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RESEARCH ARTICLE

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Comparison of pulse-dose and high-dose corticosteroids with no corticosteroid treatment for COVID-19 pneumonia in the intensive care unit

Hamid Yaqoob[1] | Daniel Greenberg[2] | Frank Hwang[3] | Curtis Lee[3] | David Vernik[3] | Ravi Manglani[1] | Zhen Wang[4] | M. Hassan Murad[4] | Dipak Chandy[1] | Oleg Epelbaum[1]

[1]Division of Pulmonary, Critical Care, and Sleep Medicine, Westchester Medical Center, Valhalla, New York, USA

[2]Department of Medicine, Westchester Medical Center, Valhalla, New York, USA

[3]New York Medical College, Valhalla, New York, USA

[4]Evidence-Based Practice Center, Mayo Clinic, Rochester, New York, USA

Correspondence
Hamid Yaqoob, Division of Pulmonary, Critical Care, and Sleep Medicine, Westchester Medical Center, 100 Woods Road Macy Pavilion Pulmonary Lab, Valhalla, NY 10595, USA.
Email: hamid.yaqoob@wmchealth.org

Abstract

Corticosteroid dosing in the range of 0.5–2 mg/kg/day of methylprednisolone equivalents has become a standard part of the management of intensive care unit (ICU) patients with COVID-19 pneumonia based on positive results of randomized trials and a meta-analysis. Alongside such conventional dosing, administration of 1 gm of methylprednisolone daily (pulse dosing) has also been reported in the literature with claims of favorable outcomes. Comparisons between such disparate approaches to corticosteroids for Coronavirus disease 2019 (COVID-19) pneumonia are lacking. In this retrospective study of patients admitted to the ICU with COVID-19 pneumonia, we compared patients treated with 0.5–2 mg/kg/day in methylprednisolone equivalents (high-dose corticosteroids) and patients treated with 1 gm of methylprednisolone (pulse-dose corticosteroids) to those who did not receive any corticosteroids. The endpoints of interest were hospital mortality, ICU-free days at Day 28, and complications potentially attributable to corticosteroids. Pulse-dose corticosteroid therapy was associated with a significant increase in ICU-free days at Day 28 compared to no receipt: adjusted relative risk (aRR): 1.45 (95% confidence interval [CI]: 1.05–2.02; $p = 0.03$) and compared with high-dose corticosteroid administration ($p = 0.003$). Nonetheless, receipt of high-dose corticosteroids—but not of pulse-dose corticosteroids—significantly reduced the odds of hospital mortality compared to no receipt: adjusted Odds ratio (aOR) 0.31 (95% CI: 0.12–0.77; $p = 0.01$). High-dose corticosteroids reduced mortality compared to pulse-dose corticosteroids ($p = 0.04$). Pulse-dose corticosteroids—but not high-dose corticosteroids—significantly increased the odds of acute kidney injury requiring renal replacement therapy compared to no receipt: aOR 3.53 (95% CI: 1.27–9.82; $p = 0.02$). The odds of this complication were also significantly higher in the pulse-dose group when compared to the high-dose group ($p = 0.05$ for the comparison). In this single-center study, pulse-dose corticosteroid therapy for COVID-19 pneumonia in the ICU was associated with an increase in ICU-free days but failed to impact hospital mortality, perhaps because of its association with

development of severe renal failure. In line with existing trial data, the effect of high-dose corticosteroids on mortality was favorable.

KEYWORDS
corticosteroids, COVID-19, glucocorticoids, intensive care unit, methylprednisolone, pneumonia, pulse, SARS-CoV-2

