Title: The effect of the timing of dexamethasone administration in patients with COVID-19 pneumonia

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Abstract

Background: Despite the proven benefits of dexamethasone in hospitalized COVID-19 patients, the optimum time for the administration of dexamethasone is unknown. We investigated the progression of COVID-19 pneumonia based on the timing of dexamethasone administration.

Methods: A single-center, retrospective cohort study based on medical record reviews was conducted between June 10 and September 21, 2020. We compared the risk of severe COVID-19, defined as the use of a high-flow nasal cannula or a mechanical ventilator, between groups that received dexamethasone either within 24 hours of hypoxemia (early dexamethasone group) or 24 hours after hypoxemia (late dexamethasone group). Hypoxemia was defined as room-air SpO2 <90%.

Results: Among 59 patients treated with dexamethasone for COVID-19 pneumonia, 30 were in the early dexamethasone group and 29 were in the late dexamethasone group. There was no significant difference in baseline characteristics, the time interval from symptom onset to diagnosis or hospitalization, or the use of antiviral or antibacterial agents between the two groups. The early dexamethasone group showed a significantly lower rate of severe COVID-19 compared to the control group (75.9% vs 40.0%, P-value=0.012). Further, the early dexamethasone group showed a significantly shorter total duration of oxygen supplementation (10.45 d vs. 21.61 d, P-value=0.003) and length of stay in the hospital (19.76 d vs. 27.21 d, P-value=0.013). However, extracorporeal membrane oxygenation and in-hospital mortality rates were not significantly different between the two groups.
Conclusion: Early administration of dexamethasone may prevent the progression of COVID-19 to a severe disease, without increased mortality.

Keywords (MESH terms)
- Coronavirus disease 2019 (COVID-19)
- Pneumonia
- Inhalation Therapy, Oxygen
- Dexamethasone
- Respiratory Failure

Abbreviation list
- ARDS, acute respiratory distress syndrome
- BMI, body mass index
- CCI, Charlson comorbidity index
- CIs, confidence intervals
- COVID-19, coronavirus disease 2019
- CT, computed tomography
- ECMO, extracorporeal membrane oxygenation
- HFNC, high flow nasal cannula
- HRs, hazard ratios
- IQR, interquartile range
- ORs, odds ratios
- qRT-PCR, real-time reverse transcription-polymerase chain reaction
- RCTs, randomized controlled trials
- RR, rate ratio
- SAPS, simplified acute physiology score
- SOFA, sequential organ failure assessment
- SpO2, pulse oximeter oxygen saturation
Introduction

Systemic administration of corticosteroids has been associated with decreased in-hospital mortality in coronavirus disease 2019 (COVID-19) patients with hypoxemia \(^1\). Among systemic corticosteroids, dexamethasone has been demonstrated to improve mortality in COVID-19 patients in two randomized controlled trials (RCTs) \(^2,3\), but the benefit of hydrocortisone or methylprednisolone is not as clear \(^1,4,5\). However, 36.2% (166/459) of patients who used dexamethasone eventually died \(^1\), suggesting that dexamethasone should be used in a timely manner only in selective patients \(^6\). Nevertheless, there is little information concerning the prognosis for COVID-19 patients that relates to different times of dexamethasone administration.

The efficacy of dexamethasone in protecting against acute respiratory distress syndrome (ARDS) is likely to be related to the time of initial drug administration. A recent RCT showed that dexamethasone administration within 30 hours of ARDS onset decreased the duration of mechanical ventilation and mortality rates \(^7\). COVID-19 studies also showed a potential benefit of early dexamethasone treatment in improving the prognosis in patients with acute respiratory failure. In the CoDEX trial, dexamethasone administration within 48 hours of the onset of ARDS significantly increased ventilator-free days in the COVID-19 patients \(^3\). A quasi-experimental study of moderate-to-severe COVID-19 cases found that systemic corticosteroid administered from the first day of oxygen supplementation reduced a composite of primary outcomes, including intensive care unit (ICU) care, progression to respiratory failure, and in-hospital mortality \(^8\). In addition, there was a positive correlation between early corticosteroid treatment and a better clinical prognosis in severe acute respiratory syndrome \(^9\).
The timing of dexamethasone administration is of special concern in those COVID-19 patients who need only oxygen therapy. This study determined whether there is a difference in the rate of ARDS progression, based on the time of dexamethasone administration, in COVID-19 patients who needed only oxygen therapy without either high-flow nasal cannula therapy or a mechanical ventilator.
Materials and Methods

