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ORIGINAL RESEARCH

A Retrospective Cohort Study of Corticosteroid Use in Intensive Care Unit Patients with Coronavirus Disease 2019

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Introduction

Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), first emerged from Wuhan, China in late 2019.[1] By March 2020, this highly pathogenic and deadly infection was characterized as a pandemic by the World Health Organization (WHO).[2] Given the link between elevated inflammatory markers, such as ferritin and interleukin-6 (IL-6), and increased mortality in COVID-19, the pathogenesis for disease severity and late-stage pulmonary injury seen in many patients was thought to be largely driven by virally induced hyperinflammation and cytokine release syndrome (CRS).[3–6]

Early recommendations from the WHO and other systematic reviews cautioned against the use of corticosteroids in COVID-19 due to its lack of historical efficacy in other respiratory viral illnesses such as influenza,[7] severe acute respiratory syndrome 1 (SARS),[8] and Middle East respiratory syndrome (MERS).[9,10] However, early observation of COVID-19 pneumonia suggested that an exaggerated inflammatory response may play a role in morbidity and mortality. As such, we suspected corticosteroid administration may be effective in blunting this immune response and may improve outcomes after infection with SARS-CoV-2. At the outset of the pandemic, our single center public hospital serving the greater Los Angeles area, adopted the practice of administering corticosteroids, most often methylprednisolone, to patients with severe COVID-19 pneumonia, defined by SpO_2 less than 94% on room air or those requiring supplement oxygen.

In July 2020, positive findings from the RECOVERY trial, were released. This was the first multi-center randomized controlled trial assessing the effect of dexamethasone on outcomes in COVID-19.[11,12] The study demonstrated a significant reduction in mortality for patients receiving invasive mechanical ventilation (29.3% vs. 41.4%) and for patients requiring supplemental oxygen (23.3% vs. 26.2%).[11,12] This was the first study to show corticosteroids confer a mortality benefit in severe COVID-19 infection.[11,12] Although other corticosteroids such as hydrocortisone and methylprednisolone have not been shown to demonstrate a consistent mortality benefit,[13] the optimal class, dose, and duration of corticosteroid for treatment of COVID-19 is not well defined. We performed a single-center, retrospective cohort analysis of patients with severe COVID-19 pneumonia during the early phase of the pandemic to investigate the effect of several different corticosteroids versus usual care on outcomes after SARS-CoV-2 infection.

Methods

Study Design

This is a single-center, retrospective cohort study conducted at a 355-bed academic county hospital serving Los Angeles County, California. Since March 15, 2020, all patients admitted to the hospital were tested for severe acute respiratory syndrome-coronavirus 2 (SARS-CoV2) by nasopharyngeal reverse-transcriptase-polymerase-chain-reaction (RT-PCR) in accordance with local infection control protocol.

We defined a study period of March 15, 2020 to June 15, 2020. Patients were included in this analysis if they met the following criteria: age over 18 years, positive RT-PCR for SARS-CoV2, and admission to the ICU for any reason. There were no exclusions made based on indication for ICU admission in an effort to capture the breadth of treatment strategies for ICU level patients with COVID-19, regardless if COVID-19 was their primary indication for ICU admission. We excluded five patients who were intubated prior to the initiation of steroid therapy and three patients who were identified as DNR/DNI at the time of clinical decline and were not intubated and died.

Patients were divided into two groups: those who received steroids in addition to standard of care (SOC), “steroid group”, and those who received SOC without administration of corticosteroids, “non-steroid group”.

This study was approved by the Olive View-UCLA Medical Center institutional review board (Reference Number 1658180-1).

Interventions

All patients received SOC based on the available understanding of best practices for treatment of COVID-19 infection at the time. Available COVID-19-directed medical therapies included corticosteroids, hydroxychloroquine, tocilizumab, remdesivir, convalescent plasma, antibiotic therapy (including empiric treatment of community-acquired pneumonia or hospital-acquired pneumonia), and therapeutic anticoagulation. All other supportive critical care was provided at the discretion of the treating provider. Available supplemental oxygen and ventilation interventions included nasal cannula (NC), simple face mask (FM), non-rebreather (NRB), high flow nasal cannula (HFNC), non-invasive positive pressure ventilation (NIPPV), and invasive mechanical ventilation (IMV).

