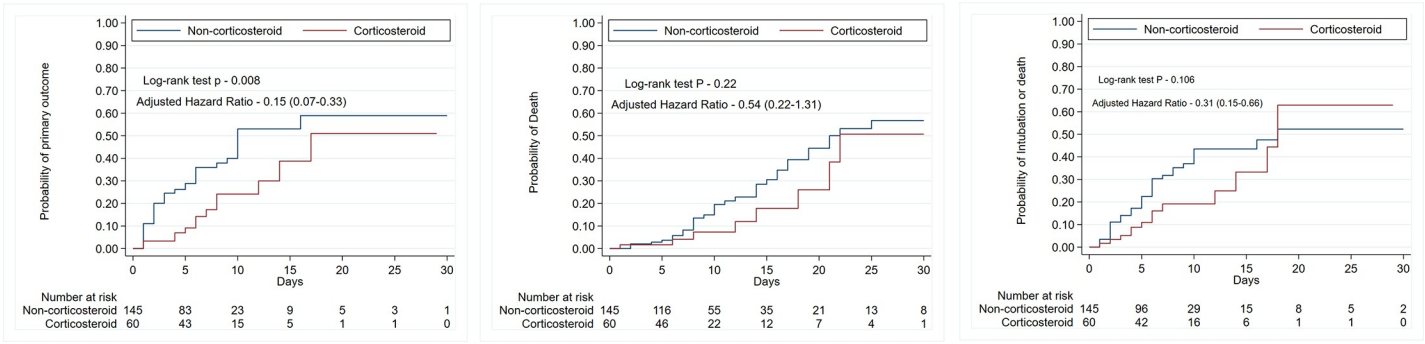

Fig 1. Kaplan-Meier curve of patients with non-severe COVID-19 pneumonia who received and did not receive corticosteroids. Panel (A) Primary Outcome. Primary outcome is a composite of ICU transfer, intubation or death. Panel (B) In-hospital Mortality. Panel (C) Composite of intubation or death.

https://doi.org/10.1371/journal.pone.0238827.g001

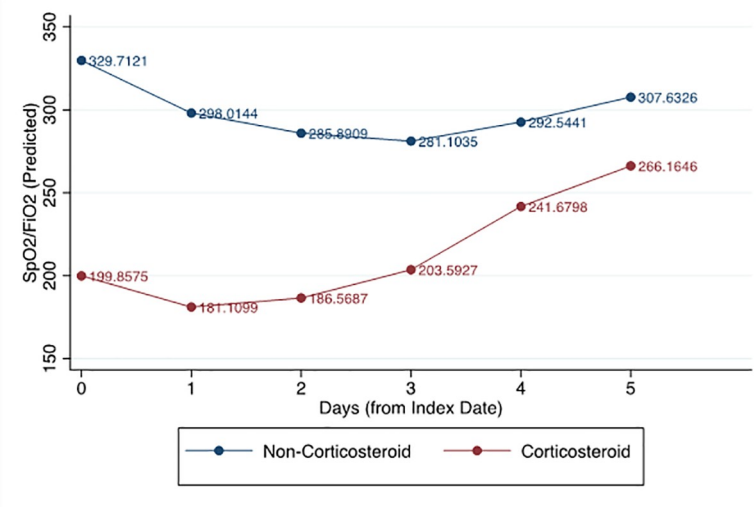

Fig 2. Comparison of trend of mean SpO_2/FiO_2 ratio since index date with and without corticosteroid.

https://doi.org/10.1371/journal.pone.0238827.g002

IQR (6–17)) compared to the non-corticosteroid cohort (7 days, IQR (5–13.5); P = 0.025) (**Tables 1 and 3**). Using multivariable linear regression, length of stay was lower in corticosteroid cohort but statistically non-significant (coefficient -1.06; 95% CI, -4.26 to 2.14; P = 0.515).

Daily trend of SpO_2/FiO_2 since the index date

Fig 2 demonstrates the comparison of a daily trend of SF ratio between patients with and without corticosteroids. The graph depicts that the corticosteroid cohort had lower baseline SF ratios (b = -185.97, p<0.001), SF ratio was found to increase over time (b = 24.48, p = 0.025). Furthermore, significant interactions between treatment and time demonstrated that the non-corticosteroid cohort experienced a decrease in SF ratio over time compared to the corticosteroid cohort, who were found to experience an increase in SF ratio over time. The likelihood ratio test vs. linear model chi-square test indicated that the use of a multilevel model was appropriate for the data.