Our study was reported in accordance with the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. 1

Study design and participants

The present retrospective cohort study included all the hospitalized patients who received dexamethasone for COVID-19 pneumonia at Seoul Metropolitan Government-Seoul National University Boramae Medical Center (SMG-SNU BMC), Seoul, between June 10 and September 21, 2020. A diagnosis of COVID-19 was confirmed through quantitative reverse transcription-polymerase chain reaction (RT-qPCR) assays using upper or lower respiratory tract samples.

Patients were admitted to the isolation ward for COVID-19 management, which has negative pressure ventilation. Dexamethasone was administered to the COVID-19 patients who required oxygen therapy or had a significant desaturation (a change in pulse oximeter oxygen saturation [SpO2] >4%) with clinical signs of aggravated pneumonia. The time of dexamethasone administration was determined by the attending physician. Oxygen supplementation was initiated when patients had a room-air SpO2 <90%, which is defined as hypoxemia. Oxygen saturation was monitored through pulse oximetry for 24 hours during oxygen supplementation. Administration of remdesivir was allowed in the patients who met all of the following criteria: 1) pneumatic infiltration was evident in a chest X-ray or chest computed tomography scan, 2) room-air SpO2 <94%, 3) oxygen supplementation, and 4) ≤10
days since symptom onset. In practice, remdesivir was administered only to patients over 70 years of age because of the limited supply of remdesivir during the study period. Administration of antibiotics for respiratory infections was also allowed when a bacterial infection had not been ruled out.

Eligibility criteria

The eligibility criteria were: 1) age >18 years old, 2) detection of SARS-CoV-2 by an RT-qPCR assay of upper or lower respiratory sample, 3) evidence of pneumonia in a chest X-ray or chest computed tomography scan (CT), and 4) administration of dexamethasone before initiation of high-flow nasal cannula (HFNC) treatment or a mechanical ventilator (MV). Exclusion criteria were immunosuppressive diseases, treatment with a systemic corticosteroid or other immunosuppressive drugs, pregnancy, terminal-stage cancer, or other end-stage diseases.

Variables and measurements

Demographic information for the study population was collected, including age, sex, body mass index, smoking status, Charlson comorbidity index (CCI), and underlying diseases (hypertension, diabetes, cerebrovascular disease, cardiovascular disease, chronic lung disease, chronic kidney disease, chronic liver disease, and cancer). Symptoms of COVID-19 were determined by medical staff when dexamethasone treatment was initiated, including abnormal senses of smell or taste, myalgia, sore throat, cough, sputum, chest discomfort,
dyspnea, fever or chills, rhinorrhea, and nausea or diarrhea. Ct-values of RT-qPCR at first
diagnosis were obtained. Clinical severity was evaluated using the sequential organ failure
assessment (SOFA) score and the simplified acute physiology score (SAPS) II, SpO₂, and
PaO₂/FiO₂ ratio at hypoxemia development. Laboratory tests included assays for white blood
cells, lymphocytes, C-reactive protein, procalcitonin, lactate dehydrogenase, troponin-I, and
D-dimer. Treatment information included the use of antiviral or antibacterial agents, total
dose of dexamethasone, duration of dexamethasone treatment, the time interval from
symptom onset or diagnosis to initiation of dexamethasone administration, and the time
interval from hypoxemia to dexamethasone administration.

