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ORIGINAL ARTICLE

Comparative 28-day Outcomes of Pulse-Dose Methylprednisolone versus Prolonged Low-Dose Dexamethasone in Hospitalized COVID-19 Pneumonia: A Cohort Study

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Abstract: **Introduction:** Corticosteroids are widely used in COVID-19 pneumonia; however, the optimal regimen remains uncertain. We compared clinical outcomes between pulse-dose methylprednisolone and prolonged low-dose dexamethasone in hospitalized patients with COVID-19 pneumonia. **Methods:** In this retrospective cohort study, adult patients hospitalized with COVID-19 pneumonia (18 April–30 August 2021), who received either pulse-dose methylprednisolone or prolonged low-dose dexamethasone, were compared regarding 28-day mortality, in-hospital mortality, and treatment-free days. Multivariable Cox regression and propensity score matching (PSM) were used to adjust for confounding. **Results:** Among 460 patients (269 pulse-dose methylprednisolone, 191 prolonged low-dose dexamethasone), no significant difference in 28-day mortality was observed in multivariable analysis (aHR: 1.51; 95% CI: 0.74–3.09, p = 0.26). After PSM, 28-day mortality remained similar (HR: 1.40; 95% CI: 0.64–3.06; p = 0.38), although a trend toward higher in-hospital mortality was noted with pulse-dose methylprednisolone (HR: 2.07; 95% CI: 0.96–4.42; p = 0.06). **Conclusion:** Pulse-dose methylprednisolone was not associated with a significant difference in 28-day mortality compared with prolonged low-dose dexamethasone. A trend toward higher in-hospital mortality was observed with pulse-dose methylprednisolone, warranting cautious interpretation due to potential residual confounding.

Keywords: Methylprednisolone; Dexamethasone; COVID-19; SARS-Cov-2; Pneumonia; Viral

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1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in late 2019 (1) and was declared a global pandemic by the World Health Organization in March 2020. While most infections are mild, approximately 10–15% of patients develop severe pneumonia requiring hospitalization and advanced respiratory support (2).

Disease progression is characterized by an initial viral phase followed, in some patients, by a dysregulated inflammatory response leading to acute respiratory distress syndrome (ARDS) (2) and increased mortality (3). Corticosteroids are widely used to modulate this hyperinflammatory state. Evidence from the RECOVERY trial supports the use of prolonged low-dose dexamethasone, demonstrating reduced mortality in patients requiring oxygen or mechanical ventilation (4).

In contrast, pulse-dose methylprednisolone is often administered in more severe cases due to its potent anti-inflammatory effects and favorable pulmonary penetration (5, 6), although its clinical benefit remains uncertain and may differ due to variations in dosing strategies and administration protocols (1, 7, 8).

In Thailand, dexamethasone is recommended for hospitalized patients with hypoxic COVID-19 pneumonia, whereas the use of methylprednisolone is not standardized and varies across clinical practice. Given the lack of definitive guidance and the limited previous studies that provide a direct comparison between pulse-dose methylprednisolone and prolonged low-dose dexamethasone in COVID-19 pneumonia, this study aimed to compare 28-day mortality between hospitalized COVID-19 pneumonia patients treated with pulse-dose methylprednisolone and those treated with prolonged low-dose dexamethasone. The main hypothesis was that COVID-19 pneumonia patients treated with pulse-dose methylprednisolone might have a lower 28-day mortality rate compared to those receiving prolonged low-dose dexamethasone.

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2. Methods

2.1. *Study design and setting*

This observational, retrospective cohort study included hospitalized adult patients with COVID-19 pneumonia admitted to Ramathibodi Hospital, a tertiary university hospital in Bangkok, Thailand, between April 18, 2021, and August 30, 2021. Patients were retrospectively followed through the hospital's electronic medical records from the date of admission until hospital discharge, death, transfer to another healthcare facility, or 28 days after admission. The hospitalized patients, who received either pulse-dose methylprednisolone or prolonged low-dose dexamethasone, were compared regarding 28-day mortality, in-hospital mortality, and treatment-free days.

The study was approved by the Committee on Human Rights Related to Research, Faculty of Medicine, Ramathibodi Hospital, Mahidol University (IRB COA. MURA2021/973; approval

date: November 18, 2021).

2.2. *Participants*

Adult patients (≥18 years) hospitalized with COVID-19 pneumonia, confirmed by clinical assessment, radiographic findings, and positive real-time reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2, were included. All patients received either dexamethasone or methylprednisolone.

COVID-19 pneumonia was defined by at least one of the following: resting SpO_2 ≤96% on room air, exertional desaturation ≥3%, or radiographic pulmonary infiltrates. The SpO_2 threshold was based on national guidelines and WHO recommendations for identifying patients at risk of clinical deterioration (9, 10).

Exclusion criteria were pregnancy and inter-hospital transfer during admission.

2.3. *Treatment group (Exposure)*

Patients were classified according to the corticosteroid regimen received. The methylprednisolone group received intravenous methylprednisolone ≥250 mg/day for 3 days (pulse-dose), followed by tapering. The dexamethasone group received oral or intravenous dexamethasone 6–24 mg/day for ≥5 days (prolonged low-dose), with tapering as clinically indicated. A subgroup analysis was performed in the methylprednisolone group based on dose (250, 500, or 1,000 mg/day).

Treatment was guided by institutional protocols and clinical judgment (9). For mild cases (radiographic evidence of pneumonia with SpO_2 ≤96% or exertional desaturation ≥3%), patients received dexamethasone 6 mg daily for 7–10 days. For moderate cases (radiographic pneumonia with a SpO_2/FiO_2 ratio <315 or SpO_2 ≤93%), dexamethasone 20 mg daily was administered for 3–5 days, followed by 10 mg daily for a total of 10 days. For severe cases (multifocal or bilateral pneumonia with a SpO_2/FiO_2 ratio <235 or SpO_2 ≤90%), methylprednisolone 500 mg daily was administered for three days. Dosing was further individualized based on clinical status and patient factors.

2.4. *Data gathering*

Patient characteristics included demographics (age, sex, body mass index [BMI]), comorbidities, duration from symptom onset to hospital admission, and time to corticosteroid initiation. Disease severity indicators included oxygen requirement, type of respiratory support, and severity of acute respiratory distress syndrome (ARDS). Hypoxemia severity was defined according to the Berlin definition using the PaO_2/FiO_2 (PF) ratio. When arterial blood gas data were unavailable, the SpO_2/FiO_2 (SF) ratio was used as a surrogate. Severity was classified as follows: mild (PF ratio: 201–300 mmHg or SF ratio: 235–315), moderate (PF ratio: 101–200 mmHg or SF ratio: 123–234), and severe (PF ratio: ≤100 mmHg or SF ratio: <123).

Laboratory parameters at admission included white blood cell count, hemoglobin, platelet count, serum creatinine, total bilirubin, C-reactive protein (CRP), lactate dehydrogenase (LDH), and D-dimer levels. Concomitant therapies, including antivirals (favipiravir, remdesivir), immunomodulators (tocilizumab, infliximab, baricitinib, tofacitinib), and anticoagulants, were also recorded.

