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ORIGINAL RESEARCH

High-dose methylprednisolone versus dexamethasone therapy for hospitalized patients with severe COVID-19: a retrospective analysis

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Abstract

This study aimed to evaluate the clinical effects of high-dose methylprednisolone therapy in hospitalized patients with severe coronavirus disease (COVID-19) who required oxygen therapy, but not noninvasive/invasive mechanical ventilation or extracorporeal membrane oxygenation therapy. This retrospective observational study that was conducted from April 2021 to October 2021 at a secondary hospital in Japan enrolled patients who were administered 6 mg/day dexamethasone as an initial corticosteroid treatment on admission (dexamethasone group) and those who were administered $\geq$ 250 mg/day methylprednisolone (methylprednisolone group). Of the 42 participants, 40.5% (17/42) were included in the methylprednisolone group. The incidence of transfer to a tertiary hospital did not differ significantly between the methylprednisolone and dexamethasone groups (5.9% *vs.* 20%, $p = 0.37$), and in-hospital mortality was similar in both the groups (0% *vs.* 4%, $p = 1.00$). Participants in the methylprednisolone group had a significantly longer duration of oxygen therapy than the dexamethasone group (median (interquartile range) 8.5 (5.5–11.2) days *vs.* 4 (2.0–7.5) days, $p < 0.05$). Compared to dexamethasone, high-dose methylprednisolone therapy did not provide any added benefits for patients with severe COVID-19 who did not require respiratory mechanical support.

Keywords

COVID-19; Severe illness; Pulse; Methylprednisolone; Dexamethasone

1. Background

The coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in the Chinese city of Wuhan in December 2019 [1] and, subsequently, the infection spread rapidly to cause a global pandemic. Although it is estimated that 20% of SARS-CoV-2-infected individuals remain asymptomatic [2], COVID-19 leads to various disease states that range from mild to severe. Mild disease comprises flu-like symptoms, including headache, fever, dry cough, dyspnea, myalgia, fatigue, sore throat, diarrhea, and nausea/vomiting [3].In contrast, approximately 17% of the hospitalized patients develop acute respiratory distress syndrome (ARDS), which requires intensive care unit admission with noninvasive/invasive mechanical ventilation or extracorporeal membrane oxygen therapy (ECMO) [1, 4–6]. Patients with severe COVID-19 are characterized by elevated levels of inflammatory markers, such as C-reactive protein, D-dimer, interleukin (IL)-6, and IL-10 [7]. Although the mechanisms of immune dysregulation are unclear, the pathogenesis of this severe disease state is considered as being predominantly immune mediated, with a dysfunctional immune response leading to uncontrolled inflammation [5].

The benefit of corticosteroids in severe infections is a controversial topic [8], although the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial showed that dexamethasone reduced the 28-day mortality rate in COVID-19 patients who received oxygen or invasive mechanical ventilation [9]. Similarly, the benefit of methylprednisolone administration has been reported in a small randomized controlled clinical trial (RCT) in hospitalized patients with severe COVID-19 [10]. Based on the results of these previous studies, anti-inflammatory therapy to suppress the cytokine storm is considered an important treatment for severely or critically ill COVID-19 patients, and this therapeutic strategy is supported by the World Health Organization (WHO) guidelines [11].

The importance of corticosteroids in COVID-19 treatment is continuously evolving; however, evidence of the use of corticosteroids for treating severe COVID-19 is limited, and the optimal type and dose remains unclear [12]. Therefore, this study aimed to determine the efficacy of high-dose methylprednisolone therapy compared to dexamethasone administration in hospitalized patients with severe COVID-19.

2. Methods

2.1 Setting

This retrospective, single-center, observational study was performed between April 2021 and October 2021 in the general ward of a secondary level hospital in Japan that could treat COVID-19 patients requiring oxygen therapy, but not those who needed noninvasive/invasive mechanical ventilation or ECMO. Patients with worsening respiratory status requiring noninvasive/invasive mechanical ventilation or ECMO were transferred to a tertiary hospital.