1 | INTRODUCTION

Following skepticism in the early phase of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic, corticosteroids were ultimately adopted as the standard of care for critically ill patients with coronavirus disease 2019 (COVID-19) pneumonia after survival benefit was demonstrated by the RECOVERY randomized controlled trial (RCT)[1] and then recapitulated by a prospective meta-analysis.[2] On this basis, guideline recommendations for the critical care of COVID-19 pneumonia[3] now advocate for corticosteroid use according to the dosage studied in the RECOVERY RCT: dexamethasone 6 mg daily, which translates to 32 mg of methylprednisolone or 40 mg of prednisone. Of the currently available major RCTs, the highest studied corticosteroid dose has been 20 mg of dexamethasone daily,[4] corresponding to 107 mg of methylprednisolone and 133 mg of prednisone. Thus, the dosing regimens used in major RCTs of corticosteroids in critical COVID-19 pneumonia are in the approximate range of 0.5–2 mg/kg/day in methylprednisolone equivalents assuming an average-sized man weighing 70 kg and an average-sized woman weighing 50 kg. Unlike for SARS,[5] no comparison exists for SARS-CoV-2 between any such high-dose corticosteroid regimen and pulse administration of corticosteroids (i.e., ≥250 mg of methylprednisolone/day). When a pulse methylprednisolone course of 250 mg daily for 3 days in hospitalized patients with COVID-19 pneumonia was prospectively compared to conventional management without corticosteroids, a mortality benefit was observed.[6] As corticosteroid regimens such as dexamethasone 6 mg daily from RECOVERY have seen widespread adoption as the standard of care for COVID-19 pneumonia, comparisons of different approaches to corticosteroid administration may be possible only through turning back to the early phase of the pandemic. In the present study, we analyzed our institutional experience from the first wave of the pandemic to compare outcomes and adverse events of three distinct corticosteroid strategies in critical COVID-19 pneumonia: pulse-dose, high-dose, and no administration.

2 | METHODS

2.1 | Patients and data collection

This retrospective, single-center study was performed at Westchester Medical Center (WMC) in Valhalla, New York State, a tertiary university academic center located in the New York City area, which was the first United States COVID-19 epicenter. All patients at least 18 years of age admitted to the intensive care unit (ICU) services at WMC between March 1, 2020, and May 31, 2020, with an International Classification of Diseases, 10th revision (ICD-10) diagnosis code of U07.1 (COVID-19 virus identified) were eligible for inclusion. SARS-CoV-2 infection was established via reverse-transcriptase polymerase chain reaction testing of nasopharyngeal swab specimens. Patients were excluded from consideration for the study if they met any of the following criteria:

(1) Death in the Emergency Department before transfer to the ICU
(2) Primary ICU diagnosis other than COVID-19 pneumonia (incidental positivity for SARS-CoV-2)

Those remaining after the application of the above initial exclusion criteria were screened for receipt of what for the purposes of this study was deemed "inappropriate" pulse administration of methylprednisolone, which was defined as either:

(A) Receipt of only a single dose of pulse corticosteroids
(B) Initiation of pulse corticosteroids >48 h after admission to the ICU

During the study period, WMC had no standard protocol (e.g., biomarker-based) for corticosteroid administration at any dose for ICU COVID-19 patients. However, all pulse corticosteroid recipients in the ICU were treated with uniform dosing of 1 gm/day of methylprednisolone but with variable timing and number of doses. The decision of whether to follow the pulse course with a lower-dose "tail" was left to the discretion of the clinical team. All patients who received corticosteroids at less than pulse-dose were treated with high-dose regimens corresponding to 0.5–2 mg/kg/day in methylprednisolone equivalents. The timing and duration of these regimens were likewise variable. Identification and exclusion of recipients of so-called "inappropriate" pulsing were intended to eliminate patients who received a course that was too abbreviated to be meaningful for study purposes (criterion A above) or who were pulsed out of desperation late in their illness with a low likelihood of efficacy (criterion B above).