Data Collection

All categories of data collection were determined by a consensus group of internal medicine housestaff and critical care faculty based on a review of available literature at time of data collection. Data were entered into a secure database with defined parameters including: age, sex, height, weight, body mass index (BMI), and pre-existing conditions (see Appendix A). Ferritin and D-dimer were collected for all patients on hospital days 0, 7, and 28. The following therapeutic interventions were recorded if received by hospital days 0, 7, and 28: corticosteroids, remdesivir, vasopressors, antibiotics, therapeutic anticoagulation, hydroxychloroquine, convalescent plasma, and tocilizumab. The following disease severity index scores were calculated at hospital days 0, 7, and 28: sequential organ failure assessment (SOFA) and World Health Organization's Ordinal Scale for Clinical Improvement from February 2020 (Ordinal Scale)[14]. For SOFA score calculation, peripheral oxygen saturation (SpO_2) values were used to estimate arterial partial pressure of oxygen (PaO_2) through a validated conversion table when arterial blood gas values were unavailable.[15,16] Additionally, intubation date, extubation date, and final disposition (i.e. home, skilled nursing facility, outside hospital transfer, deceased) were recorded for all patients who were discharged from the hospital by study completion.

The following steroid-specific data were recorded. Prior use of daily corticosteroids, start and end dates of inpatient corticosteroids, type and first 24 hours dosage of corticosteroid, inflammatory marker levels at hospital days 0, 3, 6, 9, and 12, FiO_2 at hospital days 0, 3, 6, 9, and 12 for patients receiving oxygen FiO_2 (for patients receiving HFNC, NIPPV, or IMV) or flow rate in L/min converted to FiO_2 via a validated conversion table (for patients receiving NC, FM, or NRB) published elsewhere,[15,16] and presence of adverse events. Adverse events such as gastrointestinal (GI) bleed, stroke, myocardial infarction (MI), and delirium were included if documented by the treating clinician in the patient's daily progress note and/or discharge summary. Adverse events such as hyperglycemia (defined as blood glucose levels > 140 mg/dL) and secondary infections (defined as a positive blood, respiratory, or urine culture at any time during the admission after initiation of corticosteroids) were included based on objective laboratory and microbiologic data.

Outcome Measures

The primary outcomes were 28-day mortality and overall inpatient mortality. Secondary outcomes included length of hospital stay, length of ICU stay, progression to IMV, duration of IMV, rate of adverse event occurrence (i.e. GI bleed, stroke, MI, hyperglycemia, delirium, secondary infections), trend of inflammatory markers, and FiO_2 requirement.

Statistical Analysis

Patients were divided into two groups: those who received corticosteroids during hospitalization and those who received SOC without corticosteroids. The baseline characteristics of these two groups were compared with respect to age, sex, body mass index (BMI, kg/m^2), race/ethnicity, resuscitation status, pre-existing medical comorbidities, admission from a skilled nursing facility (SNF), and SOFA and Ordinal Scale scores on admission. Continuous variables including age, BMI, SOFA score, and Ordinal Scale scores were compared using a two-sample t-test. Categorical variables including sex, ethnicity, presence of pre-existing comorbidities, and proportion of patients coming from a SNF were compared using Fisher's exact test. Similarly, therapeutics received by these two groups were compared using Fisher's exact test.

Laboratory biomarkers and oxygen requirement of these two groups over the hospitalizations were analyzed using multi-level mixed effects linear regression. For each analysis, the biomarker values or oxygen requirement was set as the dependent variable and the group as the independent variable, with random effects set at the patient level.