2.2 Study population

The inclusion criteria in the study were: age $\geq$ 18 years, SARS-CoV-2 infection confirmed by a polymerase chain reaction test, imaging-based confirmation of pneumonia (chest X-ray or pulmonary computed tomography), hospitalization with oxygen therapy for COVID-19, and administration of 6 mg/day dexamethasone or $\geq$ 250 mg/day methylprednisolone as initial corticosteroid therapy for COVID-19 patients at admission. The treatment choice for each patient was arbitrarily determined by the clinician.

Individuals were excluded from the study if they met the following criteria: hospitalization without the requirement for oxygen therapy for COVID-19, re-hospitalization for COVID-19, and requiring home oxygen therapy before developing COVID-19.

2.3 Data collection and definitions

The medical records related to hospitalization were reviewed to investigate demographics and laboratory data, including age, sex, body mass index, time from illness onset to hospital admission, dose of oxygen administration at admission, type of corticosteroid administered, history of COVID-19 vaccination, diabetes-related conditions, malignant conditions, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, smoking status, treatment for COVID-19, white blood cell count, lymphocyte count, platelet count, and serum levels of lactate dehydrogenase, ferritin, and D-dimer. Furthermore, clinical data, including complications of bacterial infection, duration of oxygen therapy, corticosteroid administration, fever, transfer to a tertiary hospital, and in-hospital mortality, were collected.

Patients with COVID-19 received oxygen therapy to maintain oxygen saturation (SpO_2) >90% after admission. The illness severity was defined as severe according to the WHO guidelines [11]. The duration of fever was counted as the period with axillary temperature above 37 °C.

2.4 Statistical analysis

Results are expressed as median (interquartile range (IQR)) for continuous data and as percentages for categorical data. The Mann-Whitney U and chi-square tests were used for continuous and categorical data, respectively. For correlation analysis, Spearman's correlation coefficient (r) was used for non-parametric correlations. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

As this is a pilot retrospective study, no statistical sample-size calculations were conducted.

All statistical analyses were performed using the EZR software program (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [13], which is a graphical user interface for the R program (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of R commander, designed to include statistical functions that are frequently used in biostatistics.

3. Results

3.1 Participant characteristics and clinical data

The demographic, laboratory, and treatment-related data of the participants are shown in Table 1. In total, 42 COVID-19 patients (median age, 50 years (IQR, 42–62 years), 59.5% men) were enrolled, were admitted at a median duration of 7 (IQR, 4–10) days after COVID-19 symptom onset, and required oxygen therapy at a median dose of 2 L/min (IQR 1–3). COVID-19 vaccination had been administered in 4 (9.5%) participants, and almost all participants received remdesivir (95.2%) for COVID-19 treatment.

In total, 59.5% (25/42) of participants were classified into the dexamethasone group (6 mg/day), and 40.5% (17/42) were included in the methylprednisolone group ($\geq$ 250 mg/day). In the methylprednisolone group, 2 (11.8%) participants received an initial dose of 250 mg/day, 9 (52.9%) received 500 mg/day, and 6 (35.3%) received 1000 mg/day. All patients in the methylprednisolone group received the initial dose for 3 days (data not shown).

There were no complications associated with bacterial infection during hospitalization in both groups.

No significant differences in demographics and initial clinical characteristics were observed between the methylprednisolone and dexamethasone groups ($p > 0.05$).

3.2 Outcomes of intergroup comparisons

The incidence of transfer to a tertiary hospital did not differ significantly between the methylprednisolone and dexamethasone groups ($p = 0.37$), and in-hospital mortality was similar in both groups ($p = 1$; Table 2).

Participants who had completed treatment for COVID-19 were selected, and treatment data were compared between the two groups (Table 3). The duration of oxygen therapy for COVID-19 treatment in the methylprednisolone group was significantly longer than in the dexamethasone group as was the duration of corticosteroid administration (both $p < 0.05$), whereas the duration of fever was similar in both the groups ($p = 0.54$).

TABLE 1. Baseline characteristics and laboratory and therapeutic data.

