Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Infection and Chemotherapy 28 (2022) 875–883

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: www.elsevier.com/locate/jic

Original Article

Delayed dexamethasone treatment at initiation of oxygen supplementation for coronavirus disease 2019 is associated with the exacerbation of clinical condition

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ARTICLE INFO

Keywords:
Coronavirus disease 2019
Dexamethasone
Acute respiratory distress syndrome
Mechanical ventilation
Mortality

ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) frequently causes inflammatory lung injury as its symptoms progress. While dexamethasone reportedly reduces inflammation and prevents progression to respiratory failure, the appropriate time to administer dexamethasone in patients with COVID-19 remains unclear.
Methods: This was a single-center, retrospective cohort study, where we consecutively enrolled patients hospitalized with COVID-19 who received oxygen and oral dexamethasone (n = 85). We assessed the association between the number of days to the initiation of dexamethasone and the cumulative rate of exacerbation defined as death or initiation of mechanical ventilation within 28 days of symptom onset.
Results: The optimal cut-off value from the initiation of oxygen supplementation to that of dexamethasone administration was two days (sensitivity, 85%; specificity, 59%), whereas that from oxygen saturation (SpO_2) < 95% to the initiation of dexamethasone administration was five days (sensitivity, 78%; specificity, 59%). adjusting for age, sex, body mass index, Charlson comorbidity index score, time of oxygen supplementation (two or more days), and SpO_2 < 95% (five or more days), Cox regression analysis results showed that delayed dexamethasone administration since the initiation of oxygen supplementation was significantly associated with a higher risk of death or greater need for mechanical ventilation (hazard ratio: 5.51, 95% confidence interval, 1.79–16.91).
Conclusions: In patients with COVID-19 and hypoxemia, early administration of dexamethasone, preferably less than two days from initiation of oxygen supplementation, may be required to improve clinical outcomes.

1. Introduction

The new coronavirus infection, first confirmed in China toward the end of 2019, is still prevalent worldwide [1]. The characteristic symptom of coronavirus disease 2019 (COVID-19) is respiratory dysfunction, which can lead to fatal comorbidities, including acute respiratory distress syndrome (ARDS) [2]. In the Wuhan province of China, 67–85% of patients admitted to the intensive care unit (ICU) due to critical COVID-19 were diagnosed with ARDS, with a mortality rate of 61.5% [3,4]. Similarly, high mortality rates have been reported in a recent study [5]. Therefore, in addition to the treatment of COVID-19, measures are needed to prevent the development of ARDS. One such treatment is the synthetic steroid dexamethasone [6], which prevents progression to ARDS associated with cytokine storm by reducing inflammatory lung injury and preventing systemic organ damage [7]. Furthermore, dexamethasone was shown to reduce 28-day mortality in patients with COVID-19 receiving either oxygen supplementation or mechanical ventilation [8]. Nonetheless, the timing of dexamethasone administration in patients with COVID-19 remains controversial. On the one hand, since ARDS can cause self-perpetuating inflammation with subsequent loss of organ function, and is associated with high mortality levels, dexamethasone should be started as early as possible following the onset of ARDS [9]. On the other, studies have shown that early corticosteroid

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https://doi.org/10.1016/j.jiac.2022.03.007
Received 18 August 2021; Received in revised form 21 January 2022; Accepted 11 March 2022
Available online 18 March 2022

Abbreviations

ARDS	acute respiratory distress syndrome
AUC	area under the curve
BMI	body mass index
CCI	Charlson comorbidity index
CI	confidence interval
CT	chest computed tomography
COVID-19	coronavirus disease 2019
HR	hazard ratio
ICU	intensive care unit
IQR	interquartile range
ROC	receiver operating characteristic
SARS-CoV-2	severe acute respiratory syndrome coronavirus

administration within seven days of symptom onset was associated with a subsequent increase in plasma viral load [10,11] and exacerbated COVID-19 symptoms [12]. There are no clinical or laboratory indications for the initiation of dexamethasone administration, and the optimal timing of treatment remains unclear.

The aim of this study was therefore to determine the optimal timing for initiating dexamethasone to prevent the exacerbation in patients with COVID-19.

2. Patients and methods

2.1. Study design and participants

This was a single-center, retrospective cohort study. We included adult patients with positive reverse transcription–polymerase chain reaction or antigen test for severe acute respiratory syndrome coronavirus (SARS-CoV-2), who received oral dexamethasone and oxygen at Sapporo Medical University Hospital between October 1, 2020, and May 31, 2021. The following patients were excluded: those who did not require oxygen supplementation at dexamethasone treatment initiation, those who received high-dose methylprednisolone prior to dexamethasone initiation, and those under 18 years. Information concerning age, sex, body mass index (BMI), vital signs, oxygen saturation (SpO_2), chest computed tomography (CT), blood biochemistry, urinalysis, coagulation function, *C*-reactive protein, comorbidities, and medications was obtained from patient files. The Charlson comorbidity index (CCI) was used to evaluate the severity of comorbidities [13,14]. This study was approved by the Clinical Investigation Ethics Committee of Sapporo Medical University Hospital (Number 322-65).