2.5. *Outcomes*

The primary outcome was 28-day mortality, defined as death from any cause within 28 days of hospital admission. Secondary outcomes included: in-hospital mortality, defined as in-hospital all-cause mortality during the index admission; 28-day ventilator-free days, defined as the number of days alive and free from invasive mechanical ventilation within 28 days of admission; 28-day inotrope-free days, defined as days alive without inotropic support within 28 days of admission; 28-day oxygen-free days, defined as days alive without supplemental oxygen use within 28 days of admission; and 28-day hospital-free days, defined as days alive and discharged from hospital within 28 days of admission.

2.6. *Statistical analysis*

Sample size was estimated based on Pinzón et al. (8), which reported 30-day mortality rates of 11.42% in the methylprednisolone group and 21.62% in the dexamethasone group. Assuming a two-sided α of 0.05, a power (1−β) of 80%, and a 1:1 allocation ratio, the minimum required sample size was 414 patients (207 per group). Because this was a retrospective cohort study, no additional participant recruitment was undertaken. Instead, all consecutive patients who met the predefined eligibility criteria and were admitted to Ramathibodi Hospital during the study period were included, resulting in a final cohort of 460 patients.

Pulse-dose methylprednisolone was preferentially administered to patients with more severe disease, which may have introduced confounding by indication. To mitigate this, propensity score matching (PSM) was applied to reduce baseline imbalances between groups. No separate a priori sample size calculation was performed for the PSM analysis because PSM was conducted as a secondary analytical approach using the available cohort. A post hoc power assessment of the matched cohort demonstrated moderate statistical power for the primary outcome (hazard ratio 1.41; power = 0.76) and high statistical power for selected secondary outcomes (hazard ratio 2.07; power = 0.99).

Continuous variables were summarized as mean (standard deviation [SD]) or median (interquartile range [IQR]), depending on distribution, and compared using the Student's t-test or Mann–Whitney U test, as appropriate. Categorical variables were presented as counts (percentages) and compared using the chi-square or Fisher's exact test. Missing data were primarily attributable to laboratory investigations that were not performed as part of routine clinical care. These missing values were handled using complete-case analysis without imputation. Loss to follow-up was minimal because outcome data were retrospectively ascertained from electronic medical records until hospital discharge, death, transfer to another healthcare facility, or 28 days after admission, whichever occurred first.

28-day and in-hospital mortality were analyzed using multivariable Cox proportional hazards regression, with results reported as hazard ratios (HRs) and 95% confidence intervals (CIs). Covariates were selected based on clinical relevance and prior literature. Continuous outcomes (28-day ventilator-free, inotrope-free, oxygen-free, and hospital-free days) were analyzed using generalized linear models.

Variables included in the multivariable Cox regression analysis for the primary outcome (28-day mortality) and in the mean difference analysis of secondary outcomes were age, sex, body mass index, days from symptom onset to corticosteroid initiation, comorbidities (diabetes mellitus, hypertension,

dyslipidemia, chronic kidney disease, heart disease, cerebrovascular disease, chronic lung disease, chronic liver disease, cancer, transplantation, and immunocompromised status), baseline PaO_2/FiO_2 ratio, initial respiratory support (oxygen nasal cannula, oxygen mask with reservoir bag, high-flow nasal cannula, non-invasive positive pressure ventilation, or endotracheal intubation), ICU admission, and remdesivir administration.

To address confounding by indication, PSM was performed using a logistic regression model incorporating pre-treatment variables, including age, sex, body mass index, comorbidities, PaO_2/FiO_2 ratio, inflammatory biomarkers (C-reactive protein, lactate dehydrogenase, and D-dimer), and baseline respiratory support. One-to-one nearest-neighbor matching without replacement was applied. Covariate balance was assessed using standardized mean differences (SMD) and histogram plots.

A sensitivity analysis was performed to assess the robustness of the primary findings. First, PSM based on baseline demographic and clinical characteristics was used to reduce confounding by indication. Primary and secondary outcomes were reanalyzed in the matched cohort using Cox proportional hazards models. Second, the matched cohort analysis was further adjusted for antiviral and immunomodulatory therapies to evaluate the potential influence of concomitant treatments. Consistency across these analyses was interpreted as supporting the robustness of the study findings.

All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant. Data analysis was conducted using Stata version 16 (StataCorp LLC, College Station, TX, USA).

3. Results

3.1. *Baseline characteristics of studied cases*

A total of 478 patients were screened, of whom 460 were included (269 pulse-dose methylprednisolone, 191 prolonged low-dose dexamethasone). The study flow diagram is presented in Figure 1.

In the dexamethasone group, most patients received > 6–20 mg/day; equivalent to 40–133.3 mg of prednisolone (80.6%), while in the methylprednisolone group, the majority received 500 mg/day (68.4%), followed by 250 mg/day (17.1%) and 1,000 mg/day (14.5%); equivalent to 625, 312.5, and 1,250 mg of prednisolone, respectively.

3.2. *Outcomes*

The primary outcome of 28-day mortality occurred in 21.9% of the methylprednisolone group and 7.9% of the dexamethasone group. Baseline characteristics are shown in Table 1. Patients receiving methylprednisolone were older (p <0.001), had higher BMI (p <0.001), and had more comorbidities (hypertension; p = 0.01, dyslipidemia; p = 0.01, heart disease; p = 0.013). They also had more severe disease (p <0.001), reflected by lower PaO_2/FiO_2 ratios, greater need for advanced respiratory support (oxygen mask with reservoir bag; p <0.001, high-flow nasal cannula; p <0.001), and higher use of adjunctive therapies (tocilizumab; p <0.001, infliximab; p = 0.045, baricitinib; p <0.001, tofacitinib; p <0.001). Inflammatory markers and cell counts were also higher in this group (CRP; p <0.001, LDH; p <0.001, D-dimer; p = 0.003, white blood cell count; p <0.001).

Table 2 summarizes primary and secondary outcomes of the total cohort, comparing patients treated with methylprednisolone and dexamethasone. Patients receiving methylprednisolone had more severe illness, with higher rates of invasive mechanical ventilation and ICU admission (15.61% vs. 3.66%; p <0.001 and 59.48% vs. 21.47%; p <0.001, respectively), lower PaO_2/FiO_2 ratios (137.4 ± 82.2 vs. 269.2 ± 96.2; p < 0.001), and higher inflammatory markers, including CRP, LDH, and D-dimer (p < 0.001, < 0.001, 0.01, respectively).

Patients receiving pulse-dose methylprednisolone had higher unadjusted 28-day mortality than those receiving prolonged low-dose dexamethasone (21.9% vs. 7.9%; p < 0.001), as well as higher in-hospital mortality (24.5% vs. 6.8%; p < 0.001). They also had fewer ventilator-free (20.56 ± 12.01 vs. 25.61 ± 7.78; P< 0.001), inotrope-free (21.01 ± 12.07 vs. 25.64 ± 7.77; p < 0.001), oxygen-free (12.87 ± 9.33 vs. 21.65 ± 7.98; p < 0.001), and hospital-free days (11.53 ± 8.15 vs. 16.93 ± 6.92; p < 0.001).