Variables	All patients (n = 42)	Methylprednisolone group (n = 17)	Dexamethasone group (n = 25)	*p*-value[#]
Age (years), median (IQR)	50 (42–62)	48 (40–58)	51 (47–66)	0.11
Sex, male, n (%)	25 (59.5)	9 (52.9)	16 (64)	0.53
Body mass index (kg/m^2), median (IQR)	25.9 (24.3–29.4)	26.4 (24.3–30.6)	25.5 (23.2–28.9)	0.30
Time from illness onset to hospital admission (days), median (IQR)	7 (4–8)	8 (7–9)	5 (3–8)	0.06
Dose of oxygen at admission (L/min), median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	0.93
COVID-19 vaccination, n (%)	4 (9.5)	2 (11.8)	2 (8)	1.00
Medical history, n (%)				
Diabetes mellitus	5 (11.9)	2 (11.8)	3 (12)	1.00
Malignant tumor	1 (2.4)	-	1 (4)	1.00
COPD	1 (2.4)	-	1 (4)	1.00
Hypertension	14 (33.3)	3 (17.6)	11 (44)	0.10
Chronic kidney disease	3 (7.1)	1 (5.9)	2 (8)	1.00
Former or current smoking, n (%)	8 (19)	4 (23.5)	4 (16)	0.69
Treatments for COVID-19, n (%)				
Remdesivir	40 (95.2)	17 (100)	23 (92)	1.00
Favipiravir	1 (2.4)	-	1 (4)	1.00
Baricitinib	21 (50)	8 (47.1)	13 (52)	1.00
Anti-coagulant				
Rivaroxaban	11 (26.2)	9 (52.9)	2 (8)	1.00
Unfractionated heparin	28 (66.7)	8 (47.1)	20 (80)	1.00
Casirivimab–imdevimab	8 (19.1)	3 (17.6)	5 (20)	1.00
Laboratory data, median (IQR)				
WBC count (× 10^3/μL)	4.8 (3.6–6.1)	4.9 (3.7–6.6)	4.3 (3.2–5.7)	0.34
Lymphocyte count (/μL)	888 (653–1054)	900 (688–1139)	888 (579–1029)	0.43
Platelet count (× 10^3/μL)	165 (124–205)	194 (145–22)	158 (124–18)	0.20
LDH (U/L)	356 (270–427)	365 (306–432)	307 (224–422)	0.10
Serum ferritin (ng/mL)	421 (254–1098)	400 (254–806)	515 (279–1166)	0.65
D-dimer (μg/mL)	0.8 (0.5–1.2)	0.8 (0.6–1.1)	0.9 (0.5–1.3)	0.90

IQR, interquartile range; COVID-19, coronavirus disease; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; LDH, lactate dehydrogenase. [#]p-values of the comparison of the methylprednisolone and dexamethasone groups.

TABLE 2. Comparison of outcome data between the methylprednisolone and dexamethasone groups.

Variables	Methylprednisolone group (n = 17), n (%)	Dexamethasone group (n = 25), n (%)	*p*-value
Incidences of transfer to a tertiary hospital	1 (5.9)	5 (20)	0.37
In-hospital mortality	-	1 (4)	1.00

TABLE 3. Comparison of treatment data for patients who completed treatment in the methylprednisolone and dexamethasone groups.

Variables	Methylprednisolone group (n = 16), median (IQR)	Dexamethasone group (n = 19), median (IQR)	*p*-value
Duration of oxygen therapy (days)	8.5 (5.5–11.2)	4 (2.0–7.5)	<0.05
Duration of corticosteroid administration (days)	10 (9.0–11.8)	9 (5–9)	<0.05
Duration of fever (days)	2 (2–2)	2 (2–2)	0.54

IQR, interquartile range.

3.3 Relationship between duration of oxygen therapy and clinical variables

The correlation analysis between duration of oxygen therapy during COVID-19 treatment in patients who had completed treatment for COVID-19, and the collected clinical data, duration of corticosteroid administration, dose of oxygen at admission, time from illness onset to hospital admission, and age is presented in Fig. 1. No statistically significant correlation was found between duration of oxygen therapy and duration of corticosteroid administration, dose of oxygen at admission, time from illness onset to hospital admission, and age; the Spearman coefficients (r) were 0.4 ($p < 0.05$), 0.38 ($p < 0.05$), -0.02 ($p = 0.93$), and 0.15 ($p = 0.4$), respectively.