2.2. Treatment

Oxygen supplementation was initiated if the SpO_2 breathing room air dropped to ≤93%, according to the US Centers for Disease Control and Prevention definition of severe disease, or if the SpO_2 was estimated to be ≤ 93% based on the chest CT findings and subjective symptoms of respiratory distress. The decision to initiate dexamethasone treatment was based on chest CT, SpO_2, and subjective symptoms of respiratory distress. Dexamethasone was administered at a dose of 6 mg once daily for up to 10 days. In addition, favipiravir, tocilizumab, remdesivir, baricitinib, antipyretics, analgesics, and intravenous insulin were administered, and oral/intravenous rehydration and electrolyte correction were performed.

2.3. Clinical outcomes

Exacerbation was defined as death or initiation of mechanical ventilation within 28 days of symptom onset. The primary outcome was the cumulative rate of exacerbation in cases of early vs. late treatment with dexamethasone. The factors associated with exacerbation were also investigated.

2.4. Study subgroups

Patients were classified into two groups: those whose symptoms improved without prior worsening (non-exacerbation group), and those whose symptoms worsened (exacerbation group). The relationship between the number of days to initiation of dexamethasone and the clinical outcomes was examined. Next, the patients were classified into the early and late treatment groups based on the optimal cut-off value determined for dexamethasone initiation.

2.5. Statistical analysis

Categorical variables are expressed as counts and percentages and continuous variables as mean and SD. Continuous numerical data were expressed as the Data are expressed as mean ± SD, median (interquartile range [IQR] 25th–75th percentile), and frequency (percentage), as applicable. Differences in continuous variables were tested using the unpaired Student's t-test and Mann–Whitney *U* test for parametric and non-parametric data, respectively. The χ^2 test or Fisher's exact test was used to compare categorical variables, as appropriate. Receiver operating characteristic (ROC) analysis was used to determine the area under the curve (AUC). To predict the outcomes of death or need for mechanical ventilation within 28 days, the optimal cut-off value was calculated for the number of days from the onset of (a) symptoms, (b) oxygen supplementation, and (c) SpO_2 < 95% until the initiation of dexamethasone administration, to predict the outcomes of death or need for mechanical ventilation within 28 days. The optimal cut-off value was determined based on the Youden index. Kaplan–Meier curves and log-rank tests were performed to assess the cumulative rates of death or mechanical ventilation from the initiation of dexamethasone treatment. Univariate and multivariate Cox regression analyses were performed to identify significant predictors across the dependent outcomes of interest. Explanatory variables were forced to incorporate the late treatment with dexamethasone in addition to age, sex, BMI, and CCI score. Statistical significance was set at $P < 0.05$. All analyses were performed using JMP® 15 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Baseline clinical characteristics of patients

One hundred and sixty-one patients received dexamethasone, and the data of 85 patients were finally used for analysis of effectiveness. Patients who did not require oxygen during dexamethasone treatment (n = 45) and those treated with high-dose methylprednisolone (n = 31) were excluded (Fig. 1).

The patients included in the study are shown in Table 1 and Table S1. The mean age of patients was 64 ± 13 years, 62 patients (73%) were male, and the median BMI was 24.4 kg/m^2 (IQR 22.6–27.8), respectively (Table 1). Forty-three patients (51%) had hypertension, 37 (44%) had chronic kidney disease, 30 (35%) had dyslipidemia, and 28 (33%) had diabetes mellitus (Table 1). Twenty-five patients (30%) received favipiravir prior to dexamethasone or in combination with dexamethasone. The median time from onset of symptoms to the initiation of dexamethasone was nine days (IQR 7–11 days).

3.2. Clinical outcomes

Seventeen of the 85 patients experienced exacerbations. Of them, five died, and 12 underwent mechanical ventilation within 28 days of onset. Of the 12 patients who were managed with ventilators, four patients improved, six did not improve and were transferred to other

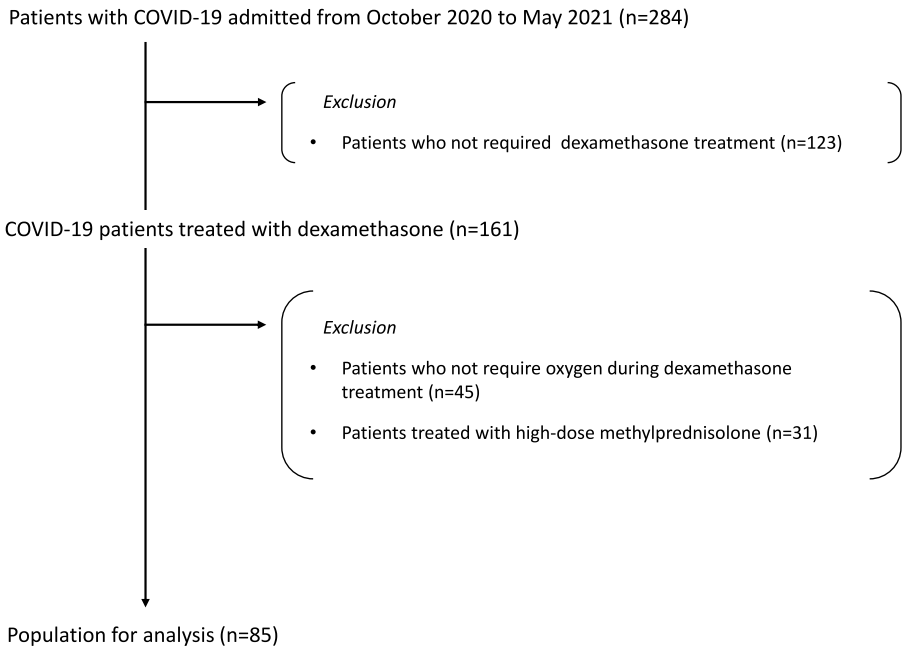

Fig. 1. Flow chart of patient selection.