After adjustment for demographics, comorbidities, disease severity, respiratory support, and concomitant treatments, methylprednisolone was associated with a non-significant increase in 28-day mortality compared with dexamethasone (adjusted HR: 1.51; 95% CI: 0.74–3.09; p = 0.26) (Figure 2).

For secondary outcomes, pulse-dose methylprednisolone was associated with higher in-hospital mortality (adjusted HR: 2.13; 95% CI: 1.03–4.40; p = 0.04) and fewer oxygen-free and hospital-free days (adjusted mean difference (aMD): −3.70 [95% CI: −5.27 to −2.13]; p < 0.001 and aMD: −1.83 [95% CI: −3.19 to −0.48]; p = 0.008, respectively). No significant differences were observed in ventilator-free or inotrope-free days (Table 3)

3.3. *PSM*

PSM was conducted using a logistic regression model including pre-treatment covariates (age, sex, BMI, comorbidities, PaO_2/FiO_2, CRP, LDH, D-dimer, and baseline respiratory support) (Table 4). Before matching, propensity scores differed significantly between groups (0.73 ± 0.25 vs. 0.41 ± 0.19; p < 0.001). After 1:1 nearest-neighbor matching, 108 patients per group remained with well-balanced scores (0.52 ± 0.20 vs. 0.50 ± 0.19; p = 0.91).

After matching (n = 216), baseline demographics, comorbidities, disease severity, respiratory support, and laboratory parameters were well balanced between groups (all standardized differences <0.2, figure 3). However, post-treatment variables remained imbalanced: patients in the methylprednisolone group more frequently received remdesivir, immunomodulators (e.g., tocilizumab, baricitinib), and anticoagulants, reflecting residual differences in disease severity and treatment intensity (Table 5).

After matching, the pulse-dose methylprednisolone group exhibited more severe ARDS, reflected by lower worst and last PaO_2/FiO_2 ratios and higher ICU admission rates. CRP was also higher during the disease course.

There was no significant difference in 28-day mortality; however, a trend toward higher in-hospital mortality was observed in the pulse-dose methylprednisolone (18.5% vs. 9.3%; p = 0.07). Pulse-dose methylprednisolone was also associated with fewer oxygen-free and hospital-free days, while differences in ventilator-free and inotrope-free days were not statistically significant (Table 6).

Following PSM, the pulse-dose methylprednisolone group was not associated with increased 28-day mortality compared with

prolonged low-dose dexamethasone (HR: 1.40; 95% CI: 0.64–3.06; p = 0.38) but showed a trend toward higher in-hospital mortality (HR: 2.07; 95% CI: 0.96–4.42; p = 0.06) (Figure 4). In a sensitivity analysis with additional adjustment for antiviral and immunomodulatory treatments, results were unchanged for 28-day mortality (HR: 1.64; 95% CI: 0.67–4.02; p = 0.28), while in-hospital mortality remained higher in the pulse-dose methylprednisolone group (HR: 2.39; 95% CI: 1.01–5.65; p = 0.04).

4. Discussion

In our cohort, patients treated with pulse-dose methylprednisolone had greater baseline disease severity, reflecting confounding by indication in routine clinical practice. After multivariable adjustment, pulse-dose methylprednisolone was associated with higher crude mortality, although this was not statistically significant for 28-day mortality. In contrast, in-hospital mortality remained significantly higher after adjustment. Following PSM, 28-day mortality was comparable between groups; however, a consistent trend toward higher in-hospital mortality and fewer oxygen-free and hospital-free days was observed in the pulse-dose methylprednisolone group. No significant differences were found in ventilator-free or inotrope-free days. These findings should be interpreted with caution, as PSM reduces sample size and reflects a selected subgroup with overlapping characteristics.

Corticosteroids are widely used in COVID-19 pneumonia due to their anti-inflammatory effects and potential to improve outcomes (4, 11). The RECOVERY trial established prolonged low-dose dexamethasone (6 mg daily for up to 10 days) as standard therapy, demonstrating a significant reduction in 28-day mortality among patients requiring oxygen or mechanical ventilation, yet no benefit and possible harm in those not requiring respiratory support (4). However, the role of pulse-dose methylprednisolone remains uncertain, particularly in real-world settings where it is often reserved for more severe disease. Previous studies have reported inconsistent findings regarding methylprednisolone. Some trials demonstrated a mortality benefit, including Edalatifard et al., who reported a reduction in mortality (5.9% vs. 42.9%; p < 0.001) (7), as well as observational studies by Ranjbar and Pinzón et al. (1, 8). Conversely, other studies, including those by Taher, Dastenae, Buso, Corral, and the MEDEAS trial, found no significant difference in 28-day mortality compared with dexamethasone (12-16). These discrepancies likely reflect variations in dosing strategies, patient populations, and disease severity.

Our results are consistent with large observational data suggesting potential harm with high-dose corticosteroid strategies. A Japanese multicenter study (17) reported increased in-hospital and 30-day mortality with high-dose methylprednisolone (500–1,000 mg/day), compared with dexamethasone (OR: 1.48, 95% CI: 1.07–2.04; and OR: 1.75, 95% CI: 1.40–2.19, respectively), while lower doses (250 mg/day) were not associated with excess risk. Similarly, other studies have demonstrated worse outcomes or no benefit with pulse-dose regimens compared with standard-dose dexamethasone, particularly in less severe disease (18, 19).

From a mechanistic perspective, differences in corticosteroid pharmacology may partially explain these findings. Low-dose corticosteroids primarily exert anti-inflammatory effects via genomic pathways, leading to gradual immunomodulation. In contrast, pulse-dose regimens may act through rapid non-genomic pathways (20), which do not appear to translate into improved clinical outcomes in COVID-19 (17).

In addition, pharmacodynamic differences, particularly mineralocorticoid activity, may influence fluid balance and lung injury (21). Methylprednisolone has both glucocorticoid and mineralocorticoid effects, whereas dexamethasone provides potent glucocorticoid activity with minimal mineralocorticoid effects, potentially making it more favorable in acute respiratory distress syndrome (4, 21).

Importantly, evidence from the MEDEAS trial (16) suggests that when methylprednisolone and dexamethasone are administered using comparable dosing strategies, clinical outcomes are similar. This supports the hypothesis that treatment regimen, particularly dose and duration, rather than the corticosteroid molecule itself, is the primary determinant of outcome.

Our PSM analysis suggests that pulse-dose methylprednisolone does not provide a mortality benefit over prolonged low-dose dexamethasone and may be associated with less favorable secondary outcomes. These findings likely reflect differences in treatment indication and dosing strategies rather than intrinsic differences between corticosteroids.

Clinically, our findings do not support the routine use of pulse-dose methylprednisolone as first-line corticosteroid therapy in hospitalized patients with COVID-19 pneumonia requiring oxygen therapy. Instead, prolonged low-dose dexamethasone (6 mg/day) should remain the preferred regimen, consistent with current clinical guidelines (22). Escalation to higher-dose corticosteroids (e.g., dexamethasone 20 mg/day) or pulse-dose methylprednisolone should be reserved for carefully selected patients with progressive disease (23) after individualized clinical assessment and exclusion of secondary infection. Given the observational design of this study, these findings should be interpreted cautiously and confirmed in prospective randomized trials before influencing routine clinical practice.

