

# Clinical Efficacy of Corticosteroids in the Early Stages of Deterioration in COVID-19 Pneumonia

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**Background:** The World Health Organization (WHO) strongly suggests using corticosteroids in patients with severe coronavirus disease 2019 (COVID-19). Similarly, a large randomized controlled clinical trial (RCT) in the UK found that dexamethasone effectively reduced the mortality rate in severe COVID-19 patients. However, the safety profile of corticosteroids has been a controversial area of study.

**Case Description:** A case of a COVID-19 patient is described and the clinical characteristics are observed as the mildly symptomatic patient progresses into a critically ill patient and during their dramatic improvement with corticosteroid therapy in the early stage of the deterioration process with COVID-19 pneumonia.

**Conclusion:** The most suitable timing and dosage for the use of corticosteroids to maximize its effect during the worsening of COVID-19 pneumonia are discussed. One of the main pathophysiological hypotheses for severe COVID-19 patients is related to cytokine storm and virus load, which can be effectively treated with corticosteroid therapy.

**Keywords:** COVID-19 pneumonia, cytokine storm, corticosteroids, clinical characteristics

## Introduction

Coronavirus disease 2019 (COVID-19) is an infectious viral disease caused by a newly discovered coronavirus, namely severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).<sup>1</sup> COVID-19 is highly infectious and can lead to fatal comorbidities, specifically acute respiratory distress syndrome (ARDS). It has been noted that the elevation of various proinflammatory cytokines is present in a proportion of patients infected with SARS-CoV-2, suggesting the possible existence of a cytokine storm.<sup>2</sup> In addition, patients requiring intensive care unit (ICU) admission showed higher concentrations of particular cytokines compared with those not requiring ICU admission, indicating that the levels of proinflammatory cytokines are associated with disease severity.<sup>3,4</sup> Therefore, it is essential to develop an effective treatment strategy to control the spread of the virus and prevent the development of a cytokine storm. Corticosteroids can be used to suppress the cytokine storm and have been used in some patients.<sup>5-8</sup> In the recent RECOVERY trial, the effectiveness of dexamethasone was evaluated, and reduced 28-day mortality in patients requiring oxygen therapy or mechanical ventilation was shown.<sup>9</sup> On the other hand, corticosteroids did not provide a survival benefit for patients with Middle East respiratory syndrome and ARDS,<sup>10</sup> rather, they prolonged virus clearance time. Nevertheless, based on a moderate certainty of evidence, systemic corticosteroid usage is strongly recommended over not using them to treat patients with severe and critical COVID-19.<sup>11</sup> In another study, low-dose (not high) corticosteroids

reduced mortality in people with ARDS,<sup>12</sup> suggesting that dosage may be an important covariate in data analyses. As a result, questions related to the timing and dosage of corticosteroids administration are discussed.

## Case Description

On February 8, 2020, a 52-year-old Chinese woman reported fever and coughing symptoms for three days. This female patient had an eight-year history of hypertension and coronary heart disease. Her daily medication included one 30 mg nifedipine extended-release tablet and one 100 mg Bayaspirin tablet, both taken orally. She denied a history of recent travel. However, she was in close contact with her son, who had been infected with COVID-19 five days previously. She was immediately isolated in an airborne infection isolation room, as her throat swab tested positive for SARS-CoV-2 on a real-time reverse transcriptase-polymerase chain reaction test.

Clinically, the body temperature, oxygen saturation (SaO<sub>2</sub>) on room air, and respiratory rate of the patient were 38.6°C, 91%, and 20 breaths/min, respectively. On examination, her lungs were clear on auscultation. Laboratory investigations revealed a white blood cell count of  $5.3 \times 10^9/L$ , a lymphocyte count of  $1.12 \times 10^9/L$ , a hemoglobin level of 12.6 g/dL, and a platelet count of  $153 \times 10^9/L$ . C-reactive protein was elevated, at 75.6 mg/L (normal value  $\leq 7.5$  mg/L), and procalcitonin was  $<0.1$  ng/mL (normal value  $\leq 0.5$  ng/mL).