Patients remaining after the application of the above exclusion criteria formed the study population, which was then divided into three groups according to corticosteroid dosing: no corticosteroids (control), high-dose corticosteroids, and pulse-dose corticosteroids. Relevant demographic, historical, clinical, and COVID-19 treatment characteristics of these patients were extracted from the institutional electronic medical

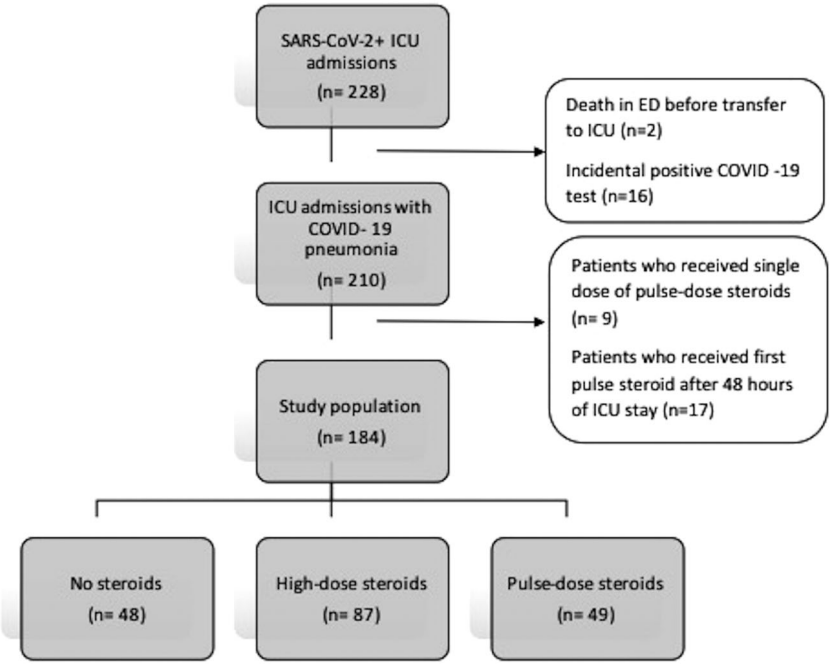

FIGURE 1 Diagram illustrating patient selection and grouping for this study

record and tabulated. Chronic disease burden was summarized using the Charlson Comorbidity Index;[6] critical illness severity was measured by the Acute Physiology and Chronic Health Evaluation IV score.[7] Also obtained were serum levels of four biomarkers commonly tracked in COVID-19 patients at our institution (without a formal protocol):

(1) D-dimer: normal range <0.59 mg/L
(2) Lactate dehydrogenase (LDH): normal range 125–220U/L
(3) C-reactive protein (CRP): normal range <0.5 mg/dl
(4) Ferritin: normal range 18–370 µg/L

The primary outcome measures of interest were:

(1) Mean ICU-free days at Day 28.
(2) Overall hospital mortality.

The following ICU adverse events were deemed potential complications of corticosteroid therapy and were compared among the three groups as secondary outcomes:

(1) Acute kidney injury (AKI) requiring renal replacement therapy (RRT)
(2) Pneumothorax
(3) Positivity of sterile site cultures (e.g., blood, pleural, peritoneal, cerebrospinal fluid)
(4) Cerebrovascular accident (CVA) (ischemic or hemorrhagic)

The institutional review board (IRB) of New York Medical College and the clinical research institute of WMC approved this study (protocol #14318). The requirement for informed consent was waived by the IRB. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

2.2 | Statistical analysis

Categorical variables are expressed as frequency (percentage) and were compared using Fisher's exact test. The Shapiro–Wilk test was used to test the normality of continuous variables. Continuous variables that are normally distributed are expressed as mean ± *SD* and were compared using the one-way analysis of variance test. Continuous variables violating normality are expressed as median (interquartile range [IQR]: 25–75th percentile), and statistical significance was assessed by the Kruskal–Wallis nonparametric test. Multiple logistic regression was performed to estimate the treatment effect of pulse-dose and conventional-dose corticosteroid groups for binary outcomes (mortality and complications) and zero-inflated Poisson regression was used for the continuous outcome (ICU-free days). The adjusted variables were selected based on clinical significance and consisted of age, mechanical ventilation, CRP level, and azithromycin receipt. A sensitivity analysis controlling for (1) vasopressor administration and (2) exposure to angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) as potential additional confounders was also performed. The difference between pulse-dose and high-dose steroid groups was assessed using the Wald test. A two-tailed p value ≤0.05 was considered statistically significant. Statistical analyses were conducted using Stata version 14.1 (StataCorp LLP).

