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Timing of Initiation of Methylprednisolone Pulse Therapy in Patients with COVID-19

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Abstract: High-dose methylprednisolone pulse therapy is widely used in patients with severe COVID-19. This therapy is known to have sufficient clinical effectiveness, but the optimal administration method is not known. In this study, we assessed the deterioration of oxygenation after methylprednisolone pulse therapy in patients with COVID-19 according to disease severity (oxygen requirement) at initiation of therapy. Ninety-nine patients with COVID-19 who received methylprednisolone pulse therapy at Saitama Medical University Hospital in Japan between October 2020 and October 2021 were retrospectively reviewed. Clinical outcomes were compared according to the fraction of inspired oxygen as a measure of disease severity at initiation of methylprednisolone pulse therapy. Based on the F_IO_2 level at initiation of methylprednisolone pulse therapy, patients were classified into an early treatment group ($F_IO_2 \leq 0.39$; $n = 21$), a middle treatment group (F_IO_2 0.40–0.69; $n = 38$), and a late treatment group ($F_IO_2 \geq 0.70$; $n = 40$). The frequency of administration of mechanical ventilation and the days of oxygen therapy in the middle group were lower than in the other groups. The frequency of adverse events was also lower in the middle group. Both late and early methylprednisolone pulse therapy may lead to further deterioration of COVID-19 and an increase in adverse events.

Keywords: COVID-19 pneumonia; high-dose methylprednisolone pulse therapy; corticosteroids; severity; timing; fraction of inspired oxygen

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1. Introduction

Coronavirus disease 2019 (COVID-19) is an illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The number of patients with COVID-19 has been increasing since the first report of SARS-CoV-2 from China in December 2019. A proportion of people with COVID-19 develop the severe life-threatening disease. Risk factors for severe COVID-19 include male sex, older age, diabetes, hypertension, dyslipidemia, chronic lung disease, smoking, and obesity [1]. Some patients have acute exacerbation of respiratory condition on the 7th to 9th day after onset, and they have respiratory failure requiring mechanical ventilation or Extracorporeal Membrane Oxygenation (ECMO) [1]. Severe COVID-19 is characterized by a cytokine storm and disseminated intravascular coagulation (DIC) [2]. The release of a large amount of pro-inflammatory cytokines causes acute respiratory distress syndrome (ARDS) [2]. Antiviral agents, corticosteroids, Janus kinase

inhibitors, and anti-interleukin-6 receptor antibodies have been used to treat patients with COVID-19 pneumonia [3].

Corticosteroids (dexamethasone, hydrocortisone, methylprednisolone) are the therapy of choice for patients with COVID-19 who require oxygen support. In an open-label randomized controlled trial (RCT) known as RECOVERY, dexamethasone 6 mg/day for up to 10 days reduced the 28-day mortality rate in patients with COVID-19 [4]. Various doses of methylprednisolone pulse therapy (MPT) have also been used to treat COVID-19 [5,6]. A small single-blind RCT by Edalatifard et al. showed that short-term, high-dose MPT (250 mg/day for 3 days) reduced mortality in patients with severe COVID-19 [7]. However, the efficacy and safety of short-term, high-dose MPT (up to 1000 mg/day for 3 days) have not been well investigated. In particular, the optimal timing for initiating MPT in patients with COVID-19 is not known.

In this study, we sought to determine the optimal timing of MPT by investigating the clinical outcomes and treatment-related adverse events in patients with COVID-19 according to fraction of inspired oxygen (F_IO_2) as a measure of disease severity at the initiation of MPT.

2. Materials and Methods

2.1. Design Overview

This retrospective study was performed at Saitama Medical University Hospital in Japan and included hospitalized adults (aged 18 years or older) who had laboratory-confirmed COVID-19 and required oxygen support between October 2020 and October 2021. We treated COVID-19 according to the new COVID-19 clinical guidelines issued by the Ministry of Health, Labor and Welfare from time to time [3]. Patients who have acute exacerbation of respiratory condition received MPT (methylprednisolone 1000 mg/day intravenously for 3 days, followed by intravenous or oral administration of dexamethasone 6 mg/day). Patients who did not receive MPT were excluded (Figure 1).