Table 1
Baseline characteristics.

Characteristic	Total patients (n = 85)
Age, mean (SD), years	64 (13)
male, n (%)	62 (73)
BMI, median (IQR), kg/m^2	24.4 (22.6–27.8)
≥25 kg/m^2, n (%)	37 (44)
SpO_2 at hospitalization, median (IQR), %	94 (92–96)
SpO_2 at dexamethasone administration, median (IQR), %	93 (90–95)
Nasal cannula, n (%)	75 (88)
Oxygen mask, n (%)	10 (12)
Progress since symptom onset, median (IQR), day	
To hospitalization	8 (6–10)
To oxygen supplementation	9 (7–11)
To dexamethasone administration	9 (7–11)
Comorbidities, n (%)	
Hypertension	43 (51)
Chronic kidney disease	37 (44)
Dyslipidemia	30 (35)
Diabetes	28 (33)
Charlson comorbidity index score, median (IQR)	0 (0–1)
Additional or combination medication, n (%)	
Insulin	31 (36)
Favipiravir	25 (29)
Anticoagulant drug	20 (24)
Tocilizumab	18 (21)
Remdesivir	5 (6)
Baricitinib	1 (1)
Laboratory variables	
Creatinine, median (IQR), mg/dL	0.9 (0.7–1.0)
Hemoglobin, mean (SD), g/dL	14.4 (1.9)
White blood cell, median (IQR), × 1000/μL	5.4 (3.9–7.1)
Lymphocyte, median (IQR),/μL	888 (621–1133)
Platelets, mean (SD), × 1000/μL	183 (83.1)
CRP, median (IQR), mg/dL	6.9 (3.8–10.8)

Data are presented as mean (standard deviation [SD]) or median (interquartile range [IQR] 25th–75th percentile) or numbers (with percentages). Abbreviations: BMI, body mass index; CRP, *C*-reactive protein.

hospitals, and two died.

During the study period, elevated blood glucose levels due to dexamethasone occurred in 36 (42%) patients, of whom 20 had diabetes mellitus as a comorbidity. Insulin was continuously infused to 31 patients. Most cases of inadequate glycemic control were resolved by the time of discharge. Other common adverse events of dexamethasone, such as thrombosis, gastrointestinal disorders, and bacterial infections, were not observed.

3.3. Number of days to initiation of dexamethasone

The number of days from each event to the initiation of dexamethasone administration was compared between the exacerbation and non-exacerbation groups (Fig. 2). There was no difference between the groups in the number of days from symptom onset to initiation of dexamethasone administration (9 [IQR 7–11] vs. 9 [IQR 7–11] days, $p = 0.658$) (Fig. 2a). The duration from oxygen treatment to initiation of dexamethasone administration was significantly longer in the exacerbation group compared with the non-exacerbation group (1 [IQR 1–2] vs. 2 [IQR 1–3] days, $p < 0.001$) (Fig. 2b). In addition, the time for SpO_2 to fall below 95% to initiation of dexamethasone administration was longer in the exacerbation group compared with the non-exacerbation group (2 [IQR 1–4] vs. 5 [IQR 2–9] days, $p = 0.029$) (Fig. 2c).

We performed a subgroup analysis (Table 3). Regarding the time from onset of symptoms to the initiation of dexamethasone, there was a significant difference in sex and SpO_2 at the time of hospitalization between the early and late dexamethasone treatment groups (Table 3). Regarding the time from oxygen supplementation, there was a significant difference in CCI score and favipiravir treatment (Table 3). Regarding the time from SpO_2 falling below 95%, there was a significant difference in dyslipidemia, CCI score, and favipiravir and tocilizumab treatment (Table 3).

3.4. Optimal cut-off value for the number of days until initiation of dexamethasone for clinical outcome

ROC curves were drawn to calculate the optimal cut-off values for the number of days until initiation of dexamethasone for various clinical outcomes occurring within 28 days of symptom onset. The cut-off value from symptom onset to the initiation of dexamethasone was nine days (AUC, 0.54; sensitivity, 49%; specificity, 67%), and the cut-off value from the initiation of oxygen supplementation to the initiation of dexamethasone was two days (AUC, 0.72; sensitivity, 85%; specificity,