4. Discussion

This study showed that high-dose methylprednisolone administration as initial corticosteroid therapy for patients with severe COVID-19 who did not require noninvasive/invasive mechanical ventilation or ECMO conferred no additional benefits than dexamethasone therapy in the events, transfer, death, and duration of fever. In contrast, the duration of oxygen therapy during the treatment period for COVID-19 was prolonged in the methylprednisolone group compared to the dexamethasone group. Despite a weak correlation between the duration of oxygen therapy and of corticosteroid administration, or dose of oxygen at admission, factors that strongly affected the duration of oxygen therapy could not be determined, except for the factors with an intergroup difference.

A previous report emphasized three factors for the effectiveness of corticosteroid administration in COVID-19 patients [14]. The first factor was the timing of corticosteroid administration. Although corticosteroid administration within 7 days from illness onset may inhibit antibody production during infection [15], the median time from symptom onset to admission and corticosteroid administration in this study was 7 days. Liu et al. reported that earlier corticosteroid administration might impair clearance of SARS-CoV-2, as suggested by delayed viral clearance in steroid-treated patients [16]. In the same study, SARS-CoV-2 ribonucleic acids (RNA) clearance was affected by early corticosteroid initiation (at $\leq$ 3 days of hospitalization) in patients with severe COVID-19, with a 9-day median duration between COVID-19 onset and hospital admission. Although the antibody response and SARS-CoV-2 RNA clearance were not evaluated in our study, the influence of early corticosteroid administration on antibody production and viral clearance is a major concern. The importance of the timing of antiviral therapy relative to corticosteroid administration was reported by Wong *et al.* [17] who showed that, in patients with moderate COVID-19, initiating remdesivir treatment prior to or simultaneously with corticosteroid administration was associated with a significantly shorter time to clinical improvement, decreased length of hospital stay, and lower risk of in-hospital mortality than the late introduction of remdesivir after dexamethasone or not using the antiviral at all. This previous study is justifiable based on the theoretical understanding of the progression of a viral infection, where the early introduction of antivirals might inhibit viral replication and possibly prevent the "cytokine storm," followed by the addition of anti-inflammatory agents (*e.g.*, corticosteroids) to suppress hyperinflammation. In line with this theory, in this study, almost all patients (97.6%, 41/42) received antiviral therapy, with either remdesivir or favipiravir, and corticosteroids were administered simultaneously upon admission.

The second factor was the corticosteroid dose. The clinical benefits of high-dose methylprednisolone therapy compared to standard therapy have been reported in a small RCT [10]; however, other previous studies reported that the effect of corticosteroids on viral shedding in patients with COVID-19 might occur in a dose—response manner [18, 19]. Furthermore, Buso