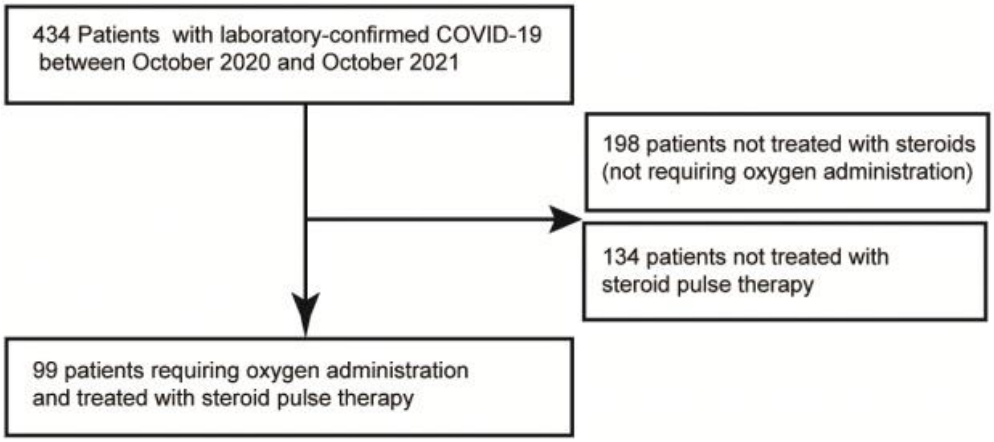

Figure 1. Flow diagram for selection of patients in this study.

The patients were grouped according to F_IO_2 at the initiation of MPT into an early treatment group ($F_IO_2 \leq 0.39$), a middle treatment group (F_IO_2 0.40–0.69), and a late treatment group ($F_IO_2 \geq 0.70$). Information on baseline demographic and clinical characteristics, treatments administered (oxygen administration, Anticoagulation, Remdesivir, Favipiravir, Baricitinib, Tocilizumab), adverse events (pulmonary complications, hemorrhage, and infection), and clinical outcomes (require mechanical ventilation, 28-day mortality rate, length of hospital stay, days of oxygen administration, oxygen requirement) was obtained from the electronic medical records and compared between the three groups. The primary outcomes were the relationship between disease severity at the initiation of MPT and clinical outcomes. The secondary outcomes were the relationship between adverse events and disease severity at the initiation of MPT.

The study was approved by the Institutional Review Board of Saitama Medical University Hospital (approval number 2021-098) and conducted in accordance with the tenets of the Declaration of Helsinki. The requirement for informed consent was waived because this study had a retrospective design.

2.2. Definitions

The F_IO_2 calibration scale used in this study is shown in Table 1 [8]. Laboratory-confirmed COVID-19 was defined as the detection of SARS-CoV-2 RNA by reverse transcription polymerase chain reaction in a nasopharyngeal swab or sputum sample according to the national guideline [9]. Adverse events included infectious disease caused by another pathogen, hemorrhage, and lung complications during hospitalization. Infectious disease was defined as the detection of a causative microorganism in blood, urine, sputum, or other specimen and contamination were excluded. All medical records were reviewed retrospectively, and cases of the non-infectious disease were excluded. Bleeding included gastrointestinal or intramuscular hemorrhage and hemothorax. Pulmonary complications included pneumothorax, mediastinal emphysema, and subcutaneous emphysema. ΔF_IO_2 was defined as the maximum F_IO_2 minus F_IO_2 at the initiation of MPT. Obesity was defined as a body mass index >25.

Table 1. F_IO_2 calibration scale.

Oxygen Devices	Oxygen (L)	F_IO_2 (%)
Nasal cannula	1	24
	2	28
	3	32
Face mask	4	30
	5	40
	6	50
Reservoir face mask	7	70
	8	80
	9	90
	10	99

F_IO_2, fraction of inspired oxygen.

