*Original Article*

# Methylprednisolone pulse therapy for critically ill patients with coronavirus disease 2019: A single-center retrospective observational study

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*Aim:* This study compared the clinical outcomes of critically ill patients with coronavirus disease (COVID-19) pneumonia treated with high-dose methylprednisolone and other steroids.

*Methods:* This retrospective observational study included critically ill COVID-19 pneumonia adult patients with tracheal intubation treated between April 1, 2020, and September 15, 2021. Of the 46 patients who met the inclusion criteria, 36 received steroid pulse therapy (Group P) and 10 received steroids without pulse therapy (Group NP). Subgroup analyses in Group P by methylprednisolone dose of 1000 or 500 mg for 3 days during intensive care unit stay were carried out. The primary and secondary outcomes were 28-day mortality and steroid-associated complications, respectively.

*Results:* In the Kaplan–Meier curve analysis, there was no difference in the 28-day survival between P and NP groups (log–rank P = 0.046). Univariate Cox proportional hazard model also showed that Group P had a decreased 28-day mortality (hazard ratio 0.30; [95% confidence interval, 0.20–0.44]; P < 0.01). After adjusting for covariates (age, sex, remdesivir, baricitinib, and favipiravir), using the multivariate Cox proportional hazards model, Group P had improved 28-day mortality (0.50 [0.30–0.85], P = 0.01).

*Conclusion:* Steroid pulse therapy might improve the 28-day and in-hospital mortality in critically ill patients with COVID-19 pneumonia.

**Key words:** COVID-19, mechanical ventilation, methylprednisolone, steroid pulse therapy, tracheal intubation

## BACKGROUND

CURRENTLY, THERE IS no steroid-free effective coronavirus disease (COVID-19) treatment. Dexamethasone decreased the 28-day mortality rate in patients with COVID-19 pneumonia who required supplemental oxygenation.[1] Although the effectiveness of other steroids has been previously tested,[2,3] the optimal dose and duration of steroid therapy remains unclear.[4–6] In Japan, high-dose steroids (e.g., methylprednisolone [mPSL] 1000 mg/day) are routinely used for treating interstitial pneumonia, whereas steroid pulse therapy (SPT) has been prescribed for critically-ill COVID-19 pneumonia patients.[7–9] Three randomized controlled trials (RCTs) showed that high-dose steroid therapy improved outcomes in moderate to critically ill COVID-19 pneumonia patients.[4,5,10] However, Japanese COVID-19 guidelines include "no recommendation" for SPT,[11] based on only one low-quality RCT[5] using a non-standard corticosteroid dose in Japan. Only one small-sample RCT (unadjusted for background factors)[10] has specifically examined the efficacy of high-dose SPT (mPSL 1000 mg/day) in moderate to critically ill COVID-19 pneumonia cases.

Therefore, the efficacy of high-dose steroid therapy has not been fully investigated. This study compared the clinical outcomes following high-dose mPSL (500–1000 mg/day) or other steroid treatment in critically ill patients with COVID-19 pneumonia.

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## METHODS

### Study design, setting, and participants

THIS single-center, retrospective, observational study was approved by the Ethics Committee of National Hospital Organization Yokohama Medical Center (No. 2021-14) and enrolled critically ill COVID-19 pneumonia patients with tracheal intubation treated from April 1, 2020 to September 15, 2021. The inclusion criteria were: (i) age ≥ 18 years; (ii) confirmed COVID-19 diagnosis. We excluded patients with: (i) a "do not attempt to resuscitate" order; (ii) tracheal intubation except due to respiratory failure caused by COVID-19 pneumonia.

Participants were classified into either the SPT (Group P) or steroids without pulse therapy (Group NP) groups. Following intensive care unit (ICU) admission, Group P received steroid therapy with mPSL 1000 or 500 (at the physician's discretion), 250, and 125 mg/day on ICU days 1–3, 4–6, and 7–9, respectively. In the NP group, each physician could administer 6 mg dexamethasone or 1–2 mg/kg methylprednisolone. The standard duration of steroid treatment was 10 days.