Study groups and outcomes

We defined the initiation time of dexamethasone treatment as the time interval from
occurrence of hypoxemia to initiation of dexamethasone treatment. The distribution of the
initiation time of dexamethasone was largely divided into two groups based on the criteria of
24 hours in a pilot analysis. The patients with the initiation time of dexamethasone treatment
<24 hours were defined as early dexamethasone group and those ≥24 hours were defined as
late dexamethasone group. The primary outcome was to compare the rate of HFNC or MV
treatments between early and late dexamethasone group. HFNC was used when oxygen
supplementation with nasal prong 6L/min or more was required. The secondary outcome was
to compare the total duration of oxygen supplementation and the length of stay in hospital for
the two groups.
Statistical analyses

Demographic information, symptoms, clinical features, clinical severity, and study outcomes were compared between the early and late dexamethasone groups. We conducted Shapiro-Wilk normality test for each continuous variable before statistical tests. Categorical variables were analyzed with Pearson’s chi-squared test or the Fisher’s exact test. Continuous variables were analyzed with the Student’s t-test or Mann–Whitney U test. Repeated measure analysis of variance was conducted for analysis of serial physiologic parameters (respiratory rate, heart rate, and SpO2) and laboratory results (complete blood count). Logistic regression analysis was used to determine whether the timing of dexamethasone administration correlated with HFNC or MV treatments by calculating odds ratios (ORs) and 95% confidence intervals (CIs). To exclude potential bias due to confounding factors associated with the use of HFNC or MV treatments, we conducted a multivariate analysis. Independent variables were selected on the basis of their statistical significance in the univariate analysis. The criterion for inclusion of a variable in the multivariate analysis was based on the clinical significance. The Kaplan–Meier curve was used to visualize the difference in the time to HFNC or MV treatment between the early and late dexamethasone groups, and the statistical significance was estimated by the log-rank test. Univariable and multivariable Cox regression analyses were used to evaluate hazard ratios (HRs) for prolonged time to HFNC or MV treatments. Multivariable analyses were conducted using two models. In model 1, early dexamethasone group was used as a categorical variable for multivariable analysis. In model 2, initiation time of dexamethasone treatment was used as a continuous variable for multivariable analysis. We considered P-values <0.05 as statistically significant. All the statistical analyses were conducted using R statistical software (R Core Team, version 3.5.1,
2018, Vienna, Austria).

Ethics

The Institutional Review Board Committee of Seoul National University Seoul Metropolitan Government (SNU-SMG) Boramae Medical Center approved the study protocol and waived the need for informed consent for access to the electronic medical records (IRB No. 20-2020-33).
**Results**

Among a total of 212 patients hospitalized for treatment of COVID-19, 62 (29.2%) were treated with dexamethasone. After excluding three patients who received dexamethasone after HFNC treatment, 59 (27.8%) patients were placed in two groups: an early dexamethasone group (30 patients) and a late dexamethasone group (29 patients) (Figure 1).

*Time interval from hypoxemia to dexamethasone administration was median 0 (interquartile range [IQR] = 0–0) day in early dexamethasone group and median 2 (IQR = 1–2) days in late dexamethasone group.* The time interval from symptom onset to diagnosis of COVID-19 was a median 3.0 (IQR = 0–5.0) days. The median time interval from symptom onset to hospitalization for COVID-19 was 3.0 (IQR = 1.0–6.5) days. All the patients showed evidence of pneumonic infiltration in the initial chest X-ray at admission.

**Baseline characteristics and clinical features of the study population**

In baseline characteristics, age, percentage of current smokers, and CCI were higher in the late dexamethasone group, but the values were not statistically significant (Table 1). The frequency of each symptom was not significantly different between the early and late dexamethasone groups.

In terms of clinical features, early dexamethasone group showed a higher SOFA score and SAPS II at hypoxemia development (Table 2). PaO2/FiO2 ratio was lower in the early dexamethasone group. While heart rate serially decreased, SpO2, applied oxygen flow rate, white blood cells, and platelet were increased during initial 3 days after dexamethasone
administration (Supplementary information 1). In terms of treatments, the rate of remdesivir use or antibiotic use was very similar in the early and late dexamethasone groups. The dose of dexamethasone and the duration of dexamethasone treatment were similar between the two groups. Two patients in the early dexamethasone group started dexamethasone 1.5 (±0.7) days before oxygen supplementation because they showed imminent hypoxemic respiratory failure with fever, a progression of pneumonic infiltration, and decreasing SpO2.