2.3. Statistical Analysis

Continuous variables are expressed as the mean and standard deviation or the median (interquartile range (IQR)). The Kruskal–Wallis test was used for comparisons involving more than two groups. Categorical variables are expressed as the number (percentage) and were compared using Fisher's exact test with Bonferroni correction. All statistical analyses were performed using EZR software (Saitama, Japan) [10]. A two-sided *p*-value of <0.05 was considered statistically significant.

3. Results

3.1. Patient Characteristics

Ninety-nine patients with COVID-19 pneumonia who were treated with MPT during the study period were enrolled (Figure 1). Their clinical characteristics at the initiation of MPT are shown in Table 2. There were 21 patients in the early treatment group, 38 in the middle treatment group, and 40 in the late treatment group.

Table 2. Summary of patient demographic and clinical characteristics (n = 99).

Baseline Clinical Characteristics of 99 Patients at the Start of MPT					
	Total, n = 99	**Early Treatment Group, n = 21 ($F_IO_2 \leq 0.39$)**	**Middle Treatment Group, n = 18 (F_IO_2 0.40–0.69)**	**Late Treatment Group, n = 40 ($F_IO_2 \geq 0.70$)**	***p*-Value**
Demographic characteristics					
Age (years)	64 (21–94)	55 (40–76)	56 (21–94)	74 (35–91)	<0.001 ‡
Male sex (%)	79 (79.9)	17 (81.0)	30 (78.9)	32 (80.0)	1 †
Body mass index	25 (17–41)	24 (17–30)	26 (17–41)	24 (17–30)	0.168 ‡
Comorbidities					
Malignant tumor (%)	10 (10.1)	3 (14.3)	2 (5.3)	5 (12.5)	0.468 †
Asthma or COPD (%)	11 (11.1)	4 (19.0)	3 (7.9)	4 (10.0)	0.417 †
Chronic kidney disease (%)	12 (12.1)	0 (0.0)	7 (18.4)	5 (13)	0.096 †
Diabetes mellitus (%)	33 (33.3)	5 (23.8)	18 (47.4)	10 (12.5)	0.072 †
Hypertension (%)	39 (39.4)	4 (19.0)	20 (52.6)	15 (37.5)	0.04 †
Hyperlipidemia (%)	18 (18.1)	4 (19.0)	9 (23.7)	5 (12.5)	0.445 †
Obesity (%)	47 (47.5)	7 (33.3)	23 (60.5)	17 (42.5)	0.095 †
History					
COVID-19 vaccination (%)	6 (6.0)	0 (0.0)	4 (10.5)	2 (5.0)	0.258 †
Smoker (%)	29 (29.3)	5 (23.8)	11 (28.9)	13 (32.5)	0.779 †
Treatment					
Days from onset to hospitalization	7 (0–19)	3 (0–11)	6 (0–11)	6 (0–19)	0.150 ‡
Days from onset to start of oxygen therapy	7 (0–20)	7 (0–20)	7 (0–19)	7 (0–19)	0.240 ‡
Days from onset to start of corticosteroid therapy	7 (0–19)	6 (0–11)	8 (0–11)	7 (0–19)	0.365 ‡
Anticoagulation (%)	40 (40.4)	8 (38.1)	14 (36.8)	18 (45.0)	0.778 †
Remdesivir (%)	79 (80.8)	18 (85.7)	30 (78.9)	31 (77.5)	0.768 †
Favipiravir (%)	8 (8.0)	0 (0.0)	4 (10.5)	4 (10.0)	0.354 †
Baricitinib (%)	47 (47.4)	5 (23.8)	23 (60.5)	19 (47.5)	0.025 †
Tocilizumab (%)	24 (24.2)	3 (14.3)	8 (21.1)	13 (32.5)	0.290 †
Dexamethasone (%)	53 (53.5)	11 (52.4)	25 (65.8)	17 (42.5)	0.060 †
Oxygen devices					
HFNC (%)	29 (29.3)	1 (4.8)	13 (34.2)	15 (37.5)	0.012 †
Ventilator (%)	12 (12.1)	0 (0.0)	1 (2.6)	11 (27.5)	<0.001 †

Data are presented as the number (percentage) or as the median (interquartile range) unless otherwise specified. Abbreviations: COPD, chronic obstructive pulmonary disease; HFNC, high-flow nasal cannula. † Fisher's exact test with Bonferroni correction; ‡ Kruskal–Wallis test.