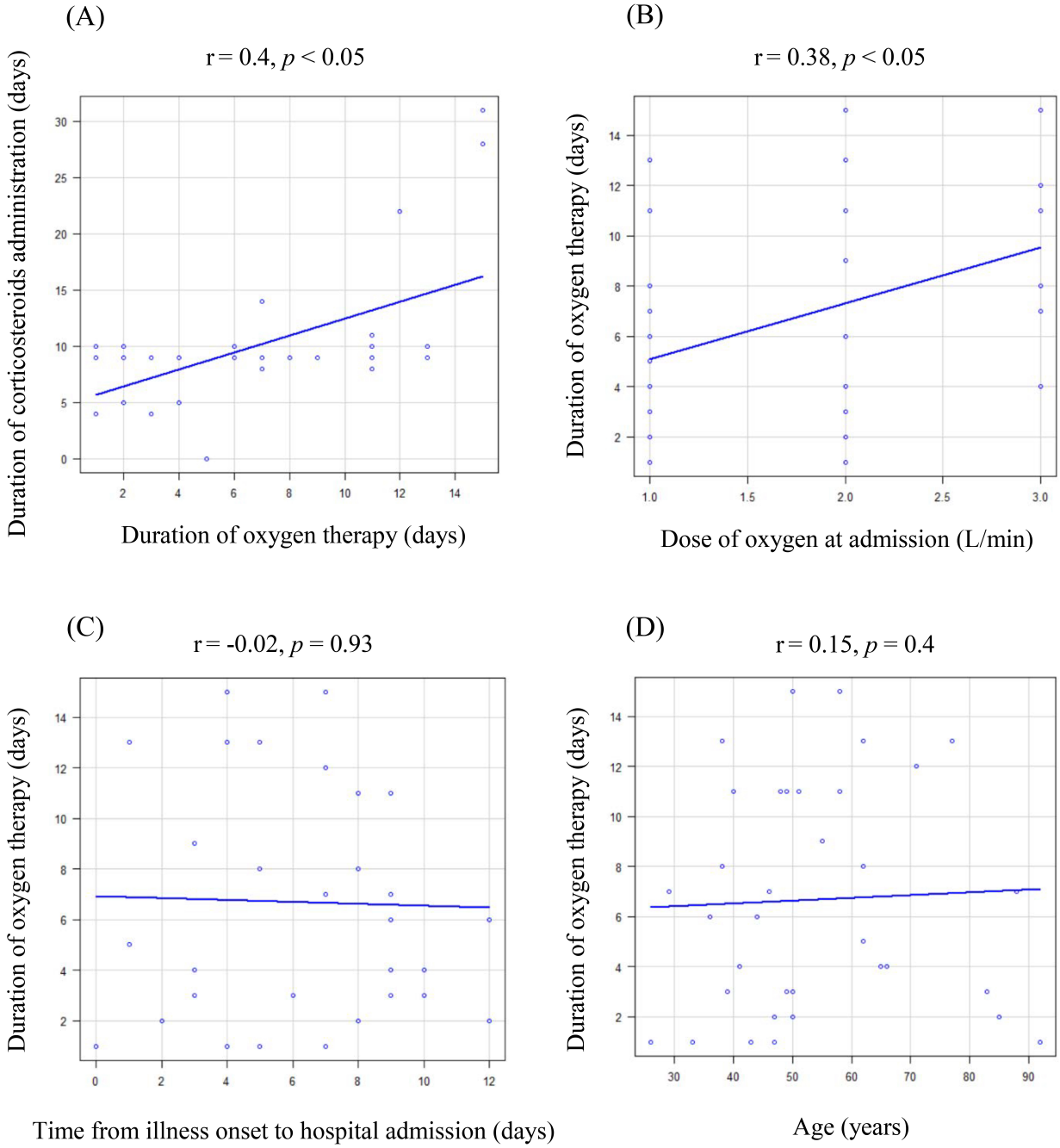

FIGURE 1. Correlation between the duration of oxygen therapy and the duration of corticosteroid administration (A), dose of oxygen at admission (B), time from illness onset to hospital admission (C), and age (D). No significant correlation was observed.

et al. [20] showed that the time of SARS-CoV-2 RNA clearance did not differ in patients with severe COVID-19 based on the two types of corticosteroid administration (standard dose methylprednisolone (60 mg/day) and dexamethasone (6 mg/day)). As there was an increment in the period of oxygen therapy for patients receiving high-dose methylprednisolone compared to those receiving dexamethasone in this study, it is possible that the delayed SARS-CoV-2 RNA clearance due to the high-dose corticosteroid treatment may have influenced the period of oxygen therapy in patients with severe COVID-19 who did not require noninvasive/invasive mechanical ventilation or ECMO with reference to the previous studies [18–20].

The third factor was the severity of COVID-19. Several reports have supported corticosteroid use to treat patients with severe or critical COVID-19 and avoidance of corticosteroids for those with non-severe COVID-19 [9, 11, 21, 22]. Although the optimal type of corticosteroids that would provide good clinical outcomes for patients with severe or critical COVID-19 are still unknown, methylprednisolone reportedly achieved higher lung tissue-to-plasma levels compared to dexamethasone in animal models [23]. It may thus improve the clinical course of patients with severe or critical COVID-19 due to its effectiveness in lung injury compared to dexamethasone. However, previous direct comparative studies of dexamethasone (6 mg/day) and standard-dose methylprednisolone (2 mg/kg/day or 60 mg/day), which mostly targeted patients with