After assessment by several intensivists, participants with a type H or type L computed tomography (CT) image (based on the classification of Gattinoni *et al.*[12]) at presentation were assigned to the P and NP groups, respectively.

### Diagnosis of COVID-19

A COVID-19 diagnosis was based on a positive result on nasopharyngeal or oropharyngeal swabs for severe acute respiratory syndrome coronavirus 2 polymerase chain reaction testing (bioMerieux Japan Ltd, Tokyo, Japan).

### Data collection

Data on the participant's sex, age, medical history, clinical outcomes, signs, symptoms, oxygen saturation, and laboratory findings at ICU admission were analyzed. The following comorbidities were collected: ischemic heart disease, cerebrovascular disease, hypertension, and cancer; and in the last year: chronic kidney disease, chronic obstructive pulmonary disease, asthma, obesity, diabetes, and immunosuppressed conditions.[13]

### Outcomes

The primary outcome investigated was the 28-day mortality from admission. The secondary outcome was steroid-associated complications, including hemorrhagic complications (gastrointestinal bleeding requiring endoscopic hemostasis, cerebral hemorrhage, and intramuscular hematoma), thrombotic complications (cerebral infarction and pulmonary embolism), pneumothorax and pneumomediastinum, COVID-19-associated pulmonary aspergillosis (CAPA), and cytomegalovirus infection, that occurred within 28 days. In a subgroup analysis, we compared patient outcomes after treatment with mPSL 1000 or 500 mg/day protocols in the P group.

### Data analysis

Results are expressed as the median and 25th and 75th quartiles (Q1–Q3) for quantitative data and as number and percentage for categorical data. Two-sided $\chi^2$-test or Fisher's exact test was used to assess the associations between intervention groups and categorical variables. The Mann–Whitney *U*-test was used for intergroup comparison of continuous variables. Kaplan–Meier survival curve analysis was used to analyze time to death between both study groups. The treatment effects of both groups were estimated and expressed as hazard ratios (HR) with 95% confidence intervals (CI) using a univariate Cox proportional hazard model. Multivariate Cox proportional hazards modeling was used to adjust for covariates.

All statistical analyses were undertaken using SPSS (version 28.0; SPSS, Inc, Chicago, IL, USA). A two-sided $P < 0.05$ indicated statistical significance. This manuscript conforms to the STROBE guideline for cohort and cross-sectional studies.[14]

## RESULTS

### Participant characteristics

FORTY-six COVID-19 pneumonia patients met our inclusion criteria and were enrolled in Group P ($n = 36$) or Group NP ($n = 10$; Fig. 1). At baseline, there were no significant intergroup differences in comorbidities, $PaO_2/FiO_2$ ratio, Acute Physiology and Chronic Health Evaluation (APACHE) II score,[15] interleukin-6 (IL-6) levels, or severity (Table 1).

There were no significant differences in the rate of tracheostomy, intensive care unit stay, hospital stay, and steroid therapy duration (Table 2). There was a significant intergroup difference in the use of remdesivir ($P = 0.04$), baricitinib ($P = 0.03$), and favipiravir ($P = 0.03$; Table 3).

### Clinical outcomes

Nine patients, including 5 of 36 patients treated with SPT (13.9%) and 4 of 10 patients treated with steroids without pulse therapy (40%), died within 28 days after

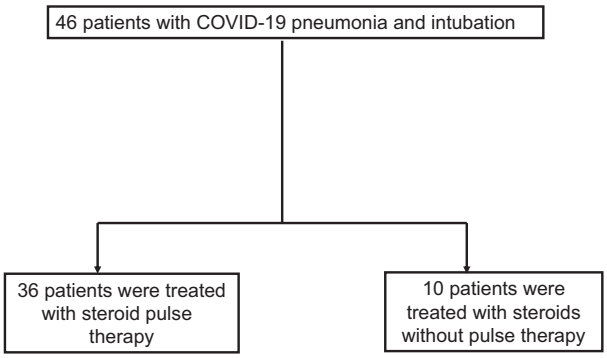


**Fig. 1.** Flow diagram of the study participant selection process, from intensive care unit admission until treatment. Forty-six patients fitted the selection criteria. These patients were subsequently divided into two groups: those treated with steroid pulse therapy ($n$ = 36) and those treated with steroids but without pulse therapy ($n$ = 10).

hospitalization (Table 4), but no significant intergroup difference in 28-day mortality was detected ($P$ = 0.07).