On admission, blood glucose was 11.28 mmol/L, and urinalysis showed glycosuria +++ and ketone bodies  $\pm$ , demonstrating abnormalities from the normal range. Her serum lactate, liver function, and renal function tests were normal. However, computed tomography (CT) of her chest showed subtle ground-glass opacities or consolidation in both lungs without pleural effusion (Figure 1: A1–A2). The patient was treated with lopinavir/ritonavir, inhaled aerosolized recombinant human interferon, and traditional Chinese medicine.

Within 48 hours of presentation, the patient experienced increasing difficulty breathing, with severe dry cough. Examination showed a body temperature of 38.1°C, respiratory rate of 34 breaths/min, and SaO<sub>2</sub> of 86% on 5L/min oxygen by face mask.

A repeat chest CT showed the rapid development of bilateral diffuse ground-glass opacities or consolidation (Figure 1: B1–B2). Considering the possibility of a cytokine storm, methylprednisolone 40 mg/day was administered intravenously for five days. The patient

received high-flow-oxygen therapy (flow rate of 60 L/min, oxygen concentration 65%) and maintained SaO<sub>2</sub> at 88%. Bedside ultrasonography revealed a left ventricular ejection fraction of 50% and ventricular wall motion normality. Kerley B lines appeared on both of the dorsal lungs. In response, 20 mg of furosemide was given intravenously. Meanwhile, the patient's activity level was reduced, and an indwelling urinary catheter was sited. After 60 hours of treatment, the patient's blood pressure was 78/50 mmHg, and she was sweating profusely. A 250 mL bolus of 0.9% saline was infused rapidly (over 10 min) without significant improvement. The vasoactive drug dopamine was then given to maintain blood pressure at approximately 95/60 mmHg. When the oxygen concentration was decreased to about 70%, the patient's SaO<sub>2</sub> fluctuated between 96% and 99%. Blood levels of troponin, amino-terminal pro-brain natriuretic peptide, and D-dimer were all normal. The oxygenation index was 122 mmHg. Thus, she was intubated and initiated on mechanical ventilation.

Despite deep sedation, significant ventilator dyssynchrony was initiated to maintain the lung's protective ventilation. The patient was supported with volume-controlled ventilation: tidal volume 350 mL, FiO<sub>2</sub> 0.8, PEEP 10 cmH<sub>2</sub>O, and a respiratory rate of 20 breaths/min with a platform pressure of 20 cmH<sub>2</sub>O. Arterial blood gas analysis showed a pH of 7.43, a CO<sub>2</sub> partial pressure of 38.8 mmHg, and an O<sub>2</sub> partial pressure of 158 mmHg. The value of FiO<sub>2</sub> was adjusted to 0.55, and she did not require prone ventilation.

After five days of mechanical ventilation, normothermia, and oxygenation, the appearance of the ground glass opacities on the chest X-ray improved, the results of all bacterial cultures were negative, and she was successfully extubated.