4.1. *Limitations*

This study has several limitations. First, its retrospective design is subject to residual confounding despite multivariable adjustment and PSM; unmeasured variables may still have influenced the results, introducing residual bias. Second, patients receiving pulse-dose methylprednisolone had greater baseline disease severity, reflecting confounding by indication; thus, residual imbalance and selection bias may persist, limiting generalizability and reducing the effective sample size after matching. Therefore, the matched cohort should be interpreted as a subgroup with comparable baseline characteristics, rather than a representative of the overall population. Third, this was a single-center study, which may reduce external validity. Fourth, the primary outcome was all-cause 28-day mortality, and cause-specific mortality, including the impact of do-not-resuscitate decisions, could not be fully ascertained. Finally, safety outcomes, including glycemic control and secondary infections, were incompletely captured. These limitations highlight the need for future multicenter, prospective studies to assess both the efficacy and safety of corticosteroid therapy in severe COVID-19 pneumonia.

The findings of this study are most applicable to hospitalized adults with severe COVID-19 pneumonia treated in tertiary-care hospitals using corticosteroid regimens similar to those evaluated during the Delta variant wave. Caution is warranted when extrapolating these results to other healthcare settings, patient populations, circulating SARS-CoV-2 variants, or

contemporary treatment strategies. External validation in multicenter studies across diverse clinical settings is needed to confirm the generalizability of these findings.

5. Conclusions

Although pulse-dose methylprednisolone was not associated with a significant difference in 28-day mortality compared with prolonged low-dose dexamethasone after PSM, it showed a trend toward higher in-hospital mortality and fewer oxygen-free and hospital-free days in the matched analysis. However, causal inference is limited by the retrospective design and potential residual confounding. Prospective randomized studies are warranted.

6. Declarations

6.1. *Acknowledgments*

We wish to acknowledge the contribution of all the medical and nursing staff of the Emergency department of Ramathibodi Hospital for their collaboration.

6.2. *Conflict of interests*

The authors declare that they have no competing interests.

6.3. *Funding and supports*

No funding was obtained for this study.

6.4. *Authors' contributions*

PS, PR, and SL designed this study and developed the protocol. PS and PR were responsible for data collection. PS and PR were responsible for data analysis. PS, PR, and SL wrote the manuscript. PS, PR, and SL provided the final approval to publish this version. PS and SL agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

6.5. *Ethical statement*

This study was approved by the Committee on Human Rights Related to Research, Faculty of Medicine, Ramathibodi Hospital, Mahidol University (IRB COA.MURA2021/973 Date November 18, 2021). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was waived by the Committee on Human Rights Related to Research as the data were collected retrospectively and anonymously.

6.6. *Informed consent*

Not applicable.

6.7. *Availability of supporting data*

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

6.8. *Using artificial intelligence chatbots statement*

While preparing this work, the authors used ChatGPT/OpenAI and Grammarly to check grammar and spelling. After using these services, the authors reviewed and edited the content as needed and took full responsibility for the publication's content.

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Table 1: Baseline characteristics of hospitalized patients with severe COVID-19 pneumonia treated with methylprednisolone or dexamethasone

Baseline characteristics	Total (n = 460)	Methylprednisolone (n = 269)	Dexamethasone (n = 191)	P-value
Age (year)				
Mean ± SD	60.37 ± 16.59	62.71 ± 15.36	57.07 ± 17.70	<0.001
Sex				
Female, n (%)	236 (51.30)	138 (51.31)	98 (51.31)	1.00
Underlying conditions				
Diabetes mellitus	174 (37.83)	110 (40.89)	64 (33.51)	0.12
Hypertension	241 (52.39)	155 (57.62)	86 (45.03)	0.01
Dyslipidemia	176 (38.26)	116 (43.12)	60 (31.41)	0.01
Chronic kidney disease	62 (13.48)	40 (14.87)	22 (11.52)	0.33
Heart disease	63 (13.70)	46 (17.10)	17 (8.90)	0.013
Cerebrovascular disease	36 (7.83)	21 (7.81)	15 (7.85)	1.00
Chronic lung disease	28 (6.09)	15 (5.58)	13 (6.81)	0.69
Chronic liver disease	19 (4.13)	12 (4.46)	7 (3.66)	0.81
Malignancy	22 (4.78)	12 (4.46)	10 (5.24)	0.83
Transplant	6 (1.3)	3 (1.12)	3 (1.57)	0.70
Immunocompromised	26 (5.65)	14 (5.20)	12 (6.28)	0.68
BMI				
Mean ± SD	26.63 ± 5.86	27.44 ± 5.96	25.49 ± 5.53	<0.001
Illness to admission (day)				
Mean ± SD	6.83 ± 3.54	6.84 ± 3.31	6.82 ± 3.85	0.96
Illness to steroid (day)				
Mean ± SD	6.09 (2.90)	5.91 (2.71)	6.34 (3.14)	0.12
Dose of steroid treatment (mg/d)				-
Mean ± SD	-	529.74 ± 214.99	14.10 ± 5.84	
Min-Max	-	250-1000	6-24	
Equivalent* (mg/d)	-	662.2	94	-
Initial PaO_2/FiO_2 ratio				
Mean ± SD	302.21 ± 89.28	269.14 ± 82.25	348.78 ± 77.37	<0.001
Initial severity of hypoxemia, n (%)				
Normal	247 (53.70)	95 (35.32)	152 (79.58)	<0.001
Mild	145 (31.52)	116 (43.12)	29 (15.18)	<0.001
Moderate	59 (12.83)	52 (19.33)	7 (3.66)	<0.001
Severe	9 (1.96)	6 (2.23)	3 (1.57)	0.74
Initial respiratory support, n (%)				
Conventional oxygen cannula	232 (50.43)	126 (46.84)	106 (55.50)	0.07
Oxygen mask with reservoir bag	39 (8.48)	34 (12.64)	5 (2.62)	<0.001
High-flow nasal cannula	103 (22.39)	87 (32.34)	16 (8.38)	<0.001
Non-invasive positive pressure ventilation	4 (0.87)	4 (1.49)	0 (0.00)	0.145
Endotracheal intubation	7 (1.52)	5 (1.86)	2 (1.05)	0.705
Initial laboratory investigation				
White blood cell (cells/mm^3)	7,278.41 ± 3,735.05	7,837.11 ± 3,913.54	6,478.99 ± 3,313.16	<0.001
Hemoglobin (g/dL)	12.84 ± 2.13	12.90 ± 2.08	12.76 ± 2.20	0.48
Platelet (cells/mm^3)	246,655.1 ± 102,898.1	237,724.6 ± 94,369.6	259,433.0 ± 113,035.1	0.03
Creatinine (mg/dL)	0.84 (0.65 - 1.13)	0.87 (0.65 - 1.15)	0.81 (0.65 - 1.13)	0.53
Total bilirubin (mg/dL)	0.65 ± 0.54	0.68 ± 0.39	0.61 ± 0.70	0.16
CRP (mg/L)	67.68 (29.9 - 117.8)	89.98 (45.1 - 143.8)	38.11 (17.3 - 69.5)	<0.001
LDH (U/L)	385.67 ± 164.39	416.92 ± 171.02	339.83 ± 142.67	<0.001
D-Dimer (ng/ml)	721 (421 - 1,157)	784 (466 - 1,250)	635 (370 - 1,048)	0.003
Antiviral drugs, n (%)				
Favipiravir	453 (98.48)	262 (97.40)	191 (100)	0.045
Remdesivir	107 (23.26)	101 (37.55)	6 (3.14)	<0.001
Immunomodulator drugs, n (%)				
Tocilizumab	37 (8.04)	36 (13.38)	1 (0.52)	<0.001
Infliximab	7 (1.52)	7 (2.60)	0 (0.00)	0.045
Baricitinib	67 (14.57)	66 (24.54)	1 (0.52)	<0.001
Tofacitinib	39 (8.48)	37 (13.75)	2 (1.05)	<0.001
Anticoagulant drug, n (%)				
Yes	342 (74.35)	249 (92.57)	93 (48.69)	<0.001