### *Primary outcome*

In the Kaplan–Meier curve analysis, there was no difference in 28-day survival between the P and NP groups (log–rank $P$ = 0.046). Analysis using the univariate Cox proportional hazards model for the 46 patients with tracheal intubation in Group P showed a significant improvement in 28-day mortality (HR 0.30; 95% CI, 0.20–0.44; $P$ < 0.01) (Fig. 2). In the multivariate Cox proportional hazards model adjusted for the covariates age, sex, remdesivir, baricitinib, and favipiravir, SPT significantly improved 28-day mortality (HR 0.50; 95% CI, 0.30–0.85; $P$ = 0.01). Covariate analysis showed that age and favipiravir use were significantly associated with mortality (Table 5).

**Table 1.** Baseline characteristics of critically ill patients with COVID-19

| | Treated with steroid pulse therapy ($n$ = 36) | Treated with steroids without pulse therapy ($n$ = 10) | $P$-value |
|---|---|---|---|
| Age (years) | 64 (56–76) | 73 (65–77) | 0.32 |
| Gender (male) | 28 (78) | 9 (90) | 0.41 |
| Body mass index (kg/m$^2$) | 25 (22–27) | 24 (21–26) | 0.39 |
| $PaO_2/FiO_2$ ratio | 105 (80–160) | 116 (83–148) | 0.89 |
| APACHE II score | 22 (10–30) | 25 (5–39) | 0.36 |
| Time from onset of first symptoms (days) | 7 (5–8) | 10 (6–17) | 0.09 |
| Comorbidity | 26 (72) | 9 (90) | 0.41 |
| Laboratory data | | | |
| D-dimer (μg/mL) | 2.1 (1.8–3.6) | 2.4 (1.7–5.6) | 0.42 |
| Lactate dehydrogenase (U/L) | 556 (450–619) | 516 (422–576) | 0.43 |
| KL-6 (U/mL) | 439 (290–616) | 482 (378–1,077) | 0.24 |
| PCT (ng/mL) | 0.23 (0.10–0.56) | 0.31 (0.15–0.48) | 0.41 |
| IL-6 (pg/mL) | 93.6 (52.2–152.9) | 94.2 (64.3–156.1) | 0.86 |
| HbA1c ≥ 6.5 | 18 (48) | 3 (30) | 0.21 |

Data are shown as $n$ (%) or median (interquartile range). APACHE, Acute Physiology and Chronic Health Evaluation; HbA1c, glycated hemoglobin; IL-6, interleukin-6; KL-6, Krebs von den Lungen-6; PCT, procalcitonin.

**Table 2.** Clinical characteristics of included critically ill patients with COVID-19

| | Treated with steroid pulse therapy ($n$ = 36) | Treated with steroids without pulse therapy ($n$ = 10) | $P$-value |
|---|---|---|---|
| Tracheostomy | 11 (31) | 3 (30) | 0.97 |
| Intensive care unit stay (days) | 9 (6–18) | 14 (9–16) | 0.36 |
| Hospital stay (days) | 24 (16–32) | 18 (15–40) | 0.71 |
| Steroid therapy duration (days) | 22 (16–31) | 16 (12–19) | 0.16 |

Data are shown as $n$ (%) or median (interquartile range).