Mortality at 28 days, length of hospital stay, length of ICU stay, days to IMV, and duration of intubation were calculated and compared between the steroid and non-steroid groups using Wilcoxon Rank-Sum due to the non-normal distribution of the data. A time-to-event analysis was performed on progression to IMV by calculating the cumulative hazard function for each group and using a log-rank test of equality between them.

P-values less than 0.05 were considered statistically significant. Stata (version 15, Stata, College Station, Texas) was used for all data analysis.

Results

There were 73 patients who met inclusion criteria. Of these patients, 53 (73%) received SOC plus corticosteroids and 20 (27%) received SOC without corticosteroids. Among those in the steroid group, the majority of patients received methylprednisolone (89.1%) as their primary steroid regimen, whereas the remainder received either hydrocortisone (7.3%) or dexamethasone (3.6%). For methylprednisolone, the mean total dose in the first 24 hours was 84mg ± 30mg. The mean [interquartile range,

IQR] time to steroid initiation was 2.8 [1-4] days from admission and the mean duration of steroids was 8.1 ± 5.1 days.

Between groups, there were no statistically significant differences in age, sex, BMI, ethnicity, underlying medication conditions, or admission SOFA scores (Table 1). In the non-steroid group, there was a higher proportion of patients with a code status of DNR/DNI recorded at the end of admission (45% vs. 18%, p=0.032), patients who presented from a SNF (35% vs. 13%, p=0.048), and a higher ordinal scale score on admis-sion (4.5 vs. 4.0, p=0.04) (Table 1). There were no differences in the other therapeutics received during hospitalization (Table 2).

Table 1. Baseline characteristics of the steroid and non-steroid groups.

		Non-steroid Group	*Steroid Group*	*p-value*
		N=20	N=53	
Patient Age, mean (SD)		64 (19)	57 (14)	0.086
Female Sex, % (n)		25% (5)	28% (15)	1.00
BMI[a], mean (SD)		28.1 (5.7)	29.7 (7.0)	0.35
Race/ethnicity, % (n)	Hispanic	60% (12)	81% (43)	0.08
	Black	5% (1)	0% (0)	
	White	15% (3)	6% (3)	
	Asian	0% (0)	8% (4)	
	Unknown	20% (4)	6% (3)	
Code status, % (n)	Full Code	55% (11)	82% (47)	**0.032**
	DNR/DNI	45% (9)	18% (10)	
Comorbidities, % (n)				
CAD		0% (0)	4% (2)	1.00
Hypertension		50% (10)	47% (25)	1.00
Type 2 Diabetes		65% (13)	55% (29)	0.60
COPD		0% (0)	2% (1)	1.00
Asthma		5% (1)	2% (1)	0.48
CKD (eGFR< 60)		25% (5)	17% (9)	0.51
CVA		0% (0)	8% (4)	0.57
Cirrhosis		10% (2)	2% (1)	0.18
Psychiatric illness		10% (2)	8% (4)	0.66
Lung Disease		5% (1)	8% (4)	1.00
Tobacco use		30% (6)	15% (8)	0.19
Cancer		10% (2)	4% (2)	0.30
From Skilled Nursing Facility, % (n)		35% (7)	13% (7)	**0.048**
SOFA Score on Admission, mean (SD)		3 (3-6)	3 (2-4)	0.17
Ordinal Scale on Admission, mean (SD)		4.5 (4-5.5)	4 (4-5)	**0.04**

Table 2. Therapeutics received during hospitalization.

	Non-steroid Group	*Steroids Group*	*p-value*
	N=20	N=53	
Remdesivir, % (n)	10% (2)	11% (6)	1.00
Vasopressors, % (n)	50% (10)	45% (24)	0.80
Antibiotics, % (n)	100% (20)	100% (53)	
Therapeutic Anticoagulation, % (n)	40% (8)	60% (32)	0.19
Hydroxychloroquine, % (n)	45% (9)	53% (28)	0.61
Convalescent Plasma, % (n)	42% (5)	70% (26)	0.094
Tocilizumab, % (n)	10% (2)	15% (8)	0.72

Primary Outcomes

There was no statistically significant difference between the steroid and non-steroid group with 28-day mortality (28% vs. 35%, p=0.58) or overall inpatient mortality (38% vs. 50%, p=0.43) (Table 3).