Discussion

The results of our study showed that the administration of corticosteroids in patients admitted to the general medical ward with AHRF and a diagnosis of COVID-19 pneumonia was associated with a lower risk of developing the primary outcome composite of ICU transfer, intubation or death. Regarding secondary outcomes, patients who received corticosteroids were found to have a lower risk of ICU transfer, intubation, in-hospital death, composite of intubation, or death and were more likely to be discharged. In the corticosteroid cohort, however, a lower hazard of mortality did not show statistical significance likely due to a smaller sample size.

As discussed in the introduction, the findings from earlier studies have indicated the controversial role of corticosteroids in COVID-19. A preliminary report from the RECOVERY trial [11] demonstrated a beneficial role of low dose (6 mg) dexamethasone in reducing the risk of death among patients who required oxygen with or without invasive mechanical ventilation. The study by Wu et al. demonstrated a beneficial role of methylprednisolone in reducing the risk of death in a subgroup analysis of 84 patients with ARDS, from an observational study of 201 patients with COVID-19 [15]. A meta-analysis of randomized clinical trials

suggested corticosteroid could reduce mortality and need for mechanical ventilation in patients with severe community-acquired pneumonia, irrespective of bacterial or viral etiology [16,17]. On the contrary, another meta-analysis showed higher mortality among patients receiving corticosteroids [18]. However, this meta-analysis included patients with SARS, MERS, COVID-19, and had high heterogeneity. A subgroup analysis from the same study reported no significant difference in mortality between two cohorts when included only COVID-19 patients [18], suggesting corticosteroids may not be harmful in these patients. We assume studies that showed higher or no difference in mortality with corticosteroid were critically ill with ARDS, on mechanical ventilation, and they might have passed the point where adverse outcomes could be modified by corticosteroid.

In COVID-19 pneumonia, lung injury is associated with a direct virus-induced injury. However, the severity of illness is associated with the virus triggered immune hyper-response that is characterized by activation of various immune cells and release of numerous pro- and anti-inflammatory cytokines, including tumor necrosis factor (TNF), Interleukin-6 (IL-6), and many more. Overwhelming secretion of cytokines leads to severe lung damage manifested as the destruction of the small airway, alveolar epithelium, and vascular endothelium that progresses to pulmonary edema and hyaline membrane formation [19,20]. In severe COVID-19 pneumonia, patients' symptoms worsen and become more hypoxic during the 4–7 days after onset of symptoms [21]. Hence, it is vital to suppress the cytokine storm before that period. We, therefore, believe a majority of patients survive and recover if they overcome the period of the cytokine storm. Corticosteroid is a classical immunosuppressive drug that helps in delaying or halting the progress of pneumonia and has been effective for the treatment of ARDS [22,23]. In addition to immunosuppressive properties, corticosteroid possesses anti-inflammatory activity that reduces systemic inflammation, decreases exudation into the lung tissue, promotes the absorption of inflammation, and prevents alveolar damage [24]. These effects of corticosteroid help in relieving hypoxemia earlier, preventing further progression of respiratory insufficiency, and hence associated with improved primary, secondary outcomes, and SF ratio in the study.

This study was also unique and different from the RECOVERY trial in the following ways. Compared with the RECOVERY trial, the average duration of corticosteroids administration was half, the median equivalent dose of dexamethasone was two times, and various types (methylprednisolone, dexamethasone, and prednisone) of corticosteroids were used. The present study cohort only included non-intubated patients admitted to general wards. In the current study, a hazard ratio of a composite of intubation or mortality was 0.31 (0.15–0.66), intubation was 0.31 (0.14–0.70), and death was 0.53 (0.22–1.31). In the RECOVERY trial, the subgroup of patients on oxygen, a hazard ratio of the composite of invasive mechanical ventilation or mortality was 0.87 (0.79–0.96), and of mortality was 0.82 (0.72–0.94) when they excluded patients who were receiving invasive mechanical ventilation at randomization. The difference in the dose and duration of corticosteroid between two studies prompts the possibility of greater beneficial effect with a higher dose and shorter duration of the corticosteroid on clinical endpoints. Traditionally corticosteroids are not used early in viral pneumonia due to concerns of delayed viral clearance. However, delayed treatment may predispose to worsening and progressive inflammatory response and multiorgan failure. Hence, the authors presume that careful monitoring of inflammatory markers might help guide the judicious use of corticosteroid. This study highlights that early administration of moderate-dose of any systemic corticosteroid (oral or intravenous) for a shorter duration in COVID-19 viral pneumonia may not be as harmful as initially suspected, and even more beneficial than shown by the RECOVERY trial. The lower hazard of ICU transfer, intubation, and a higher rate of discharge might be linked to a better quality of life of the patient if corticosteroids are given during the early

period of illness. However, data on readmission to hospital or ED visits post-discharge would be required to confirm this presumptive role.