**Table 3.** Admission period and drug type among critically ill patients with COVID-19

| | Treated with steroid pulse therapy ($n$ = 36) | Treated with steroids without pulse therapy ($n$ = 10) | $P$-value |
|---|---|---|---|
| Patient admission period | | | |
| April 2020–March 2021 | 10 | 7 | |
| April 2021–September 2021 | 26 | 3 | |
| Therapeutic drug | | | |
| Methylprednisolone, $n$ (%) | 36 (100) | 3 (30) | <0.01 |
| April 2020 to March 2021 | 10 | 2 | |
| April 2021 to September 2021 | 26 | 1 | |
| Dexamethasone, $n$ (%) | 0 (0) | 7 (70) | <0.01 |
| April 2020 to March 2021 | 0 | 5 | |
| April 2021 to September 2021 | 0 | 2 | |
| Remdesivir, $n$ (%) | 36 (100) | 8 (80) | 0.04 |
| April 2020 to March 2021 | 10 | 6 | |
| April 2021 to September 2021 | 26 | 2 | |
| Baricitinib, $n$ (%) | 25 (69.4) | 3 (30) | 0.03 |
| April 2020 to March 2021 | 0 | 0 | |
| April 2021 to September 2021 | 25 | 3 | |
| Hydroxychloroquine, $n$ (%) | 12 (33) | 7 (70) | 0.07 |
| April 2020 to March 2021 | 10 | 7 | |
| April 2021 to September 2021 | 2 | | |
| Favipiravir, $n$ (%) | 3 (8) | 4 (40) | 0.03 |
| April 2020 to March 2021 | 2 | 4 | |
| April 2021 to September 2021 | 1 | 0 | |

**Table 4.** End-points in critically ill patients with COVID-19

| | Patients treated with steroid pulse therapy ($n$ = 36) | Patients treated with steroids without pulse therapy ($n$ = 10) | $P$-value |
|---|---|---|---|
| Primary end-point | | | |
| 28-day mortality | 5 (13.9) | 4 (40) | 0.07 |
| Secondary end-point, n (%) | | | |
| Steroid-associated complications | | | |
| Bleeding complications | 9 (25) | 4 (40) | 0.35 |
| Thrombotic complications | 7 (19) | 2 (20) | 0.97 |
| Pneumothorax and pneumomediastinum | 9 (25) | 6 (60) | 0.06 |
| COVID-19-associated pulmonary aspergillosis | 3 (8.3) | 1 (10) | 0.87 |
| Cytomegalovirus infection | 7 (19.4) | 2 (20) | 0.97 |

Data are shown as $n$ (%).

## Secondary outcome

No significant increase in steroid-associated complications was noted within the 28-day period (Table 4).

## Subgroup analysis

In patients treated with 1000 and 500 mg/day protocols, analysis using the univariate Cox proportional hazards