Table 3. Mortality, length of stay, and use of mechanical ventilation.

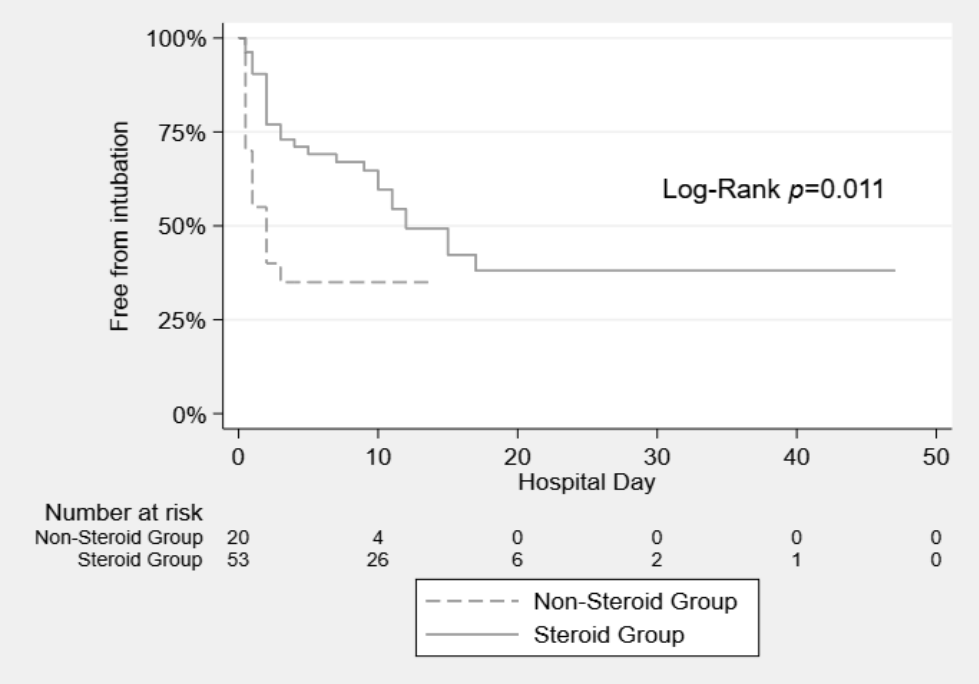
	Non-steroid Group	*Steroid Group*	*p-value*
	N=20	N=53	
28 Day Mortality, % (n)	35% (7)	28% (15)	0.58
Overall Mortality, % (n)	50% (10)	38% (20)	0.43
Length of Stay[a], mean (IQR)	14 (8-25)	17 (12-24.5)	0.40
ICU Length of Stay[a], mean (IQR)	5 (2-13)	11 (6-17)	0.087
Days to Intubation[b], mean (IQR)	.5 (0-1.5)	3 (2-11)	**<0.001**
Duration of Intubation[a], mean (IQR)	8.5 (2-20)	10 (6-15)	0.69

[a]Measured in days
[b]Days to intubation after admission to the ICU

Secondary Outcomes

There was no difference in length of stay (14 vs. 17 days, p=0.40) or length of ICU stay (5 vs. 11 days, p=0.087) between the non-steroid and steroid groups. Similarly, there was no difference in the duration of intubation between the groups (8.5 vs 10 days, p=0.69). Based on time from admission, patients in the steroid group had significantly lower rates of intubation on day of admission when compared to the non-steroid group (4% vs. 32%, p=0.006). Similarly, the median [IQR] time to intubation was 3 [2-11] days in the steroid group and 0.5 [0-1.5] days in the non-steroid group (p<0.001) (Table 3). Additionally, the steroid group had a lower likelihood of intubation throughout hospitalization with a hazard ratio (HR) of 0.44 (0.22-0.87, 95% confidence interval [CI]; p=0.01) (Figure 1).