3 | RESULTS

The flow diagram illustrating how the final study population was obtained is depicted in Figure 1. A total of 228 adult patients with COVID-19 were accepted to the ICU service of our institution between the study dates, and 184 of them remained following the application of exclusion criteria. These 184 patients were separated into the no-steroid (N = 48), high-dose steroid (N = 87), and

pulse-dose steroid ($N = 49$) groups. The median number of pulse corticosteroid doses per patient was 2 (IQR: 2–3). The median number of days from WMC admission to receipt of the first group-defining corticosteroid dose was 1 day (IQR: 0.5–2.5) in the high-dose group and likewise 1 day (IQR: 1–3) in the pulse-dose group. Given the non-protocolized approach to corticosteroid administration in our institution, increasing recognition of the potential benefit of corticosteroids for COVID-19 pneumonia resulted in this practice's gaining progressive traction outside of the ICU in the latter part of the study period. Consequently, a number of patients in each corticosteroid treated group began receiving high-dose corticosteroid therapy before arrival to the ICU: 20 patients (23%) in the high-dose corticosteroid group and 7 patients (14%) in the pulse-dose corticosteroid group, the difference not reaching statistical significance ($p = 0.65$). For those patients who received their first corticosteroid dose on the day of ICU arrival or later, the median time from ICU admission to initiation of treatment was 1 day (IQR: 0–2) in the high-dose group and similarly 1 day (IQR: 0–1) in the pulse-dose group. The baseline and clinical course characteristics of the three groups are presented and compared in Table 1. Considering demographic and historical variables, the groups were significantly different with respect to age, history of CVA, CAD, history of solid organ transplantation, and ever exposure to ACEI or ARB. Considering their ICU course, the groups differed significantly with respect to the fraction of patients who were mechanically ventilated, who received vasopressors, and who underwent tracheostomy. Also different among the groups were median levels of ferritin, LDH, and CRP measured at ICU entry. Rates of receipt of azithromycin, hydroxychloroquine, and convalescent plasma were likewise different among the groups. Finally, there was a significant difference among the groups in the rate of hospital mortality and the incidence of AKI requiring RRT.

Results of adjusted regression analyses of the outcome measures are presented in Table 2. Relative to no receipt of corticosteroids, treatment with pulse-dose corticosteroids was associated with a significant increase in ICU-free days at Day 28 [aRR: 1.45 (95% confidence interval [CI]: 1.05–2.02; $p = 0.03$). In contrast, treatment with high-dose corticosteroids resulted in a decrease in ICU-free days at Day 28 (aRR: 0.96 [95% CI: 0.80–1.15]) compared to no receipt of corticosteroids, a nonsignificant difference. When comparing the two corticosteroid treated groups to each other with respect to this endpoint, the difference favoring pulse-dose corticosteroid therapy reached statistical significance ($p = 0.003$). Relative to no receipt of corticosteroids, treatment with high-dose corticosteroids led to significantly reduced odds of hospital mortality: aOR 0.31 (95% CI: 0.12–0.77; $p = 0.01$). Treatment with pulse-dose corticosteroids, on the other hand, did not achieve statistical significance with respect to lowering the odds of hospital mortality: aOR 0.73 (95% CI: 0.27–1.96; $p = 0.73$). When comparing the two corticosteroid treated groups to each other with respect to this endpoint, the difference favoring high-dose corticosteroids reached statistical significance ($p = 0.04$).

Results of the multiple logistic regression analysis of ICU complications of interest are shown in Table 3. The only significant difference in regard to complications was in the odds of developing AKI requiring RRT, which were increased in the pulse-dose corticosteroid group relative to no receipt of corticosteroids: aOR 3.53 (95% CI: 1.27–9.82; $p = 0.02$). This complication was significantly more likely to have occurred in the pulse-corticosteroid group than in the high-dose corticosteroid group ($p = 0.05$).

A sensitivity analysis wherein the regression model was expanded to include the additional variables of vasopressor administration and exposure to ACEI/ARB yielded a minimal change in the results for primary or secondary outcomes. It did, of note, lead to a more statistically robust association between pulse-dose corticosteroids and AKI requiring RRT when compared to high-dose corticosteroids: p value for the comparison 0.03 from 0.05.