Data are presented as mean ± standard deviation (SD) or frequency (%) or median (interquartile range). BMI: Body Mass Index; CRP: C-reactive protein; LDH: Lactate Dehydrogenase. * Equivalent highest dose to prednisolone (mg/d).

Table 2: Clinical outcomes of hospitalized patients with severe COVID-19 pneumonia treated with methylprednisolone or dexamethasone

Outcome	Total (n = 460)	Methylprednisolone (n = 269)	Dexamethasone (n = 191)	P-value
Evolution of ARDS (worst)				
Normal (PF>300)	79 (17.17)	9 (3.35)	70 (36.65)	<0.001
Mild (PF=201-300)	127 (27.61)	45 (16.73)	82 (42.93)	<0.001
Moderate (PF=101-200)	135 (29.35)	111 (41.26)	24 (12.57)	<0.001
Severe (PF ≤100)	119 (25.87)	104 (38.66)	15 (7.85)	<0.001
Evolution of ARDS (last)				
Normal (PF>300)	370 (80.43)	195 (72.49)	175 (91.62)	<0.001
Mild (PF=201-300)	9 (1.96)	8 (2.97)	1 (0.52)	0.09
Moderate (PF=101-200)	0 (0)	0 (0)	0 (0)	-
Severe (PF ≤100)	81 (17.61)	66 (24.54)	15 (7.85)	<0.001
Invasive mechanical ventilator				
Yes	49 (10.65)	42 (15.61)	7 (3.66)	<0.001
PaO_2/FiO_2 ratio (worst)				
Mean ± SD	192.13 ± 109.55	137.42 ± 82.19	269.19 ± 96.20	<0.001
PaO_2/FiO_2 ratio (last)				
Mean ± SD	335.25 ± 140.87	303.05 ± 154.37	380.62 ± 103.89	<0.001
Laboratory (worst)				
CRP (mg/L)	90.32 (47.16 - 147.97)	114.4 (72.52 - 164.32)	55.66 (31.26 - 101.51)	<0.001
LDH (U/L)	481.27 ± 307.19	534.30 ± 360.50	386.99 ± 132.87	<0.001
D-dimer (ng/ml)	1,218 (683 - 3,729)	1,388 (720.5 - 4,223)	1,026 (568 - 2,159)	0.01
Laboratory (last)				
CRP (mg/L)	5.7 (2.11 - 18.86)	5.05 (2.11 - 29.04)	7.57 (1.96 - 15.83)	0.93
LDH (U/L)	348.39 ± 225.83	380.09 ± 267.74	292.98 ± 101.36	<0.001
D-dimer (ng/ml)	851 (395 - 1,906.5)	983 (455.5 - 2231.5)	602 (356 - 1241.5)	0.003
ICU admission after corticosteroid				
Yes	201 (43.70)	160 (59.48)	41 (21.47)	<0.001
In-hospital mortality				
Yes	79 (17.17)	66 (24.54)	13 (6.81)	<0.001
28-days outcomes				
Mortality	74 (16.09)	59 (21.93)	15 (7.85)	<0.001
Alive ventilator-free days	22.66 ± 10.75	20.56 ± 12.01	25.61 ± 7.78	<0.001
Alive inotrope-free days	22.93 ± 10.74	21.01 ± 12.07	25.64 ± 7.77	<0.001
Alive oxygen-free days	16.51 ± 9.80	12.87 ± 9.34	21.65 ± 7.98	<0.001
Alive hospital-free days	13.77 ± 8.11	11.53 ± 8.15	16.93 ± 6.92	<0.001

Data are presented as mean ± standard deviation (SD) or frequency (%) or median (interquartile range). ARDS: Acute respiratory distress syndrome; CRP: C-reactive protein; ICU: intensive care unit; LDH: Lactate Dehydrogenase; PF: PaO_2/FiO_2.

Table 3: Multivariable analysis of clinical outcomes comparing pulse-dose methylprednisolone (methyl) and prolonged low-dose dexamethasone (dexa) treatment among hospitalized patients with severe COVID-19 pneumonia

Outcome	Methyl (n = 269)	Dexa (n = 191)	Crude HR	P-value	Adjusted HR	P-value
28-day mortality	59 (21.93)	15 (7.85)	3.09 (1.76 - 5.46)	<0.001	1.51 (0.74 - 3.09)	0.26
In-hospital mortality	66 (24.54)	13 (6.81)	4.02 (2.22 - 7.29)	<0.001	2.13 (1.03 - 4.40)	0.04
28-day outcomes			**Crude MD (day)**	**P-value**	**Adjusted MD (day)**	**P-value**
Alive ventilator-free days	20.56 ± 12.01	25.61 ± 7.78	-5.05 (-7.00 - -3.11)	<0.001	-0.49 (-2.44 - 1.47)	0.63
Alive inotrope-free days	21.01 ± 12.07	25.64 ± 7.77	-4.63 (-6.58 - -2.68)	0.001	-0.30 (-2.27 - 1.67)	0.76
Alive oxygen-free days	12.87 ± 9.34	21.65 ± 7.98	-8.79 (-10.42 - -7.15)	<0.001	-3.70 (-5.27 - -2.13)	<0.001
Alive hospital-free days	11.53 ± 8.15	16.93 ± 6.92	-5.40 (-6.82 - -3.97)	<0.001	-1.83 (-3.19 - -0.48)	0.008

Data are presented as mean ± standard deviation (SD) or frequency (%). HR: hazard ratio; MD: mean difference. Adjusted with age, sex, body mass index (BMI), comorbidities (diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, heart disease, cerebrovascular disease, chronic lung disease, chronic liver disease, malignancy, transplant, immunocompromised host), days of illness to steroid, initial PaO2/FiO2 ratio, remdesivir received, initial respiratory support (conventional oxygen cannula, mask with bag, high-flow nasal cannula, non-invasive positive pressure ventilation, endotracheal intubation), and intensive care unit (ICU) admission. All measures are presented with 95% confidence interval.