**Association between clinical outcomes and the time of dexamethasone administration**

Twelve (40.0%) patients in the early dexamethasone group and 22 (75.9%) patients in the late dexamethasone group required HFNC or MV treatment, which was significantly different between the two groups (P-value=0.012, Table 2). MV was applied to 7 (23.3%) patients in early dexamethasone group and 13 (44.8%) patients in late dexamethasone group (P-value=0.142). Two patients in the late dexamethasone group were given extracorporeal membrane oxygenation (ECMO) and there was no difference in ECMO use between the two groups. The early dexamethasone group showed a significantly shorter duration of oxygen supplementation (10.45 d vs. 21.61 d, P-value=0.003) and length of stay in hospital (19.76 d vs. 27.21 d, P-value=0.013). We found no difference in in-hospital deaths between the two groups, which were caused in both groups by respiratory failure.

In the Kaplan-Meir estimate, the probability of HFNC or MV treatment was significantly lower in the early dexamethasone group (log-rank test=0.002, Figure 2). Univariable Cox regression analysis revealed that the probability of HFNC or MV treatment was significantly lower over time in the early dexamethasone group (HR=0.344 [95% CI=0.169–0.698], P-
value=0.003, Table 3). However, initiation time of dexamethasone treatment was not significantly associated with the probability of HFNC or MV treatment. In the multivariable Cox regression analysis, the probability of HFNC or MV treatment was significantly lower in the early dexamethasone group (HR= 0.440 [95% CI=0.211–0.915], P-value=0.028, model 1), but not significantly related with initiation time of dexamethasone treatment (model 2).
**Discussion**

Our study identified a correlation between the administration of dexamethasone within 24 hours of oxygen supplementation (early dexamethasone) and a lower rate of HFNC or MV treatment in COVID-19 patients who required oxygen therapy or had a significant desaturation. In addition, the early dexamethasone group showed a significantly shorter total duration of oxygen supplementation and length of stay in hospital. Early dexamethasone treatment was significantly correlated with a lower rate of HFNC or MV treatment, even in multivariable Cox regression analysis. However, the probability of HFNC or MV treatment was not associated with the initiation time of dexamethasone in Cox regression analyses, which finding suggests that the risk of HFNC or MV treatment was not linearly increased as the initiation time of dexamethasone was prolonged. Although the early dexamethasone group required less HFNC or MV treatment, there was no difference in ECMO use or in-hospital mortality rates between the early and late dexamethasone groups. Therefore, early dexamethasone administration for hypoxemic COVID-19 patients may reduce the need for HFNC or MV treatment without increased mortality; thus, reducing the need for scarce medical resources in the COVID-19 pandemic.

Although we know that dexamethasone is associated with a lower mortality rate in COVID-19 patients undergoing oxygen therapy alone, information is needed about when dexamethasone treatment should be initiated to maximize the benefits. Considering the evidence to date, the administration of corticosteroids seems to be more effective for COVID-19 patients with active progression to ARDS than those with early-phase pneumonia. In the RECOVERY study, dexamethasone reduced more mortality in the invasive MV group (25.2%; rate ratio=0.64 [95% CI=0.51–0.81]), in which pneumonia was more advanced, than
the oxygen-only group (37.5%; rate ratio=0.82 [95% CI=0.72–0.94]) \(^2\). In the CoDEX study, dexamethasone benefited COVID-19 patients who used a MV after ARDS developed \(^3\). A recently published meta-analysis showed that dexamethasone benefits a subgroup of patients with symptom onset \(>7\) days \(^1\). The mechanism by which dexamethasone reduces the pulmonary and systematic inflammatory process may contribute to these results \(^12\).