4 | DISCUSSION

In this single-center retrospective study, we have evaluated for the first time the impact of corticosteroid dosing intensity on ICU and hospital outcomes as well as on ICU complication rates in critically ill patients with COVID-19 pneumonia. In our sample, pulse-dose corticosteroid therapy was associated with a significant increase in ICU-free days compared to no corticosteroid receipt or receipt of high-dose corticosteroids, but this benefit did not translate into greater odds of hospital survival. In contrast, therapy with high-dose corticosteroids—the typical dosing range currently employed to treat COVID-19 pneumonia—significantly increased the odds of survival compared to no corticosteroid receipt and to receipt of pulse-dose corticosteroids. Although not classically associated with toxicity of corticosteroid administration, in the specific population of SARS-CoV-2 infected patients we found increased odds of AKI requiring RRT in those treated with pulse-dose corticosteroids. It could be reasonably hypothesized based on these findings that the adverse effect of pulse-dose corticosteroid therapy on renal function mediated the inferior survival with this approach compared to high-dose corticosteroids despite its favorable impact on ICU stay. Of note, this observation is reminiscent of the outcome of the ARDSNet RCT of high-dose methylprednisolone for ARDS published in 2006.[8] In this trial, methylprednisolone increased ICU-free days at Day 28 compared to placebo but failed to improve 60-day mortality. These discordant results occurred in the context of a significantly higher incidence of serious neuropathy or myopathy in the treatment arm of the trial.

Initial skepticism about the role of corticosteroids in the treatment of COVID-19 pneumonia was prompted by multiple considerations, including their failure to improve outcomes in the acute respiratory distress syndrome (ARDS) caused by pandemic influenza [9] as well as concerns about unchecked viral propagation from the resultant immunosuppression.[10] The scales gradually tipped in the other direction thanks to the realization that SARS-CoV-2 may produce lung damage by igniting a destructive immune response in that organ rather than through direct viral cytopathic effects[11] and the corollary that viral persistence may not be the driver of progressive

TABLE 1 Baseline and clinical course characteristics of the study patients

	No steroids (*n* = 48)	High-dose steroids (*n* = 87)	Pulse-dose steroids (*n* = 49)	*p* value
Demographics				
Age, years, mean (±*SD*)	66 (17)	60 (16)	66 (13)	**0.03**
Sex, female, *n* (%)	18 (38)	27 (31)	22 (45)	0.27
Comorbidities, *n* (%)				
Obesity	17 (35)	41 (47)	25 (51)	0.27
CKD	6 (13)	12 (14)	2 (4)	0.2
ESRD	3 (6)	3 (4)	2 (4)	0.8
COPD	3 (6)	4 (5)	1 (2)	0.6
Asthma	4 (8)	7 (8)	0 (0)	0.08
OSA	1 (0)	3 (4)	1 (2)	0.81
CAD	10 (21)	10 (12)	2 (4)	**0.04**
CHF	5 (10)	8 (9)	2 (4)	0.5
CVA	6 (13)	3 (4)	0 (0)	**0.01**
DM	17 (35)	29 (33)	13 (27)	0.6
HTN	27 (56)	35 (40)	22 (45)	0.2
Cirrhosis	2 (4)	7 (8)	1 (2)	0.3
Active malignancy	1 (2)	3 (4)	2 (4)	>0.99
History of malignancy	2 (4)	3 (4)	7 (14)	0.07
Solid organ transplant	0 (0)	8 (9)	0(0)	**0.02**
Charlson comorbidity index, mean (±*SD*)	3.8 (2.4)	2.9 (2.5)	3 (2)	0.11
Ever exposure to ACEI/ARB[a]	12 (27)	14 (19)	35 (71)	**<0.001**
Admission source, *n* (%)				
WMC ED	31 (65)	49 (56)	31 (63)	0.6
Ward/outside transfer	17 (35)	38 (44)	18 (37)	
APACHE IV score, mean (±*SD*)[b]	70.4 (37.0)	73.6 (36.8)	70.7 (33.4)	0.86
Mechanical ventilation, *n* (%)	30 (63)	70 (80)	45 (92)	**0.001**
PF ratio on intubation, median (IQR)[c]	121 (68–300)	107 (65–179)	112 (73–223)	0.56
Tracheostomy, *n* (%)	5 (9)	25 (29)	12 (25)	**0.049**
Infusion of vasopressors	43 (88)	58 (67)	22 (46)	**<0.001**
Hospital days to first group-defining steroid dose, median (IQR)	N/A	1 (0.5–2.5)	1 (1–3)	0.44
Treatment, *n* (%)				
Azithromycin	29 (60)	67 (77)	48 (98)	**<0.001**
Hydroxychloroquine	29 (60)	76 (87)	47 (96)	**<0.001**
Convalescent Plasma	11 (23)	57 (65)	25 (51)	**<0.001**
Therapeutic Anticoagulation	35 (73)	65 (75)	31 (63)	0.35
Biomarkers at ICU entry, median (IQR)				
Ferritin (μg/L)[d]	804 (326–1726)	962 (454–2125)	1761 (685–3298)	**0.02**
LDH (U/L)[e]	456 (310–642)	528 (380–722)	624 (564–875)	**<0.001**