Figure 1. Probability of intubation between steroid and non-steroid groups.



There was a higher prevalence of hyperglycemia (88% vs. 21%, p<0.001) in the steroid group compared to the non-steroid group (Table 4). No difference was found among the remainder of recorded adverse events including GI bleed, stroke, myocardial infarction, delirium, or secondary infection (Table 4).

Table 4. Adverse events in steroid versus non-steroid group.

	Non-steroid Group	*Steroid Group*	*p-value*
	N=20	N=53	
Intubation	65% (13)	49% (26)	0.30
GI Bleed	5% (1)	6% (3)	1.00
Stroke	5% (1)	0% (0)	0.27
Myocardial Infarction	5% (1)	2% (1)	0.48
Hyperglycemia	21% (4)	89% (47)	**<0.001**
Delirium	25% (5)	25% (13)	1.00
Secondary Infection	55% (11)	45% (24)	0.60

There was no statistically significant association between the use of corticosteroids and the trend of laboratory biomarkers, including ferritin (p=0.624), CRP (p=0.733), and LDH (p=0.845), during hospitalization. Likewise, there was no statistically significant association between the use of corticosteroids and oxygen requirements (p=0.314) during hospitalization.

Discussion

We report a retrospective analysis of corticosteroid use among patients admitted to the intensive care unit with severe COVID-19 pneumonia. We found that steroid use, predominantly methylprednisolone, was associated with decreased risk of intubation on day of admission in addition to a decreased likelihood of intubation throughout hospitalization. This finding is similar to results from the RECOVERY trial, which found a decreased risk of progression to IMV in patients who received dexamethasone,[11] and other smaller studies examining the effects of methylprednisolone on intubation rates in patients with COVID-19 pneumonia.[17,18] One retrospective cohort study found methylprednisolone was associated with faster improvement in SpO_2 and decreased progression to IMV in patients with severe COVID-19 pneumonia,[17] while another found that a short course of methylprednisolone (0.5 to 1 mg/kg/day for 3 days) led to a reduction in the primary composite endpoint of death, ICU transfer, and mechanical ventilation in patients with moderate to severe COVID-19 pneumonia.[18] Cumulatively, these findings suggest that patients with severe disease defined by SpO_2 less than 94% on room air or hose requiring supplement oxygen may benefit most with early administration of corticosteroids, especially as a means to avoid IMV.

Our analysis did not find any mortality benefit associated with the use of corticosteroids, predominantly methylprednisolone, among our ICU cohort with COVID-19. This is in keeping with the literature that suggests that methylprednisolone and hydrocortisone do not consistently improve survival after severe infection with COVID-19.[13,19–21] For example, while one early retrospective cohort study found that methylprednisolone was associated with a reduced risk of death in patients with COVID-19 who had progressed to acute respiratory distress syndrome (ARDS), it also found that methylprednisolone was more likely to be given to patients with a higher pneumonia severity index score and associated with an increased risk for progression to ARDS.[19] This prompted the researchers to interpret the mortality benefits with caution due to potential bias and residual confounding within a small sample size.[19] Another early retrospective observational study found that methylprednisolone, when given for persistently high fevers or evidence of disease progression on imaging results, showed no difference in disease progression or mortality.[20] More recently, the Metcovid trial, a double-blind randomized control trial (RCT) conducted at a single hospital in Brazil, found that a short course of high-dose methylprednisolone (0.5 mg/kg twice daily for five days) was associated with no difference in 28-day mortality when compared to placebo among patients with suspected COVID-19 pneumonia requiring supplemental oxygen therapy.[21] However, it is important to note that their COVID-19 diagnoses were based on clinical, epidemiological, and radiological criteria, not RT-PCR or serologic testing for SARS-CoV2.[21] Additionally, a sub-group analysis did demonstrate a mortality benefit with methylprednisolone in patients over 60 years old, who were also noted to have higher CRP values.[21] Although our literature review found one multi-center RCT from China examining the effect of five days of intravenous methylprednisolone on a number of outcomes including all-cause mortality and Murray lung injury scores in patient with COVID-19 pneumonia, the results are not yet publicly available.[22] As a result, the variability in outcomes, small sample sizes among published cohort studies, and lack of multi-center RCTs examining methylprednisolone in COVID-19 have led to continued uncertainty about the efficacy of methylprednisolone on morbidity and mortality in patients with COVID-19.