The progression of COVID-19 pneumonia from mild to severe disease can be characterized by initial mild infection phase followed by pulmonary inflammation phase, and then systemic hyper-inflammation phase \(^13,14\). Down-regulation of pulmonary and systemic inflammation is considered one of the most decisive factors for restoration to normal physiology in COVID-19 pneumonia \(^15\). Therapeutic strategy for ARDS due to COVID-19 should be based on suppression of pathological inflammation by controlling macrophage activation and cytokine release \(^16\). The clinical benefits of glucocorticoid in ARDS have been explained by improved profiles of biologic markers for alveolar–capillary membrane permeability and mediators for inflammation and tissue repair \(^17\). In RCTs that proved the efficacy of dexamethasone in ARDS, dexamethasone treatment was initiated in the early phase of ARDS (within 48 hours of onset) \(^3,7\). Therefore, we can speculate that early administration of dexamethasone may attenuate the extent of lung injury or systemic organ damage and prevent progression to severe ARDS or systemic cytokine storm.

In our study, the number of patients in the early and late dexamethasone treatment groups was almost the same and two groups were distributed relatively evenly over study period, which reflects the controversy in clinical practice concerning the optimum time for dexamethasone administration. In the late dexamethasone group, it is likely that the physician did not expect the oxygen demand of the patient to increase; thus, dexamethasone would not
have been prescribed immediately. In fact, before studies on mortality reduction by
dexamethasone were published, we had COVID-19 pneumonia cases where the oxygen
demand gradually decreased without dexamethasone. However, there is still no good tool
to predict whether COVID-19 pneumonia will worsen. Serious adverse events were no
different between patients treated or not treated with dexamethasone, while the benefit of
dexamethasone was significant only in the oxygen group. In our study, dexamethasone
treatment within 24 hours of oxygen supplementation decreased the need for HFNC or MV
interventions. The mean time from symptom onset to dexamethasone treatment was about 7.4
days. Therefore, when oxygen supplementation is needed, especially after 7 days of symptom
onset, prompt administration of dexamethasone may be advantageous.

The present study has several limitations. First, it should be noted that there is a risk of
bias in generalizing our results to all the patients with COVID-19 pneumonia. This study was
a single center retrospective observational study with a small number of patients. Our study
population was highly selective by narrow range of inclusion criteria and confounding factors
were not controlled. Some differences in baseline condition may not be detected by type II
error. Second, the early dexamethasone group may have included more patients with less
severe COVID-19 pneumonia, although there was no difference in SOFA scores and SAPS II
between the early and late dexamethasone groups. The late dexamethasone group received
dexamethasone only after progression of hypoxemia, whereas in the early group
dexamethasone was administered as soon as hypoxemia occurred. Therefore, the patients
with a milder disease, who improved without dexamethasone, may not have been included in
the late dexamethasone group, but would have been included in the early dexamethasone
group. Third, our study did not include very severe cases with rapid progression to ARDS.
We excluded three patients who had severe hypoxemia at admission and needed HFNC treatment immediately, before dexamethasone was started. Although the anti-inflammatory effect of dexamethasone is likely to be most pronounced in ARDS patients with rapid progression, our results cannot be extrapolated to these patients. Fourth, the early and late dexamethasone groups had similar rates of remdesivir treatment; however, the timing of remdesivir administration was as late as that of dexamethasone in the late dexamethasone group.

In conclusion, the administration of dexamethasone within 24 hours of oxygen supplementation correlated with a lower rate of HFNC or MV treatment in patients with severe COVID-19 pneumonia. The duration of oxygen supplementation and length of hospital stay were shorter in the early dexamethasone treatment group. Early administration of dexamethasone may also be beneficial in the prevention of ARDS progression and may prevent the need for HFNC or MV treatment, without an increase in fatal events.
Conflict of interest statement
The authors declare no support from any organization for the submitted work, no financial relationship with any organization that might have an interest in the submitted work within the previous 3 years, and no other relationship or activity that could appear to have influenced the submitted work.