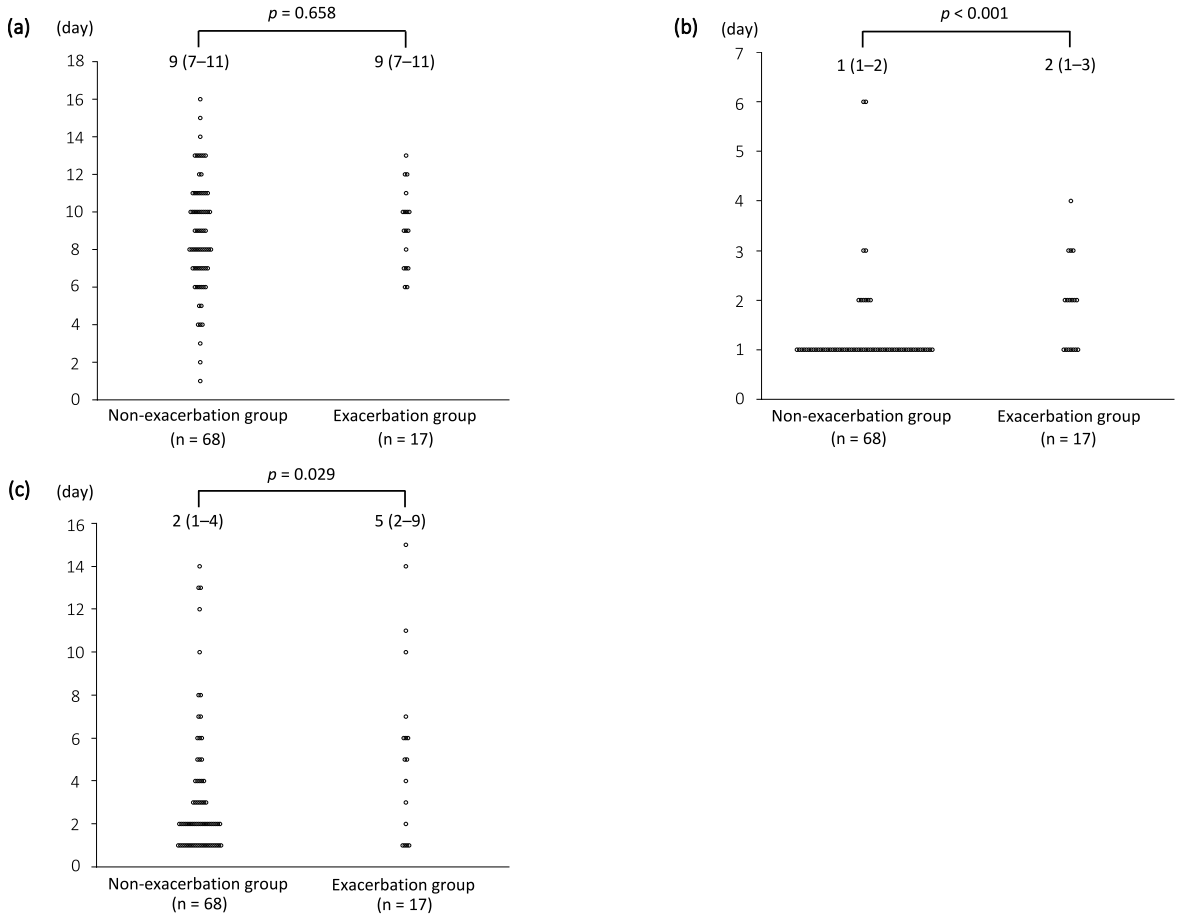

Fig. 2. Days to initiation dexamethasone treatment. Data are presented as median with interquartile range [IQR]. Exacerbation was defined as death or initiation of mechanical ventilation within 28 days of symptom onset. The number of days from the onset of (a) symptoms, (b) oxygen supplementation, and (c) SpO_2 falling <95% until the initiation of dexamethasone administration.

Table 2
Optimal cut-off value to initiation of dexamethasone.

	AUC	95% CI	Cut-off value	Sensitivity	Specificity	PPV	NPV	Accuracy
From onset of symptoms	0.54	0.39–0.68	9	0.49	0.67	0.24	0.85	0.52
From the start of oxygen supplementation	0.72	0.59–0.85	2	0.85	0.59	0.50	0.89	0.80
From oxygen saturation falling <95%	0.69	0.51–0.83	5	0.78	0.59	0.40	0.88	0.74

Abbreviations: AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

59%) (Table 3). The cut-off value from SpO_2 < 95% to the initiation of dexamethasone was five days (AUC, 0.69; sensitivity, 78%; specificity, 59%) (Table 2).

3.5. Clinical outcomes of the early and late treatment groups

The patients were divided into subgroups (early and late treatment groups) based on the optimal cut-off value. First, the subgroups stratified by the optimal cut-off value for the number of days from symptom onset to initiation of dexamethasone administration had no difference in the cumulative rate of exacerbation (Fig. 3a). Regarding that from oxygen treatment, the cumulative rate of exacerbation was significantly lower in the early treatment group (<two days) than in the late treatment group (≥two days) (p < 0.001, Fig. 3b). Regarding that from SpO_2 < 95%, the cumulative rate of exacerbation was lower in the early treatment group (<five days) than in the late treatment group (≥five days) (p = 0.015, Fig. 3c).

Furthermore, considering the cumulative rate of deaths, the optimal cut-off value for all the three durations between the two subgroups had no significant difference (Fig. 4).

3.6. Factors related to clinical outcomes

Late-treatment was defined as dexamethasone initiation two days after the initiation of oxygen supplementation and five days from SpO_2 < 95%.

Univariate analysis revealed that late treatment from the initiation of oxygen supplementation (hazard ratio [HR]: 7.25, 95% confidence interval [CI]: 2.61–20.13, p < 0.001), SpO_2 < 95% (HR: 3.13, 95% CI: 1.18–8.33, p = 0.022), and age (HR: 1.05, 95% CI: 1.00–1.09, p = 0.035) were significantly associated with exacerbation (Table 4).