Table 4: Derivation of the propensity score equation (PSE) for the likelihood of receiving methylprednisolone, based on pre-treatment covariates in a multivariable logistic regression model

Pre-treatment covariates	Odds ratio	95% CI	p -value
Age	1.01	[0.99, 1.03]	0.11
Female	0.85	[0.53,1.38]	0.51
Body mass index	1.09	[1.04,1.15]	0.001
Diabetes mellitus	0.67	[0.40,1.15]	0.15
Hypertension	1.08	[0.59,1.98]	0.80
Chronic kidney disease	1.12	[0.49,2.55]	0.79
Cardiovascular disease	3.44	[1.53,7.71]	0.003
Chronic lung disease	1.05	[0.38,2.94]	0.93
Oncology	0.86	[0.26,2.82]	0.80
Immunocompromised	0.77	[0.28,2.14]	0.62
Initial PaO_2/FiO_2 ratio	0.99	[0.98,0.99]	<0.001
Invasive respiratory support	0.13	[0.02,1.00]	0.05
Initial C-reactive protein	1.01	[1.00,1.01]	<0.001
Initial Lactate Dehydrogenase	1.00	[0.99,1.00]	0.79
Initial D-dimer	1.00	[0.99,1.00]	0.83

CI: confidence interval.

Table 5: Baseline characteristics of hospitalized patients with severe COVID-19 pneumonia treated with pulse-dose methylprednisolone or prolonged low-dexamethasone after propensity score matching

Baseline characteristics	Total (n = 216)	Methylprednisolone (n = 108)	Dexamethasone (n = 108)	P-value	Post-matched SMD
Pretreatment factor					
Age (year)					
Mean ± SD	59.75 ± 16.71	59.12 ± 16.84	60.38 ± 16.63	0.58	0.07
Sex					
Female	112 (51.85)	55 (50.93)	57 (52.78)	0.89	0.03
Underlying conditions					
Diabetes mellitus	81 (37.50)	38 (35.19)	43 (39.81)	0.57	0.09
Hypertension	104 (48.15)	50 (46.30)	54 (50.00)	0.68	0.07
Dyslipidemia	75 (34.72)	35 (32.41)	40 (37.04)	0.56	0.09
Chronic kidney disease	22 (10.19)	11 (10.19)	11 (10.19)	1.00	0.00
Heart disease	22 (10.19)	12 (11.11)	10 (9.26)	0.82	-0.06
Cerebrovascular disease	19 (8.80)	8 (7.41)	11(10.19)	0.63	0.09
Chronic lung disease	13 (6.02)	7 (6.48)	6 (5.56)	1.00	0.19
Chronic liver disease	10 (4.63)	6 (5.56)	4 (3.70)	0.75	-0.08
Malignancy	10 (4.63)	5 (4.63)	5 (4.63)	1.00	0.00
Transplant	3 (1.39)	2 (1.85)	1 (0.93)	1.00	-0.07
Immunocompromised	13 (6.02)	7 (6.48)	6(5.56)	1.00	-0.03
BMI (Mean ± SD)	26.36 ± 5.51	26.39 ± 5.10	26.33 ± 5.01	0.93	-0.01
Illness to admission (days)					
Mean ± SD	6.49 ± 3.54	6.14 ± 2.91	6.84 ± 4.07	0.15	0.19
Illness to steroid (days)					
Mean ± SD	5.71 ± 2.72	5.36 ± 2.21	6.07 ± 3.12	0.06	0.26
Dose of steroid treatment (mg/d)					
Mean ± SD	-	520.83 ± 232.13	15.5 ± 5.44	-	-
Min-Max	-	250-1000	6-24	-	-
Initial PaO_2/FiO_2 ratio					
Mean ± SD	320.99 ± 71.62	322.21 ± 67.46	319.77 ± 75.86	0.80	-0.03
Initial severity of hypoxemia					
Normal	139 (64.35)	65 (60.19)	74 (68.52)	0.26	0.17
Mild	63 (29.17)	38 (35.19)	25 (23.15)	0.07	-0.26
Moderate	12 (5.56)	5 (4.63)	7 (6.48)	0.77	0.08
Severe	3 (1.39)	1 (0.93)	2 (1.85)	1.00	0.07
Initial respiratory support					
Conventional oxygen cannula	141 (65.28)	72 (66.67)	69 (63.89)	0.77	-0.05
Oxygen mask with reservoir bag	8 (3.70)	6 (5.56)	2 (1.85)	0.28	-0.19
High flow nasal cannula	31 (14.35)	16 (14.81)	15 (13.89)	1.00	-0.02
NIPV	1 (0.46)	1 (0.93)	0 (0.00)	1.00	-0.13
Endotracheal intubation	4 (1.85)	2 (1.85)	2 (1.85)	1.00	0.00
Initial laboratory investigation					
White blood cell (cells/mm^3)	7,296.97 ± 3,831.54	7,684.80 ± 3,876.71	6,909.13 ± 3,766.93	0.17	-0.07
Hemoglobin (g/dL)	12.75 ± 2.14	12.87 ± 2.17	12.63 ± 2.13	0.43	-0.05
Platelet (cells/mm^3)	254,293.5 ± 107,603.9	248,8152.2 ± 96,224.2	260,434.8 ± 118,106.2	0.44	0.16
Creatinine (mg/dL)	0.80 (0.64 - 1.05)	0.81 (0.62 - 1.03)	0.79 (0.66 - 1.18)	0.50	-0.01
Total bilirubin (mg/dL)	0.5 (0.4 - 0.7)	0.5 (0.4 - 0.8)	0.5 (0.4 - 0.7)	0.55	0.05
CRP (mg/L)	49.4 (21.39 - 85.40)	53.62 (25.20 - 84.2)	48.2 (18.0 - 91.33)	0.40	-0.06
LDH (U/L)	338 (255 - 416)	343.5 (260.5 - 412)	329 (253.5 - 436.5)	0.86	0.03
D-Dimer (ng/ml)	662 (391 – 1,130)	704.5 (414.5–1,283.5)	625 (371.5–1,086)	0.23	-0.15
Post treatment factors					
Antiviral drugs, n (%)					
Favipiravir	214 (99.07)	106 ((98.15)	108 (100)	0.49	0.19
Remdesivir	29 (13.43)	26 (24.07)	3 (2.78)	<0.001	-0.65
Immunomodulator drugs					
Tocilizumab	11 (5.09)	10 (9.26)	1 (0.93)	0.01	-0.38
Infliximab	2 (0.93)	1 (1.85)	0 (0.00)	0.49	-0.19
Baricitinib	23 (10.65)	22 (20.37)	1 (0.93)	<0.001	-0.66
Tofacitinib	10 (4.63)	9 (8.33)	1 (0.93)	0.02	-0.35
Anticoagulant drugs					
Yes	169 (87.50)	97 (89.81)	72(66.67)	<0.001	-0.58

Data are presented as mean ± standard deviation (SD) or frequency (%) or median (interquartile range). SMD: standardized mean difference; BMI: Body Mass Index; NIPV: Non-invasive positive pressure ventilation; CRP: C-reactive protein; LDH: Lactate Dehydrogenase.