(Continues)

TABLE 1 (Continued)

	No steroids ($n = 48$)	High-dose steroids ($n = 87$)	Pulse-dose steroids ($n = 49$)	p value
CRP (mg/dl)[f]	13 (4–19)	15 (6–25)	18 (10–27)	**0.03**
D-dimer (mg/L)[g]	2.7 (0.9–8)	2.7 (1–8.4)	3 (1.3–23.8)	0.26
ICU-free days at Day 28 median (IQR)	0 (0–26)	0 (0–28)	0 (0–25)	0.09
Hospital mortality, *n* (%)	22 (46)	26 (30)	27 (55)	**0.01**
Complications, *n* (%)				
AKI requiring new RRT[h]	8 (18)	29 (35)	27 (57)	**<0.001**
Pneumothorax	4 (8)	13 (15)	5 (10)	0.56
Positive sterile fluid culture	7 (15)	24 (28)	15 (31)	0.15
CVA	5 (9)	6 (7)	5 (10)	0.66

Note: Bold numbers indicate statistically significant p values.

Abbreviations: AKI, acute kidney injury; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVA, cerebrovascular accident; DM, diabetes mellitus; ED, emergency department; ESRD, end-stage renal disease; HTN, hypertension; ICU, intensive care unit; LDH, lactate dehydrogenase; N/A, not applicable; OSA, obstructive sleep apnea; PF, PaO_2/FiO_2; RRT, renal replacement therapy; WMC, Westchester Medical Center.

[a]Based on $n = 44$ in No steroid group, $n = 75$ in High dose steroid group, and $n = 49$ in Pulse dose steroid group.

[b]Based on $n = 42$ in No steroid group, $N = 83$ in High dose steroid group, and $N = 45$ in Pulse dose steroid group.

[c]Based on $n = 28$ in No steroid group, $N = 65$ in High dose steroid group, and $N = 46$ in Pulse dose steroid group.

[d]Based on $n = 43$ in No steroid group, $N = 85$ in High dose steroid group, and $N = 49$ in Pulse dose steroid group.

[e]Based on $n = 42$ in No steroid group, $N = 84$ in High dose steroid group, and $N = 49$ in Pulse dose steroid group.

[f]Based on $n = 43$ in No steroid group, $N = 85$ in High dose steroid group, and $N = 49$ in Pulse dose steroid group.

[g]Based on $n = 43$ in No steroid group, $N = 85$ in High dose steroid group, and $N = 49$ in Pulse dose steroid group.