Multivariate analysis for cumulative clinical outcomes identified delayed treatment from the initiation of oxygen supplementation (HR: 6.66, 95% CI: 2.24–19.83, p < 0.001) as an independent risk factor (Model 1). Late-treatment from SpO_2 < 95% (HR: 3.01, 95% CI: 1.12–8.07, p = 0.029) was also identified as an independent risk factor (Model 2). In Model 3, which was additionally adjusted for the late administration of dexamethasone from the initiation of oxygen

Table 3
Baseline characteristics of the three subgroups.

Characteristic	From the onset of symptoms					From oxygen supplementation					From oxygen saturation falling <95%				
	Early treatment (<9 days) n = 39		Late treatment (9 ≥ days) n = 46		*P* value	Early treatment (<2 days) n = 65		Late treatment (2 ≥ days) n = 20		*p* value	Early treatment (<5 days) n = 60		Late treatment (5 ≥ days) n = 25		*p* value
Age, mean (SD), years	62	(13)	61	(13)	0.975	60	(13)	65	(12)	0.346	60	(14)	65	(10)	0.059
male, n (%)	33	(85)	29	(63)	0.026	46	(71)	16	(80)	0.417	43	(72)	19	(76)	0.682
BMI, median (IQR), kg/m^2	24.4	(22.8–28.0)	24.4	(22.1–27.6)	0.603	24.2	(22.4–26.4)	26.2	(23.6–29.3)	0.091	24.8	(22.7–27.8)	23.9	(22.1–27.9)	0.701
SpO_2 at hospitalization, median (IQR), %	94	(91–95)	95	(94–96)	0.002	94	(93–96)	95	(92–97)	0.316	94	(92–95)	95	(93–97)	0.067
SpO_2 at dexamethasone administration, median (IQR), %	93	(90–94)	94	(90–95)	0.471	94	(91–95)	93	(90–95)	0.851	94	(90–95)	93	(90–95)	0.969
Progress since symptom onset, median (IQR), days															
To hospitalization	6	(4–7)	11	(8–11)	<0.001	8	(6–10)	7	(3–11)	0.382	8	(6–11)	6	(4–8)	0.003
To oxygen supplementation	7	(5–8)	10	(9–12)	<0.001	9	(7–10)	9	(5–11)	0.502	9	(7–11)	8	(6–10)	0.091
To dexamethasone administration	7	(6–8)	11	(10–12)	<0.001	9	(7–10)	10	(7–13)	0.177	9	(7–11)	9	(7–10)	0.423
Comorbidities, n (%)															
Hypertension	19	(49)	24	(52)	0.751	31	(48)	12	(60)	0.336	28	(47)	15	(60)	0.263
Chronic kidney disease	15	(38)	22	(48)	0.386	26	(40)	11	(55)	0.237	25	(42)	12	(48)	0.592
Dyslipidemia	14	(36)	16	(35)	0.915	20	(31)	10	(50)	0.116	17	(28)	13	(52)	0.038
Diabetes	12	(31)	16	(35)	0.695	19	(29)	9	(45)	0.189	20	(33)	8	(32)	0.905
Charlson comorbidity index score, median (IQR)	0	(0–1)	0	(0–1)	0.824	0	(0–1)	1	(0–2)	0.034	0	(0-0)	1	(0–3)	<0.001
Additional or combination medication, n (%)															
Insulin	15	(38)	16	(35)	0.726	22	(34)	9	(45)	0.365	21	(35)	10	(40)	0.663
Favipiravir	13	(33)	12	(26)	0.466	11	(17)	14	(70)	<0.001	9	(15)	16	(64)	<0.001
Anticoagulant drug	9	(23)	11	(24)	0.928	17	(26)	3	(15)	0.304	13	(22)	7	(28)	0.531
Tocilizumab	7	(18)	11	(24)	0.502	16	(25)	2	(10)	0.162	18	(30)	0	0	0.002
Remdesivir	4	(10)	1	(2)	0.115	5	(8)	0	0	0.201	5	(8)	0	0	0.137
Baricitinib	1	(3)	0	0	0.275	1	(2)	0	0	0.577	1	(2)	0	0	0.516
Creatinine, median (IQR), mg/dL	1.0	(0.8–1.0)	0.9	(0.7–1.0)	0.965	0.9	(0.7–1.0)	0.9	(0.7–1.2)	0.137	0.9	(0.7–1.0)	0.9	(0.7–1.1)	0.286
Hemoglobin, mean (SD), g/dL	14.2	(2.0)	14.5	(1.9)	0.895	14.2	(1.8)	14.3	(2.3)	0.367	14.3	(19)	14.1	(2.0)	0.946
White blood cell, median (IQR), × 1000/μL	5.5	(3.5–7.1)	5.1	(4.1–7.1)	0.993	5.1	(3.9–6.9)	5.6	(3.6–7.3)	0.860	5.7	(3.7–7.1)	5.0	(4.1–7.1)	0.828
Lymphocyte, median (IQR),/μL	954	(627–1121)	875	(557–1192)	0.594	938	(621–1181)	766	(521–1039)	0.348	884	(604–1125)	888	(648–1197)	0.497
Platelets, mean (SD), × 1000/μL	178	(78)	198	(87)	0.435	187	(74)	194	(109)	0.909	190	(89)	185	(68)	0.927
CRP, median (IQR), mg/dL	7.1	(4.2–10.3)	2.8	(2.8–12.1)	0.975	6.9	(4.3–10.8)	7.1	(2.7–11.3)	0.690	7.1	(4.9–10.9)	4.8	(2.5–11.1)	0.140

Data are presented as mean (standard deviation [SD]) or median (interquartile range [IQR] 25th–75th percentile) or numbers (with percentages). Abbreviations: BMI, body mass index; CRP, *C*-reactive protein. $P < 0.05$ was considered statistically significant.