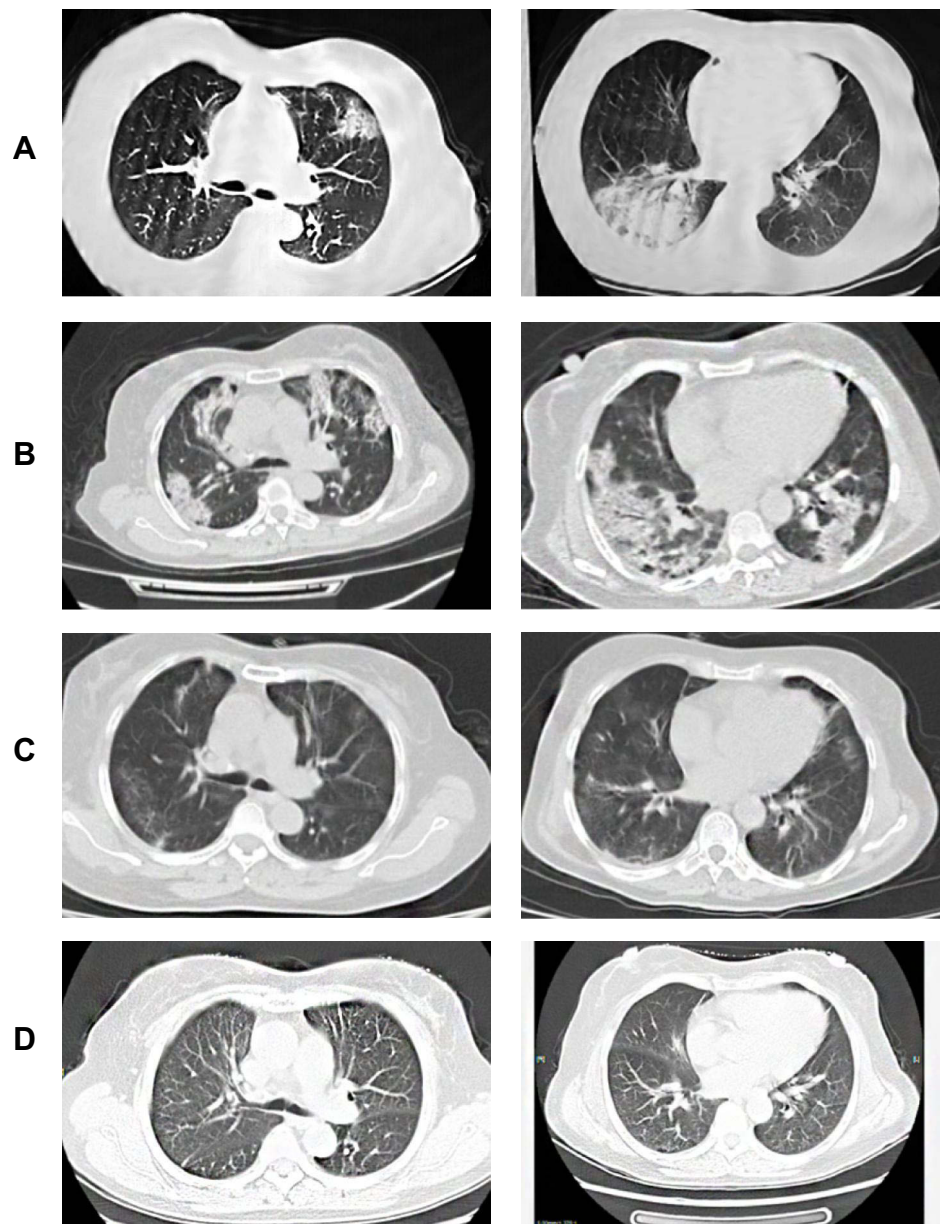
On the 15<sup>th</sup> day of admission, a pharyngeal swab for COVID-19 was negative (Table 1).

On follow-up after discharge, the patient had no complications, and chest CT appearances continued to improve at one, three, and six months (Figure 1).

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Petroleum Clinical Medical College of Hebei Medical University. The consent from the patient for the publication of the case was obtained.

## Discussion

According to the data analysis by the World Health Organization (WHO), China had approximately 17,000



**Figure 1** Chest CT images of a 52-year-old woman with COVID-19 pneumonia. Chest CT images (**A1** and **A2**) show patchy ground glass opacities with alveolar consolidation in dependent segments of both lungs with an asymmetric distribution. Three days later, CT images (**B1** and **B2**) revealed a marked increase in lesions. CT images (**C1** and **C2**) on day eight, after five days of corticosteroid use, showed a significant decrease in lesions. CT images (**D1** and **D2**), after six months of follow-up, are normal.

COVID-19 patients when SARS-CoV-2 was first identified. Among those patients, 80% had mild disease, 15% had severe disease, and 3% were critically ill. Overall, the mortality rate was 2%. However, 50% of the mortality was associated with critically ill patients.<sup>1,5,8</sup> Thus, we intended to pay more attention to the characteristics and intervention of patients during the transition process where mildly infected patients become severely infected patients. In our patient, we described the clinical course of COVID-

19 infection that rapidly developed into ARDS requiring intubation. This case highlights that at-risk patients can be promptly identified and closely monitored.