severe COVID-19 who did not require invasive mechanical ventilation, showed no significant difference in the 28- or 30-day mortality between the two groups [20, 24]. Conversely, Ko J *et al.* [25] showed that standard dose methylprednisolone (1 mg/kg/day) treatment could lead to decreased 50-day mortality for critically ill patients with COVID-19 who required invasive mechanical ventilation as compared to dexamethasone (6 mg/day). In addition, a previous study, with a larger sample comprising of patients with more severe COVID-19 than in our study, reported that high-dose methylprednisolone treatment (250–500 mg/day) was superior with respect to the recovery time defined as a subjective improvement of dyspnea than dexamethasone treatment (6 mg/day); no superiority was observed in in-hospital mortality [26]. Furthermore, Ikeda *et al.* [15] showed that the duration of invasive mechanical ventilation in critically ill patients with COVID-19 who required intubation was significantly shorter in the high-dose methylprednisolone group (initial dose $\geq$ 250 mg/day) than in the standard-dose group (initial dose $<$250 mg/day). However, high-dose methylprednisolone treatment could not prevent the worsening of the respiratory condition and consequent requirement of invasive mechanical ventilation, which is similar to the results of our study. Based on the results of the present and previous studies, the effectiveness may not differ between standard dose methylprednisolone therapy and dexamethasone therapy in patients with severe COVID-19 not requiring invasive mechanical ventilation; high-dose methylprednisolone therapy may be inferior to dexamethasone therapy in terms of clinical course among patients with COVID-19 of the same severity. However, standard dose methylprednisolone, compared with dexamethasone, may be effective for critically ill patients with COVID-19 requiring invasive mechanical ventilation, whereas high-dose methylprednisolone may be even better. A recent meta-analysis, which included not only critically ill patients with COVID-19 who required invasive mechanical ventilation but also patients who did not require invasive mechanical ventilation, showed that high-dose corticosteroid treatment was associated with similar clinical outcomes, such as mortality, need for endotracheal intubation, and length of stay, compared to standard-dose treatment [27]. The results of this meta-analysis might support our theory. Additional evidence on critically ill patients with COVID-19 requiring mechanical respiratory support is needed to confirm the optimal dose of methylprednisolone for treating COVID-19.

In this study, the duration of corticosteroid administration during the treatment period for COVID-19 in the methylprednisolone group was significantly longer than that of the dexamethasone group. As high-dose methylprednisolone therapy commonly requires tapering periods [19], the methylprednisolone group in this study had a longer administration time than the dexamethasone group.

The duration of fever was similar between the two groups. Previous studies showed that corticosteroid therapy could shorten the duration of fever in patients with severe COVID-19 compared to standard therapy [10, 22]. However, the present results suggest that the duration of fever and the type and dose of corticosteroid therapy might not be related.

This study had several limitations. First, this was a small-sample retrospective observational study, and there was a potential patient selection bias. Second, as some older patients could not complain of subjective symptoms, such as dyspnea or fatigue, subjective symptoms were not included in the evaluation. Third, axillary temperature, as an objective symptom, is peripheral temperature and is not accurate when compared to core body temperature [28]. Fourth, comorbidities such as diabetes were only assessed for their presence or absence and not for the severity of illness. Fifth, the dose had a wide range (250–1000 mg/day) in the methylprednisolone group. Finally, the tapering of high-dose methylprednisolone therapy and transfer to high-level hospitals in this study was not protocolized and was performed at the discretion of the attending physician.

5. Conclusions

High-dose methylprednisolone therapy for patients with severe COVID-19, not requiring noninvasive/invasive mechanical ventilation or ECMO, was not beneficial for the events, transfer, or death compared to dexamethasone therapy. Furthermore, the methylprednisolone group had a longer duration of oxygen therapy during the treatment period. Further studies that target critically ill patients with COVID-19, especially those requiring invasive mechanical ventilation or ECMO, are needed to determine the efficacy of high-dose methylprednisolone therapy.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

YK—Investigation, Data curation, Writing—original draft, Writing—review & editing; YO, HY, TH, NI, and SH—Writing—review & editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Research Ethics Committee of Hakujyuji Hospital, Fukuoka, Japan (No. 164). Patients were given the opportunity to opt out via the institutional website notice, and the requirement for individual written informed consent for study participation was waived.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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