The median age was 64 years. Patients in the late group were significantly older than those in the other two groups ($p < 0.001$). There were no significant differences between the groups in sex, days from symptom onset to hospitalization, days from symptom onset to start of oxygen therapy, days from symptom onset to start of corticosteroid therapy, or use of corticosteroids before the start of MPT. Twelve patients were on a ventilator and 29 received oxygen via a high-flow nasal cannula (HFNC) at the initiation of MPT. The most common comorbidities were hypertension (n = 39, 39.4%), diabetes mellitus (n = 33,

33.3%), and obesity (n = 47, 47.5%). There was a significant difference among the groups in the frequency of hypertension (early, 19.0%; middle, 52.6%; late, 37.5%; p = 0.043).

There was no significant difference in days from symptom onset to the start of initial dexamethasone therapy among the three groups. Corticosteroids were used concomitantly with anticoagulants, remdesivir, favipiravir, baricitinib, and tocilizumab. Baricitinib was used significantly more often in the middle group (n = 23, 60.5%) than in the early group (n = 5, 23.8%) or late group (n = 19, 47.5%) (p = 0.025).

3.2. Primary Outcomes: Relationship between Disease Severity at the Initiation of MPT and Clinical Outcomes

Ultimately, 29 (29.3%) required mechanical ventilation and 8 (8.1%) died within 28 days. The median duration of oxygen support was 15 days (IQR, 3–86) and the median length of hospital stay was 22 days (IQR, 3–85).

Patients in the middle group were significantly less likely to require mechanical ventilation (n = 5, 13.2%) than those in the early group (n = 6, 28.5%) or late group (n = 18, 45.0%) (p = 0.008) (Figure 2A). There was no significant difference in the 28-day mortality rate (Figure 2B) or length of hospital stay (Figure 2C) among the three groups. The median duration of oxygen therapy was significantly shorter in the middle group (13 days, IQR, 3–55) than in the late group (20 days, IQR 7–73; p = 0.029) and was also shorter than in the early group (20 days, IQR 7–86), although the difference did not reach statistical significance (p = 0.080) (Figure 2D). The median ΔF_IO_2 value was significantly higher in the early group (32, IQR 0–79) than in the middle group (0, IQR 0–40; $p < 0.001$) or late group (15, IQR 0–30; p = 0.017) but was lower in the middle group than in the late group, but the difference was not statistically significant (p = 0.071) (Figure 2E).

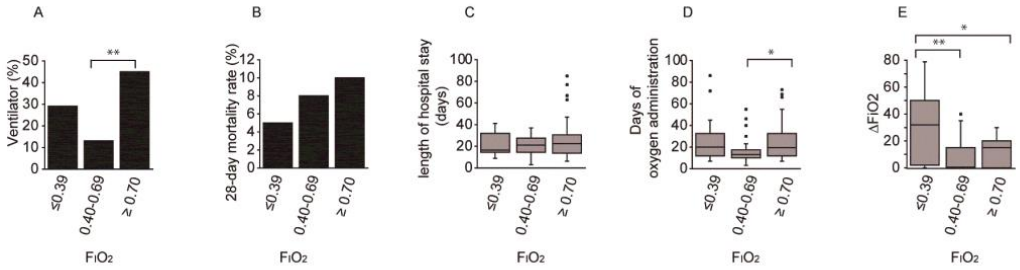

Figure 2. Analysis of clinical outcomes. (**A**) Frequency of ventilator use and (**B**) 28-day mortality rate were compared using Fisher's exact test with Bonferroni correction. (**C**) Length of hospital stay, (**D**) duration of oxygen administration, and (**E**) ΔF_IO_2 are shown as the median and interquartile range (IQR). They were analyzed using the Kruskal–Wallis test with Bonferroni correction. * $p < 0.05$ and ** $p < 0.01$. Only combinations with significant differences are shown.