### Theories of “Viral Load,” “Cytokine Storm,” and Clinical Manifestations

According to Zhou’s paper in *The Lancet*,<sup>7</sup> inflammation and the immune response are the main mechanisms that result in viruses getting “killed.” The inflammatory

**Table 1** Clinical Course of Patient on Admission

Day of illness	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Day of hospitalization	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Temperature (°C)	37.0	38.6	39.0	36.8	37	36.8	37.0	36.5	36.0	36.4	36.0	36.4	36.4	36.5
Neutrophil count (10 <sup>9</sup> /L)	3.96			6.40	5.74	6.48	4.74	5.74		12.0	8.35	7.88	6.53	
Lymphocyte count (10 <sup>9</sup> /L)	1.12			0.59	0.71	0.48	0.59	0.94		1.13	0.55	1.12	1.10	
Glutamic oxalacetic transaminase (U/L)	21			29		22		36		38	42		41	44
Albumin (g/L)	40.7			35		33.1		35.9		34.4	32.7		32.1	32.5
Fasting plasma glucose (mmol/L)	11.28			20.19		15.46		8.45		9.8	14.2		10.6	10.7
C-reactive protein (mg/L)	75.60					25.1				5	6.4		8.30	5
Creatinine (μmol/L)	41.6			60.3		63.3		38		36.9	32.2		31.3	33.4
Procalcitonin (μg/L)	0.1			0.16		0.19		0.15		0.10	0.10		0.10	0.13
Lactate dehydrogenase (U/L)	357			410		408		364		363	337		305	
NT-proBNP (pg/ml)				303.4		218.8							122.9	
D-dimer (ng/ml)				0.3		10	10		4.2	3.5	3.9			2.7
Oxygen supplementation	2L	5L	65%	80%	100%	60%	50%	45%	40%	40%	32%	32%	32%	32%
Mode of ventilation			High flow 60 L/min		Volume control		Pressure support		High flow 45 L/min		High flow 35 L/min			
Tide volume (ml)					450	450								

Pressure support (cmH2O)					20	15	12						
Plateau pressure (cmH2O)		23		20									
PEEP (cmH2O)		10		10	10	8	5						
Pao2/Fio2 ratio	189	132	96	104	208	337	462	252	331	531			
Propofol (mg/hour)				30	30	40	10						
Midazololun (ml/h)				4	3	6	3						
Morphine (mg/h)				3	2								
Fentanyl (ug/kg/h)						0.32	0.24						
Glasgow Coma Scale				Paralyzed	E2VTM4	E4VTM6		E4VTM6		E4V5M6			
SARS CoV-2 RT-PCR (throat swab)				Eyes open and motor withdrawal in response	Eyes open spontaneously obeys commands for movement	Eyes open spontaneously obeys commands for movement				Eyes open spontaneously Orients and obeys commands for movement			
Antimicrobial therapy	Positive									Negative			
Methylprednisolone (mg/d)	lopinavir/ritonavir			Arbidol	Arbidol	Arbidol				Arbidol			
24 hours fluid balance (ml)				40	40	40							
(Total input-total output)	620	-1350	-1060	1030	-182	-309	-880	-325	160	860	-60		120

**Abbreviations:** COVID-19, coronavirus disease 2019; CT, computed tomography; FIO<sub>2</sub>, fraction of inspired oxygen; PaO<sub>2</sub>, partial pressure of oxygen; PEEP, positive end -expiratory pressure; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV2, severe acute respiratory syndrome coronavirus 2.



response leads to a vicious cycle that continues to cascade and enlarges, producing a massive number of inflammatory mediators and cytokines. Cytokine storm is induced when the immune response and high viral load occur simultaneously.