Table 6: Clinical outcomes of hospitalized patients with severe COVID-19 pneumonia treated with pulse-dose methylprednisolone or prolonged low-dose dexamethasone after propensity score matching

Outcome	All (n = 216)	Methylprednisolone (n = 108)	Dexamethasone (n = 108)	P-value
Evolution of ARDS (worst)				
Normal (PF>300)	35 (16.20)	7 (6.48)	28 (25.93)	<0.001
Mild (PF=201-300)	81 (37.50)	30 (27.78)	51 (47.22)	0.007
Moderate (PF=101-200)	62 (28.70)	44 (40.74)	18 (16.67)	<0.001
Severe (PF ≤100)	38 (17.59)	27 (25.00)	11 (10.19)	0.007
Evolution of ARDS (last)				
Normal (PF>300)	179 (82.87)	83 (76.85)	96 (88.89)	0.03
Mild (PF=201-300)	6(2.78)	5 (4.63)	1 (0.93)	0.21
Moderate (PF=101-200)	0 (0)	0 (0)	0 (0)	-
Severe (PF ≤100)	38 (17.59)	27 (25.00)	11 (10.19)	0.007
Invasive mechanical ventilator				
Yes	16 (7.41)	12 (11.11)	4 (3.70)	0.06
PaO2/FiO2 ratio (worst)				
Mean ± SD	206.13 ± 99.93	165.95 ± 88.44	246.30 ± 94.78	<0.001
PaO2/FiO2 ratio (last)				
Mean ± SD	348.45 ± 132.17	326.64 ± 143.36	370.25 ± 116.58	0.01
Laboratory (worst)				
CRP (mg/L)	75.27 (40.45 - 123.96)	81.25 (52.40 - 130.83)	64.43 (34.75- 112.11)	0.03
LDH (U/L)	389 (325 - 497)	389.5 (344 - 4524)	385 (295.5 - 468.5)	0.08
D-dimer (ng/ml)	1138 (629 - 3148)	1215.5 (694.5 -3970)	1997 (557.5 - 2570.5)	0.17
Laboratory (last)				
CRP (mg/L)	5.55 (1.82 -17.06)	4.65 (1.8 - 17.01)	7.19 (1.82 - 17.06)	0.77
LDH (U/L)	282 (230 - 368)	301 (240 - 384)	271.5 (224 - 339)	0.11
D-dimer (ng/ml)	807 (359 - 1450)	952 (441.5 - 2069.5)	522 (354 - 1180)	0.03
ICU admission after corticosteroid				
Yes	83 (38.43)	54 (50.00)	29 (26.85)	0.001
In-hospital mortality				
Yes	30 (13.89)	20 (18.52)	10 (9.26)	0.07
28-days outcome				
mortality	26 (12.04)	15 (13.89)	11 (10.19)	0.53
Alive ventilator-free days	23.78 ± 9.86	22.47 ± 10.92	25.09 ± 8.51	0.05
Alive inotrope-free days	23.96 ± 9.83	22.80 ± 10.92	25.12 ± 8.50	0.08
Alive oxygen-free days	17.35 ± 9.29	14.45 ± 9.29	20.25 ± 8.39	<0.001
Alive hospital-free days	14.44 ± 7.71	12.60 ± 7.82	16.28 ± 7.16	<0.001

Data are presented as mean ± standard deviation (SD) or frequency (%) or median (interquartile range). ARDS: Acute respiratory distress syndrome; CRP: C-reactive protein; ICU: intensive care unit; LDH: Lactate Dehydrogenase; PF: PaO_2/FiO_2.

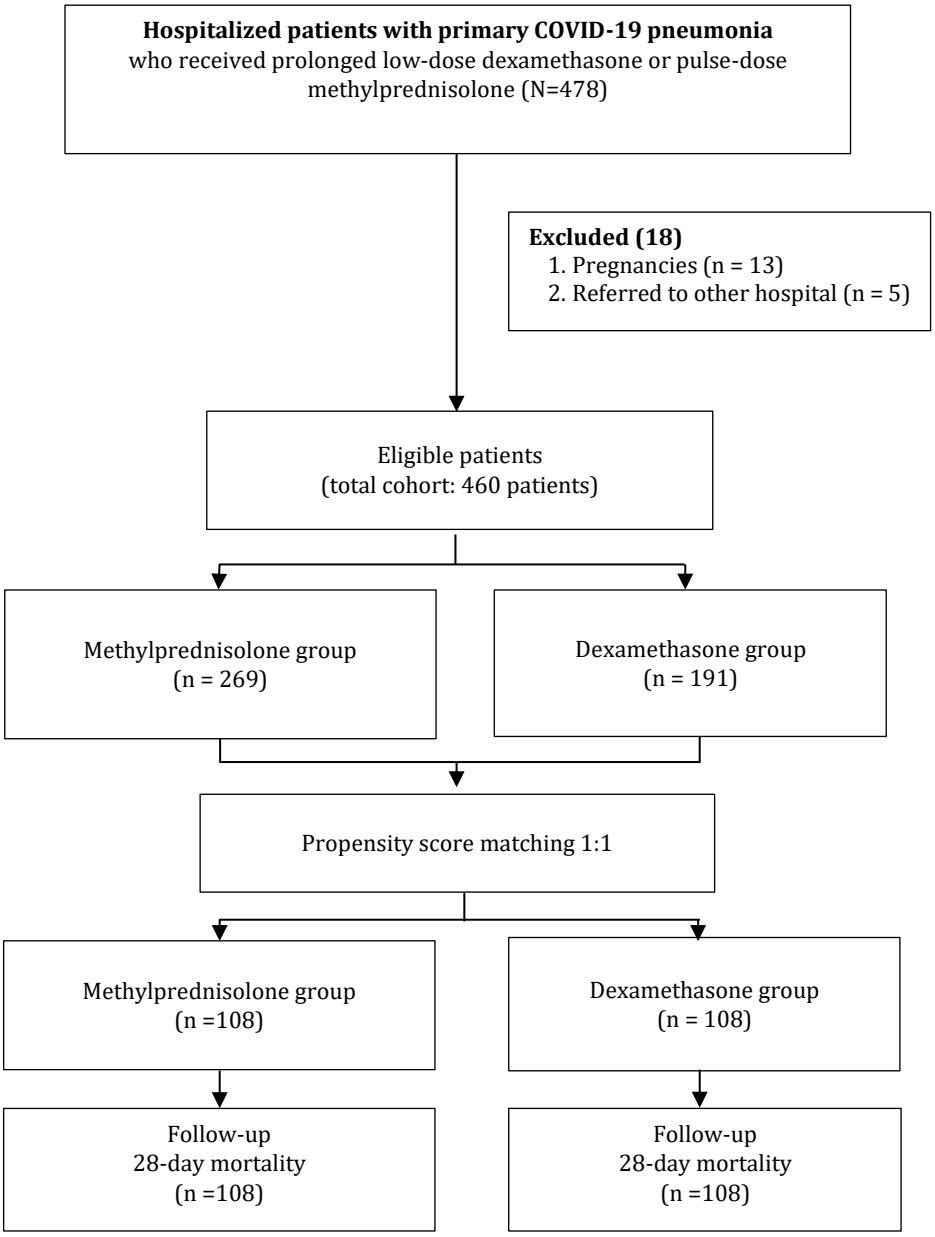


Figure 1: Flowchart showing patient inclusion.