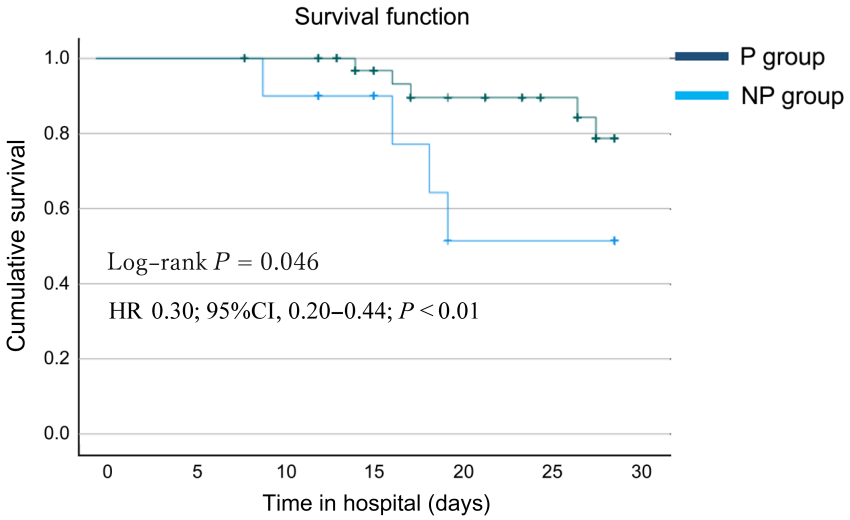


**Fig. 2.** Twenty-eight-day cumulative survival graph of critically ill patients with COVID-19 with tracheal intubation. In the Kaplan–Meier curve analysis, there was no difference in 28-day survival between patients treated with steroid pulse therapy (P group) and those treated with steroids but without pulse therapy (NP group) (log–rank $P = 0.046$). However, in the univariate analysis using the Cox proportional hazards model, steroid pulse therapy decreased the risk of death in critically ill patients with COVID-19 pneumonia (hazard ratio [HR] 0.30; 95% confidence interval [CI], 0.20–0.44; $P < 0.01$).

**Table 5.** Factors associated with 28-day mortality in critically ill patients with COVID-19

| | HR | 95% CI | *P*-value |
|---|---|---|---|
| Steroid pulse therapy | 0.50 | 0.30–0.85 | 0.01 |
| Age | 1.02 | 0.99–1.05 | 0.21 |
| Gender (male) | 2.16 | 1.13–4.16 | 0.02 |
| Remdesivir | 1.21 | 0.59–2.50 | 0.60 |
| Favipiravir | 2.66 | 1.58–4.50 | <0.01 |
| Bacitirinib | 1.41 | 0.77–2.59 | 0.27 |

CI, confidence interval; HR, hazard ratio.

model showed no difference in improvement in the 28-day mortality (HR 0.54; 95% CI, 0.09–3.23; $P = 0.50$).

## DISCUSSION

THIS IS THE first observational study to evaluate and determine that high-dose steroid therapy (mPSL 500 or 1000 mg/day) decreased the 28-day mortality of critically ill COVID-19 patients with pneumonia in Japan.

Steroid treatment is important in COVID-19 pneumonia.[16] The cytokine release syndrome, characterized by increased levels of cytokines (e.g., IL-6), that can cause or worsen acute respiratory distress syndrome and multiorgan failure,[17] is an increasingly crucial issue in COVID-19. In critically ill COVID-19 patients, the high mortality rate is attributable to the rapid development of organized pneumonia secondary to COVID-19, which necessitates treatment with high-dose corticosteroids ("pulse" doses) for a longer duration.[18]

In a meta-analysis, Cui *et al.*[19] showed that SPT is effective. In Japan, there have been several reports of good outcomes with SPT for critically ill patients with COVID-19.[8,9] Therefore, SPT could be a realistic treatment option, considering its low cost and widespread use.

Three RCTs of COVID-19 pneumonia patients evaluated the efficacy of high-dose steroid therapy.[4,5,10] Pinzón *et al.*[4] found that, compared with 6 mg dexamethasone for 7–10 days, high-dose mPSL (250–500 mg/day) for 3 days followed by oral prednisone for 14 days significantly decreased recovery time and ICU admission rates in moderate COVID-19 pneumonia. However, their results are difficult to compare with our results showing that the mPSL group had lower in-hospital mortality[4] as they enrolled non-ICU COVID-19 pneumonia patients.

Edalatifard *et al.*,[5] in a single-blind RCT mainly comprising nonintubated patients (79%), showed that mPSL pulse therapy decreased the 50-day mortality rate (250 mg/day for 3 days) compared with the standard care group (5.9% versus 42.9%; $P < 0.001$).

Thus, RCTs with moderate and critically ill COVID-19 pneumonia patients have reported improved outcomes, but without sufficient independent evidence for the efficacy of

SPT as the analysis did not adjust for confounding covariates and tracheal intubation may have contributed to the improvement. Farahani *et al*.[10] carried out an RCT in critically ill COVID-19 pneumonia patients who were intubated and received 1000 mg/day mPSL (or 1 mg/kg prednisolone) for 3 days. Although their study is similar to ours in that they included only intubated patients, the outcomes reported constitute a major difference (improvement in clinical symptoms versus mortality). Moreover, their study has a high risk of bias as the methods used for blinding of investigators with regard to the intervention are unknown, and has a high risk of reporting bias as 60-day mortality, which is the primary outcome in the preregistration protocol (https://en.irct.ir/trial/47088), has not been reported.