[h]Excludes ESRD patients $n = 45$ in No steroid group, $n = 84$ in High dose steroid group, and $n = 47$ in Pulse dose steroid group.

lung disease in SARS-CoV-2.[12] Once RCTs evaluating corticosteroid therapy were launched, the dosing regimens resembled those of favorable prior studies of early corticosteroid administration in mixed ARDS populations: for example, methylprednisolone 1 mg/kg/day in the trial by Meduri et al.[13] and dexamethasone 20 mg once daily followed by 10 mg once daily in the trial by Villar et al.[14] The belief in some circles that COVID-19 pneumonia differs from routine ARDS in the degree of maladaptive exaggeration of the lung immune response led to sporadic reports[15–18] of the use of corticosteroids at pulse dose of 1 gm/day for at least 2 days as defined in the present study and as might be done for immune-mediated lung diseases such as pulmonary vasculitis or primary lung allograft dysfunction. Administration of corticosteroids at this magnitude has not been studied systematically in any COVID-19 pneumonia population before the present study. Although lower pulse-dose corticosteroid therapy, namely methylprednisolone 250 mg/day, has been studied in such patients previously,[19–21] in contrast to the present study none of the studies was restricted to patients managed in the ICU. To illustrate, in an entirely non-ICU 242-patient sample, Ruiz-Irastorza et al.[18] found a borderline significant beneficial association between receipt of pulse methylprednisolone at a dose of 125–250 mg/day for 3 days during the second week of symptoms and the composite endpoint of death or intubation (hazard ratio [HR]: 0.28 [95% CI: 0.89–0.95]; $p = 0.072$). Fernández-Cruz et al.[21] compared 396 steroid recipients to 67 nonrecipients with ICU patients comprising 6.5% of the study population. The vast majority of steroid recipients (78%) received 1 mg/kg/day of methylprednisolone equivalents, with the remainder receiving a median of three pulse doses ranging up to 500 mg/day. A subset (22.5%) of the nonpulse group received rescue pulses. Although corticosteroid administration, on the whole, was associated with reduced mortality (propensity score-matched HR: 0.36 [95% CI: 0.14–0.93]; $p = 0.035$), there was no significant difference according to the dosing regimen, keeping in mind that rescue pulsing was performed in a substantial number of nonpulse patients. Finally, Edalatifard et al [19] performed a small RCT comparing methylprednisolone 250 mg/day for 3 days to standard care minus corticosteroids. None of the patients was receiving invasive mechanical ventilation. There were significantly more survivors in the corticosteroid arm (32/24, 94%) than in the standard care arm (16/28, 57%), p value <0.001, and corticosteroid recipients exhibited significantly faster improvement (11.8 vs. 16.4 days; $p = 0.011$).

The significance of the increased rate of AKI requiring RRT in the pulse-dose corticosteroid group of the present study remains to be further elucidated. Unlike the lower respiratory tract, the kidney has a high density of the angiotensin-converting enzyme-2 receptor used by SARS-CoV-2 to penetrate cells.[22] This observation, coupled with autopsy data[23] suggests that, in contrast to lung disease, renal injury in COVID-19 is possibly a direct virus-mediated phenomenon. It has

TABLE 2 Results of multiple logistic regression and zero-inflated Poisson regression for the outcomes of interest

Outcome measure	No steroids	High-dose steroids	Pulse-dose steroids	High-dose vs. pulse-dose[a]
ICU-free days at Day 28				
aRR		0.96	1.45	
95% CI	Reference	0.80–1.15	1.05–2.02	***p* = 0.003**
p value		0.63	**0.03**	
Hospital mortality				
aOR		0.31	0.73	
95% CI	Reference	0.12–0.77	0.27–1.96	***p* = 0.04**
p value		**0.01**	0.73	

Note: Bold values indicate statistically significant *p* values.

Abbreviations: aOR, adjusted Odds ratio; aRR, adjusted relative risk; CI, confidence interval; ICU, intensive care unit.

[a]Comparison using the Wald test.