Conversely, the RECOVERY trial showed that administration of dexamethasone 6mg daily for 10 days conferred a significant survival benefit, particularly for those mechanically ventilated.[11] It is not entirely clear why dexamethasone has shown consistent benefit over other corticosteroids. Dexamethasone has glucocorticoid activity only, whereas prednisone, methylprednisolone, and hydrocortisone all have some degree of mineralocorticoid activity in addition to the glucocorticoid activity.[23] Perhaps the addition of the mineralocorticoid somehow blunts the beneficial glucocorticoid activity necessary to mitigate the inflammatory response to SARS-CoV-2. While glucocorticoid receptor activity appears to globally suppress the production of pro-inflammatory cytokines and immune cells such as lymphocytes and monocytes, mineralocorticoid receptors (MRs) have a variety of downstream effects depending on their tissue expression.[23] For example, MR activity leads to several pro-inflammatory changes including increased reactive oxygen species in endothelial cells, increased production of tissue necrosis factor-alpha (TNF-a) and IL-6 in myeloid cells, increased platelet activation, and upregulation of a pro-inflammatory phenotype on CD4 T cells.[23] However, high doses of fludrocortisone, a potent mineralocorticoid, have been shown to paradoxically produce anti-inflammatory effects in vivo.[23] This suggests that mineralocorticoids have the potential to produce anti-inflammatory effects at high doses, lower levels of mineralocorticoid activity may lead to pro-inflammatory changes. This possibly explains why corticosteroids such as methylprednisolone, which has a roughly 10:1 ratio of glucocorticoid to mineralocorticoid activity,[23] have not been able to show a consistent mortality benefit. Furthermore, MR activity in the kidneys and colon are responsible for NaCl reabsorption,[23] which may lead to more fluid retention in patients receiving corticosteroids with mineralocorticoid activity. Given the known benefits of conservative fluid management in acute lung injury,[24] this may also help to explain the lack of consistent benefit of corticosteroids with mineralocorticoid activity in patients with acute lung injury due to COVID-19 pneumonia.

Furthermore, it should be noted that there was significant variability with methylprednisolone dosing and duration of therapy across studies, ranging from 0.5 to 2 mg/kg/day or fixed dosing of 30 to 80 mg/day, given over 3 to 7 days.[17,18,20–22] Similarly, in our retrospective review, the steroid dose and duration was not uniform among patients. These dosing regimens were significantly greater than the equivalent dose of dexamethasone given in the RECOVERY trial,[11,12] suggesting that the harm of higher doses may outweigh the benefits.

Importantly, one meta-analysis of 8 RCTs (3 studying dexamethasone, 3 studying hydrocortisone, and 2 studying methylprednisolone) found systemic corticosteroids were associated with a lower 28-day all-cause mortality when administered to critically ill patients with COVID-19.[13] However, 57% of the weight in the primary meta-analysis data came from the RECOVERY trial and the 2 trials that evaluated methylprednisolone, including the Metcovid trial, failed to show a statistically significant improvement in 28-day mortality.[13]