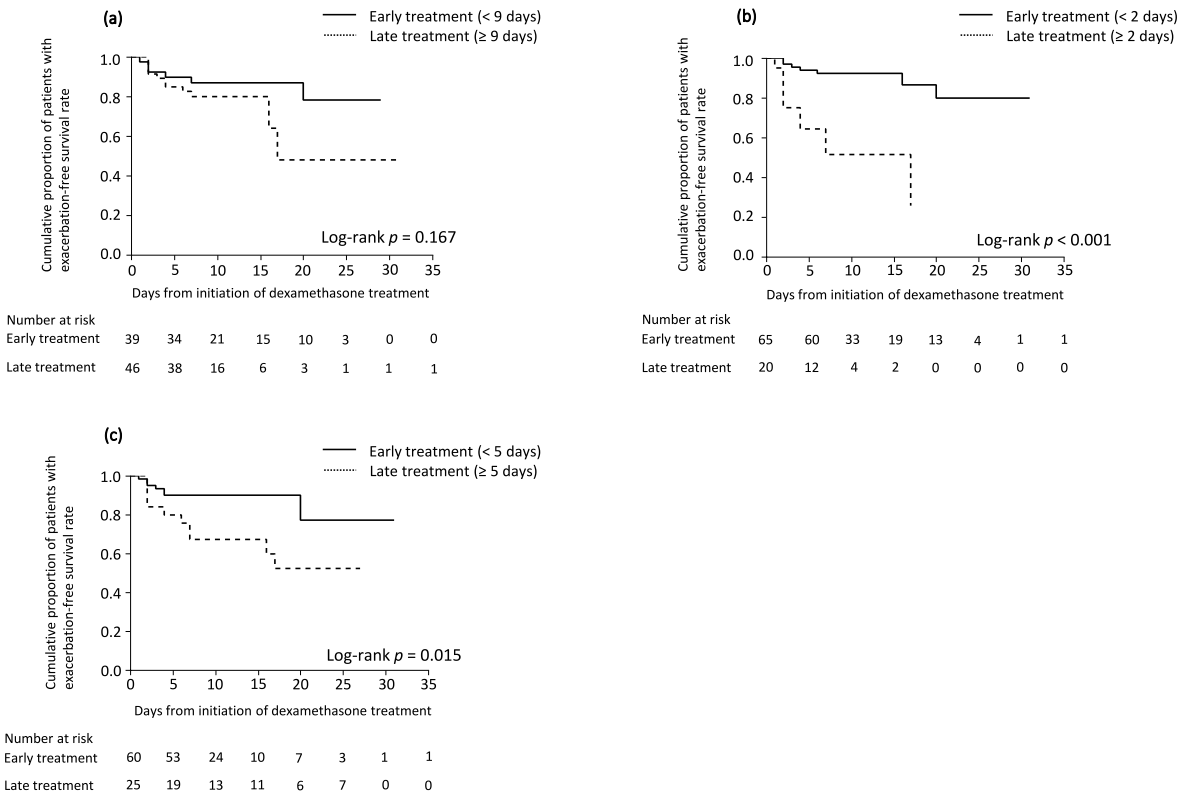

Fig. 3. The cumulative rate of death or initiation of mechanical ventilation from initiation of dexamethasone administration. The patients were divided into subgroups (early and late treatment groups) based on the optimal cut-off value calculated for the number of days from the onset of (a) symptoms, (b) oxygen supplementation, and (c) SpO_2 falling <95% until the initiation of dexamethasone administration.