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References


### Tables

#### Table 1. Baseline characteristics of COVID-19 patients in early and late dexamethasone groups

<table>
<thead>
<tr>
<th></th>
<th>Late dexamethasone group (n=29)</th>
<th>Early dexamethasone group (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (±SD)</td>
<td>70.07 (13.87)</td>
<td>65.53 (14.39)</td>
<td>0.138</td>
</tr>
<tr>
<td>Female (%)</td>
<td>12 (41.4)</td>
<td>10 (33.3)</td>
<td>0.712</td>
</tr>
<tr>
<td>Body mass index, mean (±SD)</td>
<td>24.32 (4.64)</td>
<td>24.68 (4.33)</td>
<td>0.764</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>5 (17.2)</td>
<td>2 (6.7)</td>
<td>0.394</td>
</tr>
<tr>
<td>Charlson comorbidity index, mean (±SD)</td>
<td>4.34 (2.06)</td>
<td>3.50 (2.35)</td>
<td>0.147</td>
</tr>
</tbody>
</table>

#### Underlying disease

- Hypertension (%) 15 (51.7) 15 (50.0) 1.000
- Diabetes mellitus (%) 10 (34.5) 9 (30.0) 0.928
- Cerebrovascular disease (%) 4 (13.8) 5 (16.7) 1.000
- Cardiovascular disease (%) 7 (24.1) 4 (13.3) 0.465
- Chronic lung disease (%) 5 (17.2) 3 (10.0) 0.666
- Chronic kidney disease (%) 2 (6.9) 5 (16.7) 0.449
- Chronic liver disease (%) 3 (10.3) 3 (10.0) 1.000
- Cancer (%) 5 (17.2) 2 (6.7) 0.394

#### Symptoms

- Abnormality in sense of smell and taste (%) 2 (6.9) 2 (6.7) 1.000
- Myalgia (%) 12 (41.4) 10 (33.3) 0.712
- Sore throat (%) 3 (10.3) 6 (20.0) 0.503
- Cough (%) 16 (55.2) 13 (43.3) 0.516
- Sputum (%) 12 (41.4) 8 (26.7) 0.358
- Chest discomfort (%) 1 (3.4) 3 (10.0) 0.629
- Dyspnea (%) 18 (62.1) 15 (50.0) 0.502
- Febrile or chilling sense (%) 14 (48.3) 20 (66.7) 0.244
- Rhinorrhea or nasal obstruction (%) 0 (0.0) 1 (3.3) 1.000
- Gastrointestinal symptoms (%) 4 (13.8) 3 (10.0) 0.962
- No symptoms (%) 3 (10.3) 2 (6.7) 0.968

The continuous variables are expressed as the mean (±standard deviation) or the median (interquartile range) and the categorical variables are expressed as the number of patients (percentage).
**Table 2. Clinical features and outcomes of COVID-19 patients in early and late dexamethasone groups**