3.3. Secondary Outcomes: Relationship between Adverse Events and Disease Severity at the Initiation of MPT

Adverse events included pulmonary complications, hemorrhage, and infection. Pulmonary complications occurred in 14 (14.1%) of the 99 patients and were significantly more common in the late group (30.0%, n = 12/40). There were no lung complications in the middle group (Figure 3A). Episodes of hemorrhage occurred in 16 patients (16.2%) and were significantly less common in the middle group (2.6%, n = 1/38) (Figure 3B). Infections other than COVID-19 occurred in 35 patients (35.4%) and tended to be less common in the middle group (Figure 3C).

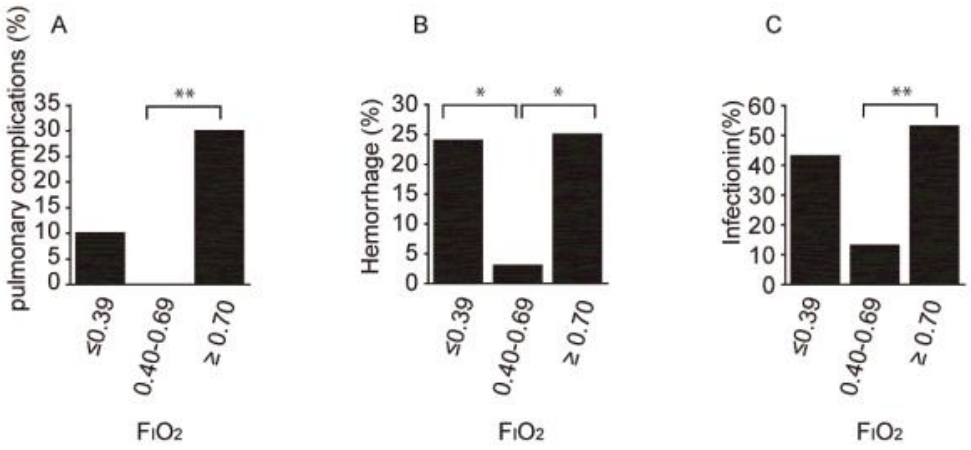

Figure 3. Analysis of adverse events. (**A**) Frequency of barotrauma, (**B**) hemorrhage, and (**C**) infection were compared using Fisher's exact test with Bonferroni correction. * $p < 0.05$ and ** $p < 0.01$. Only combinations with significant differences are shown.

4. Discussion

In this study, we analyzed the relationship between the severity of COVID-19 at the initiation of MPT and clinical outcomes and adverse events. Patients in the middle group (F_IO_2 0.40–0.69) who received MPT were less likely to require mechanical ventilation and needed a shorter duration of oxygen support than those in the early group ($F_IO_2 \leq 0.39$) and late group ($F_IO_2 \geq 0.70$). Moreover, the incidence of adverse events was lowest in the middle group. There was no significant difference in days from symptom onset to the start of corticosteroid therapy.

Previous studies that investigated the timing for initiating corticosteroid therapy in patients with COVID-19 found a relationship between the number of days from symptom onset to the start of corticosteroid therapy and the outcome of exacerbation of respiratory illness [11–13]. However, it remains controversial as to whether early corticosteroid therapy in patients with COVID-19 reduces mortality [13] or leads to exacerbation [12]. There are several problems with using the days from symptom onset as the basis for the timing of initiating therapy. One is that symptom onset is self-reported, which means that findings are subjective. Another is that the speed of exacerbation of the illness varies according to the individual patient's background characteristics. Indeed, the objective finding is more important for the timing of initiation. Therefore, we used oxygen requirement, which is an objective measure of disease severity, as the basis for the timing of initiation of therapy. To our knowledge, there are no previous reports on the relationship between disease severity as indicated by F_IO_2 or respiratory status at initiation of corticosteroid therapy and clinical outcomes and adverse events. At this point, our study is very interesting.