Limitations

This study has several limitations, given the observational nature of the study. It is a single-center study, and most of the patients were Hispanic that limits the generalizability of the study. However, this study could be taken as a role of corticosteroid in the predominantly Hispanic population. There were missing data for inflammatory markers and potential inaccuracies in the documentation of variables from the electronic health records; however, as mentioned above, two authors made sure the accuracy of the collected database. Due to the retrospective nature of the study, it was not possible to collect data on side effects such as secondary superimposed infection and hyperglycemia. Hence, one should be vigilant about these adverse effects while using it. Authors believe that the physicians are familiar with the side effects of corticosteroid and ways to prevent and treat its complications as it is a long-known drug compared with newer medications on which we have very limited data. Due to missing data for inflammatory markers, adjustment with those variables was not possible. Despite the extensive adjustments, it is still possible that unmeasured confounding prevails. We did not have longitudinal data with follow-up. A randomized clinical trial is the best approach to determine whether the benefit can be ascribed to any given therapeutic intervention as the trial design diminishes the two major hurdles of observational studies, namely unmeasured confounding and bias. A randomized clinical trial from China has been registered in which patients were randomly assigned to receive 1 mg/kg methylprednisolone (NCT04273321) or placebo. The authors tried to minimize confounding by choosing the best possible model in multivariable regression in this retrospective cohort study.

Conclusions

In our analysis of hospitalized patients in the general ward with COVID-19 pneumonia complicated by acute hypoxic respiratory failure, early use of moderate dose systemic corticosteroid for the shorter duration was associated with a significantly lower rate of the primary outcomes of ICU transfer, intubation, or in-hospital death. Given the observational design, the study should be interpreted with caution due to potential bias and residual confounders.

Supporting information

S1 Table. Definitions of variables and outcomes.
(DOCX)

S1 File. Calculation of SF ratio and PF ratio.
(DOCX)

S2 File. Multivariate cox-proportional model building.
(DOCX)

S1 Fig. Kaplan-Meier curves for intensive care unit transfer.
(DOCX)

S2 Fig. Kaplan-Meier curves for intubation.
(DOCX)

S3 Fig. Kaplan-Meier curves for discharge.
(DOCX)

Acknowledgments

We acknowledge the dedication, commitment, and sacrifice of the staff, providers, and personnel in our institution through the Covid-19 crisis and the suffering and loss of our patients as well as their families and our community. We acknowledge Ms. Ejiro C. Gbaje MPH for her help in the analysis of data.

Author Contributions

Conceptualization: Monil Majmundar, Tikal Kansara, Joanna Marta Lenik, Hansang Park, Kuldeep Ghosh, Rajkumar Doshi, Palak Shah, Ashish Kumar, Hossam Amin, Shobhana Chaudhari, Imnett Habtes.

Data curation: Monil Majmundar, Tikal Kansara, Joanna Marta Lenik, Hansang Park, Kuldeep Ghosh.

Formal analysis: Monil Majmundar, Rajkumar Doshi, Ashish Kumar.

Investigation: Monil Majmundar, Tikal Kansara, Joanna Marta Lenik, Hansang Park, Kuldeep Ghosh, Palak Shah, Shobhana Chaudhari, Imnett Habtes.

Methodology: Monil Majmundar, Tikal Kansara, Joanna Marta Lenik, Hansang Park, Kuldeep Ghosh, Rajkumar Doshi, Palak Shah, Ashish Kumar, Hossam Amin, Shobhana Chaudhari, Imnett Habtes.

Project administration: Monil Majmundar, Tikal Kansara, Joanna Marta Lenik, Hansang Park, Kuldeep Ghosh.

Resources: Palak Shah, Hossam Amin.

Software: Monil Majmundar, Kuldeep Ghosh, Rajkumar Doshi, Palak Shah, Ashish Kumar, Imnett Habtes.

Supervision: Monil Majmundar, Tikal Kansara, Hossam Amin, Shobhana Chaudhari, Imnett Habtes.

Validation: Monil Majmundar, Tikal Kansara, Joanna Marta Lenik, Hansang Park, Kuldeep Ghosh, Rajkumar Doshi, Ashish Kumar, Hossam Amin, Shobhana Chaudhari, Imnett Habtes.

Writing – original draft: Monil Majmundar, Tikal Kansara, Joanna Marta Lenik, Hansang Park, Kuldeep Ghosh, Rajkumar Doshi, Palak Shah, Ashish Kumar, Hossam Amin, Shobhana Chaudhari, Imnett Habtes.

Writing – review & editing: Monil Majmundar, Tikal Kansara, Joanna Marta Lenik, Hansang Park, Kuldeep Ghosh, Rajkumar Doshi, Palak Shah, Ashish Kumar, Hossam Amin, Shobhana Chaudhari, Imnett Habtes.