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Late dexamethasone group (n=29)</th>
<th>Early dexamethasone group (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ct-value of RT-PCR at first diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E gene, mean (±SD)</td>
<td>22.07 (6.32)</td>
<td>21.65 (4.92)</td>
<td>0.786</td>
</tr>
<tr>
<td>RdRP gene, mean (±SD)</td>
<td>21.80 (6.49)</td>
<td>20.36 (5.60)</td>
<td>0.382</td>
</tr>
<tr>
<td><strong>Clinical severity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA score at hypoxemia development, mean (±SD)</td>
<td>3.5 (1.8)</td>
<td>4.6 (2.2)</td>
<td>0.044</td>
</tr>
<tr>
<td>SAPS II at hypoxemia development, mean (±SD)</td>
<td>21.1 (6.2)</td>
<td>26.7 (9.7)</td>
<td>0.010</td>
</tr>
<tr>
<td>SpO₂ at hypoxemia development, mean (±SD)</td>
<td>88.9 (4.9)</td>
<td>87.0 (3.1)</td>
<td>0.081</td>
</tr>
<tr>
<td>PaO₂/FiO₂ ratio at hypoxemia development, mean (±SD)</td>
<td>296 (117)</td>
<td>202 (63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Laboratory test at hypoxemia development</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell counts, 10⁹/uL, mean (±SD)</td>
<td>5963 (3705)</td>
<td>6490 (2377)</td>
<td>0.517</td>
</tr>
<tr>
<td>The number of lymphocytes, 10⁹/uL, mean (±SD)</td>
<td>946 (376)</td>
<td>1018 (499)</td>
<td>0.533</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL, mean (±SD)</td>
<td>7.50 (6.34)</td>
<td>9.59 (6.50)</td>
<td>0.217</td>
</tr>
<tr>
<td>Procalcitonin ng/ml, median (IQR)</td>
<td>0.05 (0.04–0.08)</td>
<td>0.09 (0.05–0.21)</td>
<td>0.181</td>
</tr>
<tr>
<td>Lactate dehydrogenase IU/L, mean (±SD)</td>
<td>293 (220–376)</td>
<td>367 (303–450)</td>
<td>0.111</td>
</tr>
<tr>
<td>Troponin-I ng/ml, median (IQR)</td>
<td>9.1 (4.2–13.8)</td>
<td>10.2 (5.2–19.2)</td>
<td>0.124</td>
</tr>
<tr>
<td>D-dimer, mg/L, median (IQR)</td>
<td>0.8 (0.5–2.1)</td>
<td>0.8 (0.6–1.6)</td>
<td>0.640</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remdesivir (%)</td>
<td>13 (44.8)</td>
<td>12 (40.0)</td>
<td>0.911</td>
</tr>
<tr>
<td>Antibiotics (%)</td>
<td>29 (100.0)</td>
<td>30 (100.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Total accumulative dose of dexamethasone mg, mean (±SD)</td>
<td>62.62 (33.34)</td>
<td>64.17 (32.48)</td>
<td>0.857</td>
</tr>
<tr>
<td>Total duration of dexamethasone mg, mean</td>
<td>10.66 (5.58)</td>
<td>10.57 (4.48)</td>
<td>0.947</td>
</tr>
<tr>
<td>Time interval from symptom onset to dexamethasone administration d, mean (±SD)</td>
<td>7.76 (3.59)</td>
<td>7.03 (3.50)</td>
<td>0.435</td>
</tr>
<tr>
<td>Time interval from diagnosis to dexamethasone administration d, mean (±SD)</td>
<td>4.14 (3.26)</td>
<td>4.70 (3.67)</td>
<td>0.537</td>
</tr>
<tr>
<td>Time interval from hypoxemia to dexamethasone administration d, median (IQR)</td>
<td>2 (1-2)</td>
<td>0 (0-0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Clinical outcomes**

| High flow nasal cannula or mechanical ventilation (%) | 22 (75.9) | 12 (40.0) | 0.012 |
| Extracorporeal membrane oxygenation (%) | 2 (6.9) | 0 (0.0) | 0.457 |
| Total duration of oxygen supplementation a, d, mean (±SD) | 21.61 (16.42) | 10.45 (9.39) | 0.003 |
| Length of stay in hospital b, d, mean (±SD) | 27.21 (13.28) | 19.76 (8.05) | 0.013 |
| In-hospital death (%) | 1 (3.4) | 1 (3.3) | 1.000 |

* Oxygen supplementation includes oxygen inhalation through nasal prong, facial mask, high flow nasal cannula, mechanical ventilator, and extracorporeal membrane oxygenation.

* Data regarding total duration of oxygen supplementation and length of stay in hospital were missing for 1 patient in early dexamethasone group and 1 patient in late dexamethasone group.

The continuous variables are expressed as the mean (±standard deviation) or the median (interquartile range) and the categorical variables are expressed as the number of patients (percentage).