Thus, the three SPT studies[4,5,10] have limitations, and there is no definitive evidence of the efficacy of SPT for critically ill COVID-19 pneumonia patients.

To improve survival with pulsed steroid therapy, steroid-related complications should be prevented. High-dose corticosteroid therapy for early acute respiratory distress syndrome was associated with an increased risk of secondary infections,[20] and the number of complications did not increase.[21,22] Due to different definitions in previous studies, the epidemiology of steroid treatment-related adverse effects in COVID-19 pneumonia is unknown.[23] We are concerned about the increase in steroid-related CAPA despite no significant intergroup differences being detected.

Age is a key factor in a patient's ability to tolerate the complications of high-dose steroids. Ro *et al*.[8] found high and poor efficacy of mPSL (250 mg for 3 days) treatment for COVID-19 pneumonia in patients aged in their early 70s or late 70s, respectively. Treatment failure was mainly due to severe steroid-related complications (i.e., pneumothorax and pneumomediastinum, CAPA, and cytomegalovirus infections). Thus, the authors concluded that high-dose steroid therapy is effective for patients until their early 70s, but should be avoided for patients in their late 70s or older. The absence of high-dose steroid-related complications might have contributed to the good performance in the P group, and patients aged in their 60s were treated with SPT. The results of previous studies and our study suggest that SPT could improve outcome in relatively young patients with fewer complications. However, all of the abovementioned evidence is from small, observational studies and is insufficient. Future studies are needed to identify the patient groups for which steroid therapy is effective.

### Limitations

First, the single-center design and short study period resulted in a relatively small sample size, which could have influenced the accuracy of our findings. Second, the sample size might have been insufficient for multiple regression analysis, due to the small number of outcome occurrences and the inclusion of only five covariates.

Third, tracheal intubation was undertaken based on physician's judgment, and this lack of uniformity could have influenced our results. Observational studies with strict intubation criteria are necessary to overcome this limitation. Fourth, CT findings—which are particularly important in clinical practice—were not examined in this study. Fifth, infectious complications are an important mortality-related factor but were not considered in this study due to difficulties in defining them. Improved study design, with a large sample, and a focus on SPT-associated infectious complications and mortality are warranted.

Sixth, the recommended COVID-19 treatment changed during the study period.[24] Hydroxychloroquine use is not recommended in current guidelines; however, it was used by 70% of the NP group in this study. Although it is not the standard according to current Japanese guidelines,[11] some studies recommend its use in the early stages of COVID-19[25,26]; therefore, we used it. The period of each drug usage is shown in Table 3, and whether the results might have been influenced by different drug usage during different treatment periods cannot be ruled out. The use of drug combinations might have also affected prognosis; however, the small sample size makes this inconclusive.

Seventh, the different mortality rates of each strain (B.1.1.7, B.1.351, and B.1.617.2) could have influenced the outcome. Finally, the age-related effect on COVID-19[27] mortality is known and, although nonsignificant, the 10-year difference in the median age of the NP and P groups could reduce the importance of our study's results.

## CONCLUSIONS

STEROID PULSE THERAPY could improve 28-day mortality in critically ill COVID-19 pneumonia patients. However, this study included a small sample size. The safety and efficacy of high-dose corticosteroids should be determined in RCTs or big data analyses.

## ACKNOWLEDGMENTS

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## DISCLOSURE

APPROVAL OF THE research protocol: This study was approved by the Institutional Review Board for

Clinical Research of Yokohama Medical Center (approval number: 2021-14).
Informed consent: We applied an opt-out method on the institutional website to obtain patient consent.
Registry and registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None.

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