References

1. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020 [cited 6 May 2020]. https://doi.org/10.1001/jama.2020.6775
2. Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: A systematic review and meta-analysis. Crit Care. 2019; 23: 99. https://doi.org/10.1186/s13054-019-2395-8
3. Zhou Y, Fu X, Liu X, Huang C, Tian G, Ding C, et al. Use of corticosteroids in influenza-associated acute respiratory distress syndrome and severe pneumonia: a systemic review and meta-analysis. Sci Rep. 2020; 10: 1–10. https://doi.org/10.1038/s41598-020-59732-7

4. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, et al. Corticosteroid therapy for critically ill patients with middle east respiratory syndrome. Am J Respir Crit Care Med. 2018; 197: 757–767. https://doi.org/10.1164/rccm.201706-1172OC
5. Hui DS. Systemic corticosteroid therapy may delay viral clearance in patients with middle east respiratory syndrome coronavirus infection. American Journal of Respiratory and Critical Care Medicine. American Thoracic Society; 2018. pp. 700–701. https://doi.org/10.1164/rccm.201712-2371ED
6. Auyeung TW, Lee JSW, Lai WK, Choi CH, Lee HK, Lee JS, et al. The use of corticosteroid as treatment in SARS was associated with adverse outcomes: A retrospective cohort study. J Infect. 2005; 51: 98–102. https://doi.org/10.1016/j.jinf.2004.09.008
7. Chen RCR, Tang XXP, Tan SYS, Al E, Liang BL, Wan ZY, et al. Treatment of Severe Acute Respiratory Syndrome With Glucosteroids. Chest. 2006; 129: 1441–1452. https://doi.org/10.1378/chest.129.6.1441
8. Li H, Yang SG, Gu L, Zhang Y, Yan XX, Liang ZA, et al. Effect of low-to-moderate-dose corticosteroids on mortality of hospitalized adolescents and adults with influenza A(H1N1)pdm09 viral pneumonia. Influenza Other Respi Viruses. 2017; 11: 345–354. https://doi.org/10.1111/irv.12456
9. WHO. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. 2020.
10. Zhao JP, Hu Y, Du RH, Chen ZS, Jin Y, Zhou M, et al. Expert consensus on the use of corticosteroid in patients with 2019-nCoV pneumonia. Chinese J Tuberc Respir Dis. 2020; 43: 183–184. https://doi.org/10.3760/cma.j.issn.1001-0939.2020.03.008
11. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19—Preliminary Report. N Engl J Med. 2020; NEJMoa2021436. https://doi.org/10.1056/NEJMoa2021436
12. World Health Organization. Global Surveillance for human infection with coronavirus disease (COVID-19). [cited 6 May 2020]. Available: https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov)
13. Czock D, Keller F, Rasche FM, Häussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. Clinical Pharmacokinetics. Clin Pharmacokinet; 2005. pp. 61–98. https://doi.org/10.2165/00003088-200544010-00003
14. Steroid Conversion Calculator—MDCalc. [cited 13 May 2020]. Available: https://www.mdcalc.com/steroid-conversion-calculator#evidence
15. Wu C, Chen X, Cai Y, Xia JJ, Zhou XXX, Xu S, 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 [cited 12 Apr 2020]. https://doi.org/10.1001/jamainternmed.2020.0994
16. Siemieniuk RAC, Meade MO, Alonso-Coello P, Briel M, Evaniew N, Prasad M, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: A systematic review and metaanalysis. Annals of Internal Medicine. American College of Physicians; 2015. pp. 519–528. https://doi.org/10.7326/M15-0715
17. Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M. Corticosteroids for pneumonia. Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2017. https://doi.org/10.1002/14651858.CD007720.pub3
18. Gangopadhyay KK, Mukherjee JJ, Sinha B, Ghosal S. The role of corticosteroids in the management of critically ill patients with coronavirus disease 2019 (COVID-19): A meta-analysis. medRxiv. 2020; 2020.04.17.20069773. https://doi.org/10.1101/2020.04.17.20069773
19. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020; 8: 420–422. https://doi.org/10.1016/S2213-2600(20)30076-X
20. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Seminars in Immunopathology. Springer Verlag; 2017. pp. 529–539. https://doi.org/10.1007/s00281-017-0629-x
21. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; 382: 1708–1720. https://doi.org/10.1056/NEJMoa2002032
22. Thompson BT. Glucocorticoids and acute lung injury. Critical Care Medicine. 2003. https://doi.org/10.1097/01.ccm.0000057900.19201.55
23. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. Nature Reviews Immunology. Nature Publishing Group; 2017. pp. 233–247. https://doi.org/10.1038/nri.2017.1
24. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids—New mechanisms for old drugs. New England Journal of Medicine. 2005. https://doi.org/10.1056/NEJMra050541