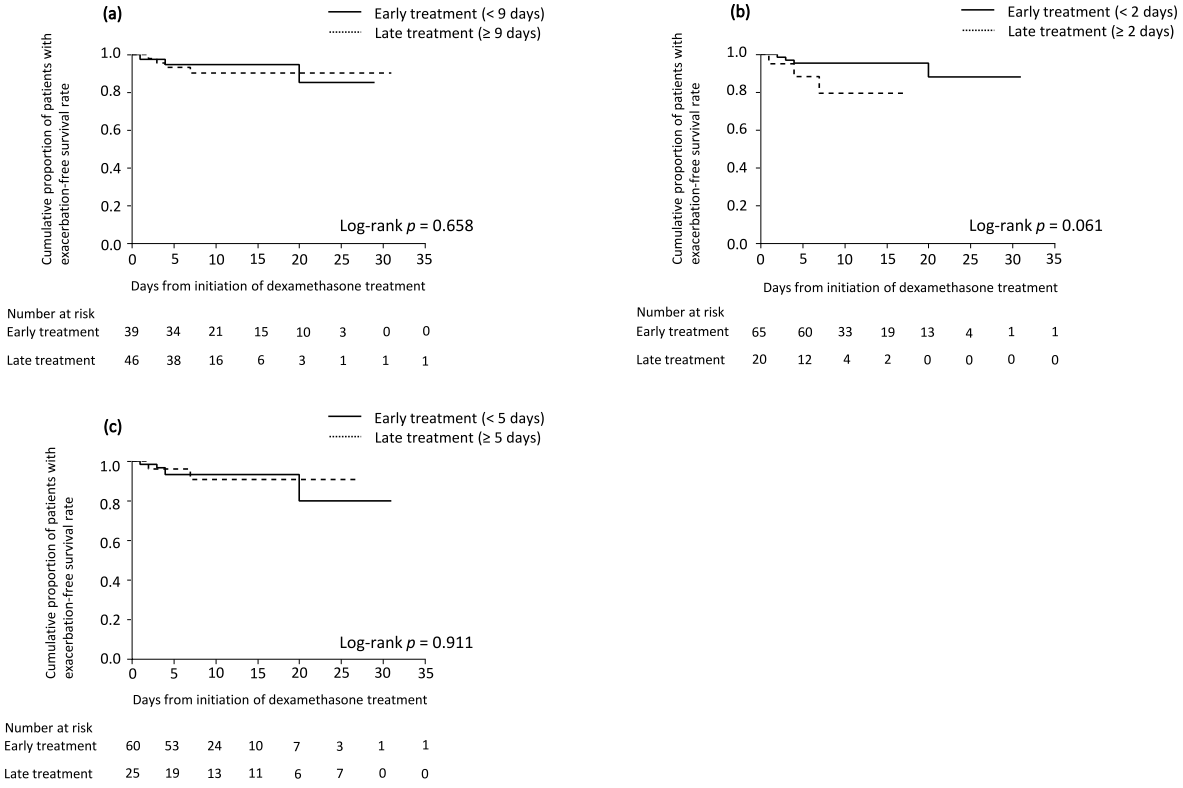

Fig. 4. The cumulative rate of death from initiation of dexamethasone administration. The patients were divided into subgroups (early and late treatment groups) based on the optimal cut-off value calculated for the number of days from the onset of (a) symptoms, (b) oxygen supplementation, and (c) SpO_2 falling <95% until the initiation of dexamethasone administration.

Table 4
COX regression analysis of factors related to clinical outcome.

	Univariate model			Multivariate model 1			Multivariate model 2			Multivariate model 3		
	HR	(95% CI)	*p* value	HR	(95% CI)	*p* value	HR	(95% CI)	*p* value	HR	(95% CI)	*p* value
Age, per 1-year increase	1.05	1.00–1.09	0.035	1.03	0.98–1.07	0.235	1.03	0.99–1.08	0.180	1.03	0.98–1.07	0.264
Sex; male	1.87	0.54–6.51	0.326	2.11	0.57–7.85	0.264	2.13	0.58–7.87	0.258	2.38	0.62–9.21	0.208
BMI; ≥ 25 kg/m^2	0.98	0.37–2.58	0.967	0.78	0.28–2.17	0.633	1.05	0.39–2.85	0.925	0.77	0.28–2.14	0.619
Charlson comorbidity index score; ≥ 1 points	2.69	0.87–8.32	0.084	1.38	0.41–4.67	0.606	2.29	0.69–7.55		1.57	0.45–5.48	0.482
Dexamethasone administration since oxygen supplementation; ≥ 2 days	7.25	2.61–20.13	<0.001	6.66	2.24–19.83	<0.001				5.51	1.79–16.91	0.002
Dexamethasone administration since oxygen saturation falling <95%; ≥5 days	3.13	1.18–8.33	0.022				3.01	1.12–8.07	0.029	2.04	0.74–5.64	0.167

$P < 0.05$ was considered statistically significant. Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index.

supplementation (≥two days) and from SpO_2 < 95% (≥five days), late administration of dexamethasone from oxygen supplementation was associated with a significantly higher risk of exacerbation (HR: 5.51; 95% CI: 1.79–16.91, p = 0.022).

4. Discussion

This study examined the association between clinical outcomes and the timing of dexamethasone initiation in patients with moderate-to-severe COVID-19 who required oxygen supplementation for hypoxemia. We revealed that the number of days from the initiation of oxygen supplementation to the initiation of dexamethasone administration is a useful indicator for the initiation of dexamethasone therapy, with an optimal cut-off value of two days. In addition, delayed administration of dexamethasone from the initiation of oxygen supplementation was a significant risk factor for poor outcomes and exacerbation in patients with moderate COVID-19.

Steroids can worsen symptoms of viral infections. The use of steroids in influenza, for example, has been reported to increase mortality [12]. In previous studies of coronavirus infections, including Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome, steroid administration was associated with worsening of prognosis, a prolonged viral shedding period, and an increased incidence of adverse events [10,11]. In the early days of the COVID-19 pandemic, the World Health Organization did not recommend the use of systemic corticosteroids for the treatment of viral pneumonia [15]. However, several studies have demonstrated the efficacy of steroid administration for COVID-19 [8,16,17].

In particular, the RECOVERY trial reported a significant reduction in 28-day mortality with the use of dexamethasone [8]. In the dexamethasone group, patients who received either invasive mechanical ventilation or oxygen supplementation showed a significant risk reduction, whereas those who were not receiving any oxygen supplementation or respiratory support showed no improvement in clinical outcomes [8]. In addition, prognosis improved when dexamethasone was administered more than eight days after onset, but not less than seven days after onset. Patients who did not require oxygen started dexamethasone earlier, whereas those who received oxygen or invasive ventilation started dexamethasone later [8]. The difference in severity of the patients may be related to the fact that dexamethasone was effective after eight days of onset.