TABLE 3 Results of multiple logistic regression for ICU complications

Complication	No steroids	High-dose steroids	Pulse-dose steroids	High-dose vs. pulse-dose[a]
AKI requiring RRT				
aOR		1.61	3.53	
95% CI	Reference	0.62–4.19	1.27–9.82	***p* = 0.05**
p value		0.33	**0.02**	
Pneumothorax				
aOR		0.99	0.55	
95% CI	Reference	0.26–3.68	0.12–2.46	*p* = 0.33
p value		0.98	0.44	
Positive sterile culture				
aOR		1.97	2.22	
95% CI	Reference	0.71–5.44	0.73–6.72	*p* = 0.78
p value		0.19	0.16	
CVA				
aOR		0.49	0.90	
95% CI	Reference	0.13–1.91	0.21–3.91	*p* = 0.37
p value		0.31	0.89	

Note: Bold values indicate statistically significant *p* values.

Abbreviations: AKI, acute kidney injury; aOR, adjusted Odds ratio; aRR, adjusted relative risk; CI, confidence interval; CVA, cerebrovascular accident; ICU, intensive care unit; RRT, renal replacement therapy.

[a]Comparison using the Wald test.

also been observed empirically that the onset of AKI in COVID-19 tends to follow the evolution of lung disease.[24] From this framework, it could be surmised that pulse corticosteroid-related profound immunosuppression induced to counter worsening COVID-19 pneumonia facilitates entry of SARS-CoV-2 at extrapulmonary sites such as the kidney, thereby putting them at greater risk for direct viral damage. Of note, antiviral therapy active against SARS-CoV-2 (e.g., remdesivir) was not routinely administered to ICU patients with COVID-19 pneumonia in our institution during the study period. To our knowledge, our results are the first suggestion of renal harm from the administration of any dose of corticosteroids for COVID-19 pneumonia. These findings warrant further investigation on a larger scale.

The current study suffers from a number of limitations, among them its single-center retrospective design and small sample size; patient distribution was notably skewed towards the high-dose corticosteroid group. Lack of protocolization of corticosteroid therapy and patient management, while reflective of the reality of the study period early in the pandemic, risks introduction of bias. There was no standardized or prospective COVID-19 data entry during the study period, leading to the potential for missing values. Due to the post hoc nature of the data collection, we were unable to confidently establish the time of symptom onset and thus could not ascertain the timing of initiation of corticosteroids relative to that reference point. We recorded corticosteroid administration only during the patients' WMC stay, so there is a small chance of pre-WMC corticosteroid exposure by patients transferred from outlying hospitals. In light of the large number of identified baseline differences among the three groups, there is a possibility of additional unmeasured confounders that have not been addressed in the logistic regression model. Randomization into treatment arms was, of course, precluded by the retrospective methodology, and the sample size was deemed insufficient for an attempt at "pseudorandomization" via propensity score matching. Finally, our study does not address longer-term outcomes following index hospitalization (e.g., 90-day mortality) nor does it address potential complications beyond the ICU stay such as the duration of detectable SARS-CoV-2 in the three study groups.

5 | CONCLUSIONS

Compared to no receipt of corticosteroids, this study found no survival advantage to pulse corticosteroid dosing at a level of methylprednisolone 1 gm/day while reaffirming the survival benefit of high-dose corticosteroids in critically ill patients with COVID-19 pneumonia. When compared to each other with respect to mortality, high-dose corticosteroids emerged superior to pulse-dose corticosteroids. Pulse-dose corticosteroid use was associated with increased odds of AKI requiring RRT in this study, an intriguing finding that may account for the observed lack of survival benefit from the pulse-dose regimen despite an increase in ICU-free days.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Conceptualization and study design: Hamid Yaqoob, Dipak Chandy, Oleg Epelbaum. *Data acquisition*: Hamid Yaqoob, Daniel Greenberg, Frank Hwang, Curtis Lee, David Vernik, Ravi Manglani. *Data analysis and statistics*: Hamid Yaqoob, Zhen Wang, M. Hassan Murad, Dipak Chandy, Oleg Epelbaum. *Manuscript preparation and writing*: Hamid Yaqoob, Oleg Epelbaum. *Review and editing of the first draft*: all authors. *Approval of the final version*: all authors. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

DATA AVAILABILITY STATEMENT

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

ORCID

Hamid Yaqoob https://orcid.org/0000-0002-1352-8811

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