IQR, interquartile range; SAPS, simplified acute physiology score; SD, standard deviation; SOFA, sequential organ failure assessment.
Table 3. Cox regression analyses to evaluate the probability for high flow nasal cannula or mechanical ventilation according to time point of dexamethasone administration

<table>
<thead>
<tr>
<th></th>
<th>Univariable analysis</th>
<th>Multivariable analysis (model 1)</th>
<th>Multivariable analysis (model 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>P-Value</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>1.020</td>
<td>0.996–1.045</td>
<td>0.101</td>
</tr>
<tr>
<td>Female</td>
<td>0.655</td>
<td>0.319–1.344</td>
<td>0.249</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2.448</td>
<td>1.009–5.944</td>
<td>0.048</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>1.147</td>
<td>0.977–1.347</td>
<td>0.095</td>
</tr>
<tr>
<td>SOFA score</td>
<td>1.245</td>
<td>1.101–1.409</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAPS II</td>
<td>1.089</td>
<td>1.049–1.131</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The number of lymphocytes at</td>
<td>0.999</td>
<td>0.998–1.000</td>
<td>0.036</td>
</tr>
<tr>
<td>development of hypoxemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rendesivir</td>
<td>2.358</td>
<td>1.184–4.695</td>
<td>0.015</td>
</tr>
<tr>
<td>Early dexamethasone</td>
<td>0.344</td>
<td>0.169–0.698</td>
<td>0.003</td>
</tr>
<tr>
<td>Initiation time of</td>
<td>1.139</td>
<td>0.902–1.439</td>
<td>0.275</td>
</tr>
<tr>
<td>dexamethasone treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The data are expressed as the odds ratio and 95% confidence interval.
In model 1, early dexamethasone (initiation time of dexamethasone treatment within 24 hours) was used as a categorical variable for multivariable analysis.
In model 2, initiation time of dexamethasone treatment was used as a continuous variable for multivariable analysis.
multivariable dox regression analysis was adjusted by covariates including SOFA score and SAPS II.
Age and SAPS II are not included in multivariable analysis due to multicollinearity (variance inflation factor >4).
CI, confidence interval; HR, hazard ratio; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment
Figure legends

Figure 1. Flow chart of patient inclusion

PCR, polymerase chain reaction; COVID-19, coronavirus disease 2019

Figure 2. Kaplan–Meier curve for probability of HFNC or MV treatment for 2 weeks after the initiation of dexamethasone administration

HFNC, high-flow nasal cannula; MV, mechanical ventilator
Time point of dexamethasone administration

- Early dexamethasone
- Late dexamethasone

Log-rank test; p-value = 0.002

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Early dexamethasone</th>
<th>Late dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone start</td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>0</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Supplementary information legends

Supplementary information 1. Serial change of physiologic parameters from the time when hypoxemia occurred (day 0) to day 3.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>D0</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate, per minute, median (IQR)</td>
<td>20 (18–22)</td>
<td>20 (18–22)</td>
<td>20 (18–22)</td>
<td>20 (18–22)</td>
<td>0.645</td>
</tr>
<tr>
<td>Heart rate, per minute, median (IQR)</td>
<td>89 (76–98)</td>
<td>85 (78.5–95.5)</td>
<td>82 (71.5–90)</td>
<td>76 (67–87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SpO₂, %, median (IQR)</td>
<td>88 (87–90)</td>
<td>95 (93–96)</td>
<td>94 (92–96)</td>
<td>95 (93–96)</td>
<td>0.011</td>
</tr>
<tr>
<td>O₂, L/min, median (IQR)</td>
<td>2 (2–3)</td>
<td>3 (2–4)</td>
<td>3 (2–6)</td>
<td>3 (1–4)</td>
<td>0.011</td>
</tr>
<tr>
<td>WBC, 10³/uL, median (IQR)</td>
<td>5440 (3910–7516)</td>
<td>5920 (4325–7735)</td>
<td>6440 (5385–8928)</td>
<td>7460 (5350–10070)</td>
<td>0.004</td>
</tr>
<tr>
<td>Hemoglobin, g/dL, median (IQR)</td>
<td>12.9 (12.0–14.2)</td>
<td>13.0 (11.9–14.0)</td>
<td>13.1 (11.5–13.9)</td>
<td>12.8 (11.8–14.1)</td>
<td>0.958</td>
</tr>
<tr>
<td>Platelet, 10³/uL, median (IQR)</td>
<td>171 (137–221)</td>
<td>195 (143–251)</td>
<td>217 (176–274)</td>
<td>243 (172–307)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

P-value was calculated by repeated measure analysis of variance.

IQR = interquartile range