However, whether a later administration of dexamethasone is more effective in patients who only received oxygen remains unclear. In our study, only those patients who required oxygen supplementation were studied, and we revealed that the day from symptom onset to the initiation of dexamethasone administration was not associated with prognosis, whereas the delay in dexamethasone administration from the initiation of oxygen supplementation was associated with poor outcomes and exacerbation. Thus, because disease progression varies significantly among individuals, we infer that disease progression as indicated by a decrease in oxygenation and the subsequent initiation of oxygen supplementation is a better indicator of the initiation of dexamethasone administration than the number of days from the onset of symptoms to the initiation of dexamethasone administration. The effect of dexamethasone treatment differs depending on the severity of COVID-19, and inappropriate initiation of dexamethasone administration may cause more harm than good. The appropriate timing for initiation of dexamethasone treatment is critical for its effective use.

Progression to severe COVID-19 pneumonia is characterized by local mild inflammation in the lung and systemic hyper-inflammation, including a cytokine storm [18]. Treatment for COVID-19 pneumonia mainly aims for the normal control of the lung and systemic inflammation and the early restoration of normal physiological function [19]. Therefore, antiviral treatment is recommended in the early stages of COVID-19 [20], but dexamethasone treatment may be effective during periods of active inflammation that progresses to ARDS [21]. Recent reports have shown that respiratory failure and ARDS caused by COVID-19 occurred approximately 10 days after the symptom onset [3,22]. This period is consistent with the number of days from symptom onset to the initiation of dexamethasone in our study.

In a randomized controlled trial that demonstrated the efficacy of dexamethasone in ARDS, dexamethasone was initiated within 48 h of the onset of ARDS [9]. Failure of initial control of tissue damage within 24–48 h of ARDS can result in self-perpetuating inflammation with subsequent loss of organ function, and a higher risk for mortality [23]. Our results support the findings of Lee et al. who reported that administration of dexamethasone within 24 h of the onset of hypoxemia could reduce the progression to severe disease [16]. Oxygen supplementation for hypoxemia is an indicator of the progression of ARDS, and our findings suggest that a delay of more than two days in starting dexamethasone once oxygen supplementation is initiated can result in worse clinical outcomes. Therefore, we speculate that early dexamethasone administration in patients requiring oxygen supplementation may reduce the degree of pulmonary and systemic organ damage, and may prevent progression to severe ARDS and systemic cytokine storm. We believe that these results are important for determining the timing of dexamethasone initiation for COVID-19.

Previous studies have reported that age, male sex, obesity, and underlying diseases such as hypertension are associated with the severity of COVID-19 [24–26]. Our results similarly showed that age and comorbidities (hyperlipidemia and chronic kidney disease) were significantly higher in the exacerbation group (Table S1). CCI score was also more prevalent in the exacerbation group. After adjusting for these factors, we found that a delay in dexamethasone administration was associated with worse clinical outcomes. Additionally, we showed that an index of dexamethasone administration initiation from oxygen supplementation might be more beneficial than that based on a decrease in SpO_2. Although the underlying causes remain unclear, underlying

conditions such as uncontrolled diabetes mellitus or hyperlipidemia can be involved. In our study, there was no difference between groups in the prevalence of diabetes mellitus, but the prevalence of dyslipidemia was higher in the late treatment group. Previous reports have shown that dexamethasone is associated with worsening of diabetes mellitus and hyperlipidemia [27]. Therefore, the start of dexamethasone administration may have been delayed due to concerns about worsening of these conditions.

In other study which examined dexamethasone therapy [28], the most commonly observed adverse event was an increase in blood glucose levels. In addition to the above, thrombosis and gastrointestinal disorders have also been reported [29]; thus, we need to exercise caution regarding these adverse events during dexamethasone treatment for COVID-19.

Dexamethasone administration may be effective when symptoms of hypoxemia and respiratory failure do not improve, and in such cases, early initiation of dexamethasone administration should be considered to prevent the development of severe COVID-19.

The present study has several limitations. First, this was a retrospective observational study on a small number of patients at a single institution; hence, there may have been selection bias in the study population. Second, the non-dexamethasone treatment group was not evaluated. Finally, the use of other treatments for COVID-19, such as remdesivir [30], may have affected the prognosis, and studies with a larger sample size are required.

In conclusion, our findings provide new insights into the timing of dexamethasone initiation in patients with COVID-19 who require oxygen. The onset and progression of respiratory failure in these patients varies among individuals. In patients who are already poorly oxygenated in the early course of COVID-19, a combination of antiviral and steroid medications should be considered. In particular, early dexamethasone treatment less than two days of the initiation of oxygen supplementation would be effective in patients with COVID-19 and hypoxia.

Authorship statement

Contributors: YI, TI, and SF were responsible for the organization and coordination of the trial. YI and TI were responsible for the data analysis. MF was the chief investigator. All authors contributed to the writing of the final manuscript and contributed to the management or administration of the trial.

Conflicts of interest disclosure

There are no conflicts of interest to be disclosed in this original research.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

We thank the Department of Infection Control and Laboratory Medicine and all colleagues at our institution for their contribution to the medical care of the patients at Sapporo Medical University Hospital.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2022.03.007.

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