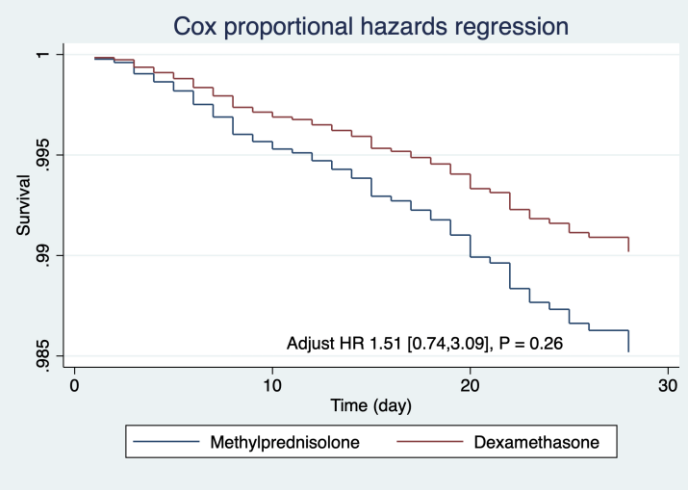


Figure 2: Cox proportional hazards regression analysis of 28-day mortality in hospitalized patients with severe COVID-19 pneumonia treated with pulse-dose methylprednisolone or prolonged low-dose dexamethasone (total cohort, N = 460). HR: hazard ratio; P: P-value. Adjusted with age, sex, body mass index (BMI), days from illness onset to steroid administration, underlying diseases (diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, heart disease, cerebrovascular disease, chronic lung disease, chronic liver disease, cancer, transplant, and immunocompromised host), initial PaO_2/FiO_2 (PF) ratio, initial respiratory support (oxygen cannula, oxygen mask with reservoir bag, high-flow nasal cannula, non-invasive respiratory support, endotracheal tube), intensive care unit (ICU) admission, and receipt of Remdesivir.

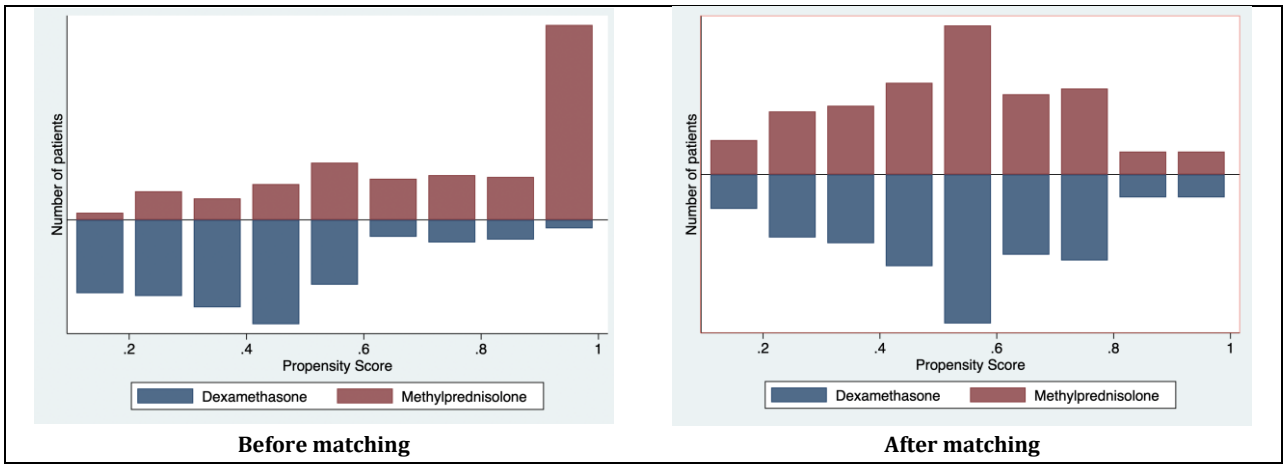
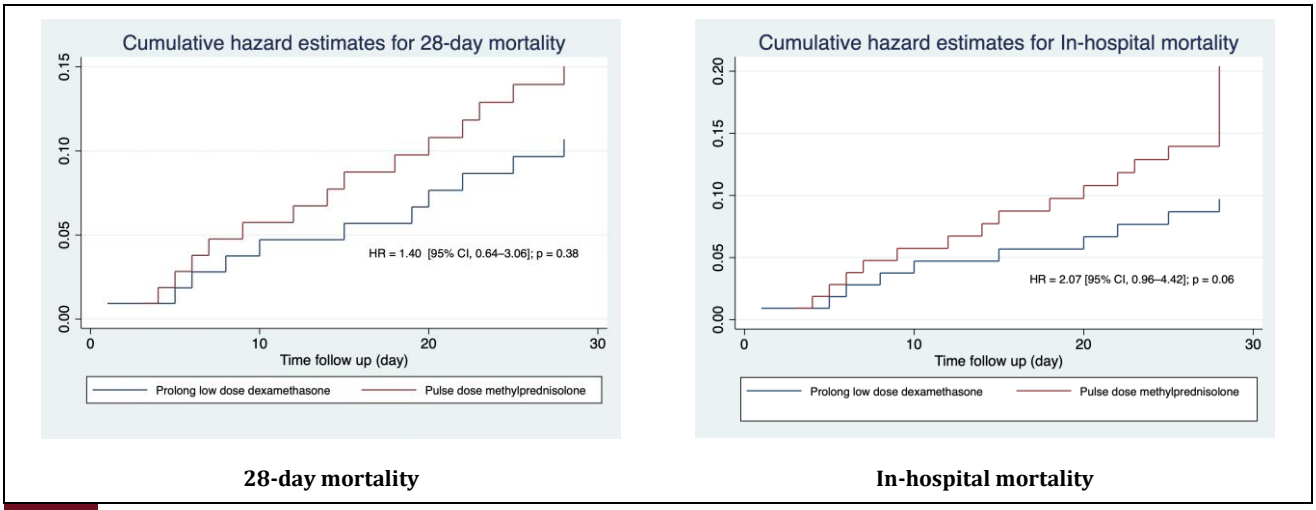


Figure 3: Distribution of propensity scores between the pulse-dose methylprednisolone and prolonged low-dose dexamethasone groups before and after matching.



28-day mortality **In-hospital mortality**

Figure 4: Cumulative hazard estimates for 28-day mortality and in-hospital mortality among hospitalized patients with severe COVID-19 pneumonia treated with pulse-dose methylprednisolone or prolonged low-dose dexamethasone after propensity score matching (N = 216). Variables included in the multivariable Cox regression analysis for the primary outcome (28-day mortality) and in the mean difference analysis of secondary outcomes were age, sex, body mass index, days from symptom onset to corticosteroid initiation, comorbidities (diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, heart disease, cerebrovascular disease, chronic lung disease, chronic liver disease, cancer, transplantation, and immunocompromised status), baseline PaO_2/FiO_2 ratio, initial respiratory support (oxygen nasal cannula, oxygen mask with reservoir bag, high-flow nasal cannula, noninvasive positive pressure ventilation, or endotracheal intubation), intensive care unit (ICU) admission, and remdesivir administration. HR: hazard ratio; CI: confidence interval; P: P-value.