We suggest four possible reasons why patients in the middle group had the best clinical outcome. First, MPT may have been administered too late in the late group to be able to prevent exacerbation. Interestingly, a previous study suggested that late corticosteroid therapy did not reduce the mortality risk in patients with COVID-19 because excessive inflammation had already progressed to cause severe ARDS before MPT was started [14]. Indeed, previous studies have found MPT to be ineffective in severe ARDS [15,16]. Second, improved respiratory status was not necessarily related to control of inflammation in patients in the early group. In general, COVID-19 progresses from a viral response phase to an overlapping phase of the viral response and host inflammatory response, and then to a host inflammatory response phase [12,17,18]. Therefore, control of the amount of virus was probably more important than control of inflammation in terms of improving the clinical outcome in the early group. A previous study has suggested that early administration of corticosteroids before antiviral therapy may lead to a worsening of respiratory status [11]. Third, in our protocol, long-term oxygen support tended to be accompanied by long-term corticosteroid or anticoagulant therapy, which may lead to an increase in adverse events.

Fourth, frequent use of mechanical ventilation may have resulted in increased barotrauma in the late group.

This study has several limitations. First, it had a small sample size and was performed at a single facility, which may have introduced a selection basis. Second, MPT was defined as intravenous administration of methylprednisolone 1000 mg/day for 3 days whereas lower doses of methylprednisolone (250 mg/day for 3 days) were used in previous RCTs of MPT [7,19,20]. The methylprednisolone dose may affect clinical outcomes and adverse events, so the generalizability of our findings may be limited. Third, our study design was retrospective, which means that the choice of drugs used in combination with MPT for COVID-19 was based on the duration of hospitalization in accordance with the therapeutic guidelines. In particular, there was a significant difference in the frequency of using baricitinib among the three groups. The different combinations of drugs (including administration of antibacterial or antifungal) used may have affected clinical outcomes and adverse events. A further RCT with a larger sample size is warranted to determine the optimal timing of initiating MPT for patients with COVID-19.

5. Conclusions

Patients with COVID-19 who received MPT in the middle phase (F_IO_2 0.40–0.69) were less likely to experience an exacerbation of respiratory symptoms, required oxygen support for a shorter period, and had fewer adverse events than those who received MPT in the early and late phases. Early or late MPT may lead not only to further deterioration of COVID-19 but also to a higher likelihood of adverse events. Further studies are warranted to determine the optimal timing of MPT in patients with COVID-19. This study is the first to investigate the relationship between COVID-19 disease severity in terms of oxygen requirement and the timing of initiating MPT, and our findings may contribute to the management of patients with severe COVID-19.

Author Contributions: M.T. collected the data. M.T., N.T. and K.I. conceived and designed the study. M.T., N.T. and K.I. wrote the manuscript. M.T., N.T., K.I., J.S., N.I., K.Y., H.N., Y.H. and S.M. treated the patients. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the revised tenets of the Declaration of Helsinki after approval by the Institutional Review Board of Saitama Medical University Hospital (approval number 2021-098, approval date 6 December 2021).

Informed Consent Statement: Although we have not received informed consent from the subjects because of the retrospective study, we have disclosed the information of the study and guaranteed the opportunity for the study subjects to refuse. The information disclosure is on the Saitama Medical University Hospital Institutional Review Board website (URL: http://www.saitama-med.ac.jp/hospital/outline/irb.html).

Data Availability Statement: The data that support the findings of this study are available from the first author, M.T., upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

COVID-19	coronavirus disease 2019
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
DIC	disseminated intravascular coagulation
ARDS	acute respiratory distress syndrome
RCT	randomized controlled trial
MPT	methylprednisolone pulse therapy
F_IO_2	a fraction of inspired oxygen
IQR	interquartile range
HFNC	high-flow nasal cannula

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