Hans Bösmüller et al<sup>13</sup> analyzed the clinical process from a pathological perspective and suggested that pulmonary COVID-19 can be subdivided into four main morphological stages, including (1) an early stage (day 0–1) with edema, incipient epithelial damage, and capillaritis/endothelialitis, (2) a stage of exudative diffuse alveolar damage (DAD) (days 1–7), and (3) an organizing (1 to several weeks) and (4) fibrotic stage of DAD (weeks to months). The early disease stage of severe COVID-19 is characterized by virally induced hyperactivation of the innate immune system, leading to the formation of a cytokine storm. The occurrence of a cytokine storm interferes with type I interferon antiviral response, subsequently resulting in endothelial and vascular damages, ultimately leading to hypercoagulability and thromboembolic events.

The clinical difference between SARS and SARS-CoV-2 is that SARS-CoV-2 patients experience a milder symptom of dyspnea relative to lung CT appearances. However, hypoxemia appears more consistent with CT imaging. Findings from many published clinical cases demonstrate that as the symptoms of SARS-CoV-2 worsen, the typical CT images show bilateral pulmonary parenchymal ground-glass and consolidative pulmonary opacities, sometimes with a rounded morphology and a peripheral lung distribution. Lung involvement with a peripheral predominance was also seen in patients with SARS-CoV and MERS-CoV infections. The chest CT showed that the disease progressed with ground-glass opacities and consolidation, which is similar to that of SARS-CoV-2 infection.<sup>14</sup>

Based on our experience, clinicians should pay attention to the following factors: a persistent fever, progressive dyspnea, continuously declining oxygenation, progressively declining lymphocyte count, and rapid expansion in lung lesions, as shown on CT. Most importantly, the increase in ground-glass opacities (50% increase in 48 hours) and consolidation should be carefully observed.<sup>15</sup> Many scholars also paid attention to the ratio of neutrophils and lymphocytes, the continuous decline in CD4+ and CD8+ T cells, and the progressive increase in IL-6 and CRP. The symptoms described above, or the change in laboratory parameters and lung CT imaging, suggest

worsening of the disease, and intervention treatments should be initiated as soon as possible.

## Corticosteroids and COVID-19

The most common complication of COVID-19 is ARDS. The occurrence of ARDS in critically ill patients is as high as 67%. When encountering the complex scenario of severely ill COVID-19 patients, a variety of protocols developed in various countries favor complementary treatments; for example, antiviral, inhaled aerosolized recombinant human interferon, and low-molecular-weight heparin.<sup>16</sup> However, these treatments have had little effect.

Corticosteroid use is considered a potential treatment for ARDS due to its role in reducing hyperinflammation and fibrosis. Methylprednisolone shortened the period of invasive mechanical ventilation needed and lowered mortality in ARDS patients.<sup>17</sup> A high number of observational studies and RCT on corticosteroids for COVID-19 suggest that administration of systemic corticosteroids demonstrate beneficial effects compared with routine care or placebo. The RECOVERY trial was the first to report that the use of dexamethasone, as opposed to standard care, reduced 28-day mortality in patients requiring oxygen therapy or mechanical ventilation.<sup>18</sup>

## Appropriate Timing for the Use of Glucocorticoids in COVID-19 Patients

The pathological manifestations of COVID-19 are mostly diffuse alveolar damage and fibrous mucus exudation with severe inflammatory lesions. Thus, critical care specialists suggest that glucocorticoid treatment is necessary to reduce or prevent the occurrence of ARDS. Clinically, some doctors use a low-to-moderate dose of glucocorticoids. The dose given depends on the rapid increase of imaging sites and the expansion of consolidation scope, and progressively worsening indicators of oxygenation.<sup>9,19</sup>

A cohort study conducted in Spain (<https://doi.org/10.21203/rs.3.rs-71610/v1>) considered 48 hours of ICU admission as the critical point of glucocorticoid usage. They compared the clinical outcomes of patients treated with early corticosteroid therapy (before or within the first 48 hours of ICU admission) and patients that did not receive early corticosteroid therapy or had no corticosteroid therapy at all. Compared with the non-early corticosteroid treated group (40.6%), patients who received early corticosteroid therapy (30.3%) had significantly lower ICU mortality (HR 0.71, 95% CI 0.57–0.89) and a higher

number of ventilator-free days (mean difference 2.5 days, 95% CI 1.3–3.8).