Corticosteroids are thought to be beneficial in COVID-19 due to their anti-inflammatory properties which target the cytokine storm hypothesized to be a contributor to ARDS and multiorgan failure in COVID-19.[3–6] As a result, many early studies emphasized the importance of recognizing hyperinflammation in COVID-19 and the empiric use of medications that target the inflammatory cascade.[3–6] Despite contradictory evidence that corticosteroids have historically provided no mortality benefit in other viral pneumonias including influenza,[7] SARS,[8] and MERS,[9] some studies report selected patients with high inflammatory levels and/or severe pneumonia have improved clinical outcomes when given steroids.[25–27] For example, one retrospective cohort study found that corticosteroids (predominantly methylprednisolone) resulted in lowered mortality and shorter hospitalization stay when used in patients with confirmed critical SARS.[25] Additionally, several studies demonstrate that patients with severe community-acquired pneumonia and CRP levels greater than 150 mg/L have reduced treatment failure and improved clinical outcomes with concurrent administration of corticosteroids.[26,27]

However, there does not appear to be any consensus on which inflammatory markers to follow, or what levels are considered representative of cytokine storm that would be useful in identifying patients who may benefit most from corticosteroids after infection with SARS-CoV-2. What is less clear is if there is any role in monitoring inflammatory markers to assess response to corticosteroids and determine the optimal duration of administration. Within our study, we found no significant difference in inflammatory markers (i.e. ferritin and D-dimer) at days 0, 7, and 28 between the steroids and non-steroids groups. Additionally, we found no identifiable trend in inflammatory markers (i.e. ferritin, CRP, LDH) from day 0 to 12 of steroid administration in the steroids group. This suggests that while inflammation may play a significant role in disease course, prognosis, and theoretically identifying patients that may benefit from steroid administration, there is no clear role for the use of inflammatory markers to guide duration of such therapy.

Limitations

While our study did not find a significant decrease in mortality with the use of corticosteroids, mainly methylprednisolone, it should be noted that our cohort specifically included patients who were in the ICU whereas many other studies, including the RECOVERY trial, included all hospitalized patients. This suggests that patient with more severe disease may be less steroid-responsive or too far along in their disease course to benefit from steroid use.

Additionally, it is notable that the non-steroid group had a statistically significant higher ordinal scale score on day of admission (4.5 vs. 4.0, p=0.04), was more likely to come from a SNF (35% vs. 13%, p=0.048), and skewed toward being older (64 vs. 57, p=0.086). However, there was no significant difference in admission SOFA scores, baseline characteristics, or COVID-19 targeted therapies received throughout admission between the two groups. Thus, while the non-steroid group may

had had slightly sicker patients by some metrics, ultimately the groups were similar.

Lastly, our study was limited by its retrospective nature, smaller size, and non-uniform steroid dosing regimen. Our steroid cohort largely received methylprednisolone 40mg twice per day, although timing of initiation and duration of treatment was variable. This heterogeneity makes interpretation of dosing regimens and efficacy more difficult. Future work should prospectively study steroid dosing by agent, dose, and duration.

Conclusions

Patients admitted to the ICU with COVID-19 had a significantly lower rate of intubation if treated with corticosteroids, the vast majority of whom received methylprednisolone. Given multiple reports demonstrating a decrease in progression to invasive mechanical ventilation with methylprednisolone in severe COVID-19 pneumonia,[17,18] methylprednisolone would be a reasonable alternative therapy in the absence of dexamethasone.[28,29] However, methylprednisolone has been unable to show consistent mortality benefit, possibly explained by the lack of multi-center RCTs, higher dosing regimens relative to 6mg of dexamethasone,[11,12,17,18,20–22] and mineralocorticoid activity, which has been linked to increased sodium absorption and several pro-inflammatory signaling cascades.[23] Based on the results of the RECOVERY trial, the current best suggested practice remains administration of dexamethasone at 6mg per day for ten days to patients with COVID-19 requiring supplemental oxygen.[11,12] Additional prospective studies should continue to examine the optimal steroid dosing and treatment duration for the management of severe COVID-19.

This study was approved by the Olive View-UCLA Medical Center institutional review board (Reference Number 1658180-1).

All the work related to this study was performed at Olive View-UCLA Medical Center.

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