A recent meta-analysis of 12 studies was conducted to evaluate the effectiveness and safety of corticosteroid usage. In three studies, corticosteroids were started at diagnosis/hospital admission.<sup>20–22</sup> In other studies, ICU admission or respiratory deterioration were the indications to start.<sup>23,24</sup>

In contrast with the aforementioned study, our study focused more on mildly symptomatic patients who were progressing to become critically ill patients rather than the timing of ICU admission. Thus, we recommend considering the following parameters for the optimal timing of glucocorticoid usage in treating COVID-19 pneumonia: (1) continuous fever, (2) respiratory rate >30 breaths/min, (3) severe respiratory distress, (4) arterial oxygen saturation measured by pulse oximeter (SpO<sub>2</sub>) ≤93% on room air, (5) progressive decline in lymphocyte count, and (6) rapid expansion of lung lesions on CT. Any changes in the factors described above should be considered the initial sign of a cytokine storm and prompt early intervention with glucocorticoids.

## Clinical Dosage of Glucocorticoid Used in Patients with COVID-19 Pneumonia

Reports showed that low-to-moderate doses of corticosteroids were also associated with reduced mortality in patients with viral pneumonia when the oxygenation index was lower than 300 mmHg.<sup>14</sup> The WHO recommends the dosage of systemic corticosteroid therapy as follows: once-daily regimens of dexamethasone 6 mg are equivalent to 160 mg of hydrocortisone (eg, 50 mg every 8 hours or 100 mg every 12 hours), 40 mg of prednisone, 32 mg of methylprednisolone (eg, 8 mg every 6 hours or 16 mg every 12 hours). Duration: up to 7–10 days.

In the 44 studies, very diverse corticosteroid strategies were used. If reported (n = 35), methylprednisolone was the most frequently prescribed (n = 28).<sup>20,25</sup> Prednisone (n = 5), dexamethasone (n = 5), and hydrocortisone (n = 4) were also used, some in studies that allowed multiple corticosteroid regimens (n = 9).

Based on our own experience, continuously taking 0.75 mg/kg of methylprednisolone once or twice per day for five days may improve symptoms, especially with difficulty in breathing. The use of corticosteroids in the early stages of deterioration is essential, as it reduces the innate immune response caused by the cytokine storm, causing less damage to lung tissues.<sup>19</sup>

Other treatments are also required in the management of severe COVID-19; for example, humidified oxygen with a high-flow rate and high-flow volume in the early stage of the disease, ventilation in the supine position, moderate fluid restriction, convalescent plasma containing anti-COVID-19 antibodies,<sup>26</sup> and subsequent mechanical ventilation and extracorporeal membrane oxygenation.

One limitation of our study is the lack of comparison between different types of corticosteroid treatments. Two types of corticosteroids were compared in a triple-blind RCT, namely methylprednisolone (2 mg/kg/day; intervention group) and dexamethasone (6 mg/day; control group). It was found that methylprednisolone provides better clinical status than dexamethasone on day five and day 10 of admission and demonstrates less ventilator usage. Thus, the effectiveness of the drug may alter depending on the type of corticosteroid usage.

Another limitation relates to the dosing of corticosteroid therapy. Our study discussed the optimal dosage of corticosteroid therapy; however, the optimal dosage for each patient remains unknown. Further research should consider formulating a more detailed calculation for each patient, including the patient's weight as a factor in the dosing calculation.

In conclusion, we have examined the optimal timing and dosage of corticosteroid usage during the worsening process of COVID-19 pneumonia. Although controversy regarding corticosteroid treatment in COVID-19 still exists, many experts believe that it is reasonable to use corticosteroids for severely ill COVID-19 patients who have not yet developed ARDS. The decision on initial corticosteroid treatment should be based on the judgment of the clinical course and assessment of the treatment response.

## Consent to Publish

The consent from the patient for the publication of the case was obtained.

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## Disclosure

The authors report no conflicts of interest in this work.

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