A critical COVID-19 patient managed with timely evaluation, early prone positioning ventilation, and a multi-pronged pharmacotherapy

Mian Peng,1 Rongsong Li,2 Weiling Cao,3 Weiqing Li,4 Ming Wu,5 Yansi Lyu,6 Xi Meng7 and Kunmei Ji8

Abstract
There is not yet a standard drug regimen for the treatment of coronavirus disease 2019 (COVID-19) patients. Here, we summarize our experience and successful treatment plan with a critical COVID-19 patient who required mechanical ventilation (MV). A 56-year-old man presented with a fever, cough, and dyspnea. He had not been to a medium/high risk epidemic area in the past year and had no family history of a disease cluster. COVID-19 was suspected based on clinical symptoms and radiologically detected ground-glass lung changes in the context of a normal white blood cell count (WBCC) and lymphocyte fraction (L%). A diagnosis of COVID-19 was confirmed by nucleic acid testing. Initially, he was started on noninvasive ventilation (NIV). Because his respiratory distress worsened over the following 2 h, he was transitioned to mechanical ventilation (MV), placed in prone positioning 12 h/day, and given a multi-pronged pharmacotherapy regimen that included an antiviral cocktail (lopinavir/ritonavir plus α-interferon), an immunity enhancer (thymosin α1), an anti-coagulant to prevent thrombosis (heparin). He was given an antibiotic to treat an opportunistic nosocomial infection. The patient has recovered well. The regimen applied in this case of timely evaluation, early prone positioning with MV, and a multi-pronged pharmacotherapy may be an effective strategy for patients with critical COVID-19, particularly with respect to preventing life-threatening worsening of the illness.

Keywords
a multi-pronged pharmacotherapy, COVID-19, critical, early prone positioning ventilation, timely evaluation

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1Department of Critical Care Medicine, The Third Affiliated Hospital of Shenzhen University, Shenzhen, China
2College of Health Science and Environmental Engineering, Shenzhen Technology University, Shenzhen, China
3Department of Pharmacy, The Third Affiliated Hospital of Shenzhen University, Shenzhen, China
4Department of Traditional Chinese Medicine, The Third Affiliated Hospital of Shenzhen University, Shenzhen, China
5Department of Critical Care Medicine, The Second People’s Hospital of Shenzhen, Shenzhen, China
6Department of Dermatology, Shenzhen University General Hospital, Shenzhen, China
7Department of Critical Care Medicine, The Third People’s Hospital of Shenzhen, Shenzhen, China
8Department of Biochemistry and Molecular Biology, Health Science Center, Shenzhen University, Shenzhen, China

Corresponding author:
Weiling Cao, Department of Pharmacy, The Third Affiliated Hospital of Shenzhen University, No. 47 Youyi Road, Luohu District, Shenzhen 518001, China.
Email: caoweiling100916@163.com
Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; formerly known as 2019 novel coronavirus) is the pathogen that causes coronavirus disease 2019 (COVID-19), which presents as a severe respiratory condition in some patients.1 Since the first infections were recognized in Wuhan (Hubei province), China, in December of 2019, SARS-CoV-2 has spread rapidly through person-to-person transmission,2 leading to a worldwide pandemic.3,4 COVID-19 morbidity and mortality has caused significant economic loss and considerable public panic. There is an urgent need for the development of effective therapeutic measures that can enable timely control of this infectious disease.

In our hospital, it has been useful to classify COVID-19 patients into four levels of severity: mild, moderate, severe, and critical. Patients are considered to have critical COVID-19 if they experience respiratory failure requiring mechanical ventilation (MV), develop septic shock, or exhibit organ failure requiring continuous monitoring and intensive care.5 Patients with critical COVID-19 have an elevated mortality risk. In a cohort of 138 consecutive hospitalized patients with confirmed COVID-19 at Zhongnan Hospital of Wuhan University in Wuhan, China from January 1 to January 28, 2020, Wand et al.6 observed an overall mortality rate of 4.3%. The key to controlling the mortality rate of COVID-19 is a reliable cure for patients whose disease becomes critical. Here, we present a critical case of COVID-19 that was managed successfully.

Case presentation

Chief complaints

A patient (56-year-old, male, 70 kg, 175 cm) came to our hospital complaining of fever, cough with a small amount of white thick sputum that started 4 days prior, and dyspnea for 1 day.

History of present illness

One day before being admitted to our hospital, February 2nd, 2020, the patient presented at Shenzhen Nanshan District People’s Hospital with dyspnea, fever, chills, cough, weakness, and poor appetite. As an emergency department patient there, his inflammatory marker blood test results were as follows: white blood cell count (WBCC) 6.5 × 10⁹/L; neutrophil count (N) (fraction (N%)), 5.36 × 10⁹/L (82.4%); leukocyte count (L) (fraction (L%)), 0.93 × 10⁹/L (14.3%); and C-reactive protein (CRP), 119.3 mg/L. He was breathing spontaneously and given a high flow nasal cannula with a 60% fraction of inspired oxygen (FiO₂). His arterial blood gas analysis results were recorded as follows: pH 7.498; PCO₂ (arterial carbon dioxide partial pressure), 30 mmHg; PaO₂ (arterial oxygen partial pressure), 71 mmHg; [HCO₃⁻](bicarbonate concentration), 21.5 mmol/L; and base excess (BE) −2 mmol/L. A SARS-CoV-2 nasopharyngeal swab nucleic acid test (Nanshan District CDC) was positive, and the patient was transferred to our institution, the Third People’s Hospital of Shenzhen, which is an COVID-19 concentrated hospital. Upon being admitted to our unit, he indicated that he had not experienced chest tightness, chest pain, or any other physical discomfort. He reported that he had not taken any drugs or visited any other clinic or hospital, and that his symptoms seemed to be getting worse.

History of past illness

The patient’s medical history included untreated hypertension for 30 years, but no other chronic or systemic diseases.

Personal and family history

Epidemiologically, the patient had not been to medium-high risk epidemic areas in the past year, had no known contact with COVID-19 patients, and did not have a family history of a disease cluster.

Physical examination upon admission

At the time of admission, on February 3rd, 2020, the patient had a low-grade fever (38°C) with a respiratory rate of 30 breaths/min, a heart rate of 84 beats/min, and a blood pressure of 124/76 mmHg. He was alert, but tachypneic with cyanosis of the mouth and lips. Crackles were heard in both lungs. No other abnormal findings were observed by physical examination.
Laboratory examinations

The patient’s inflammatory marker blood test results are reported in Table 1 (see February 3rd). Arterial blood gas testing showed a PaO₂ of 41.1 mmHg with 60% FiO₂, yielding a PaO₂/FiO₂ ratio of 68.5 mmHg. His renal and liver function test results were unremarkable.

Imaging examinations

A chest CT taken day 2 after admission showed bilateral lung changes (Figure 1).

Final Diagnosis

We diagnosed this patient with suspected COVID-19 based on the symptoms of fever and cough, a normal WBCC, a normal L%, and radiologically detected lung changes. A diagnosis of COVID-19 was confirmed with a positive SARS-CoV-2 nasopharyngeal swab nucleic acid test result. Initially, his COVID-19 was classified as severe (Table 2) because his respiratory rate was 30 breaths/min and his PaO₂/FiO₂ ratio was less than 300 mmHg. His prior diagnosis of hypertension was confirmed and he was also diagnosed with acute respiratory distress syndrome (ARDS) secondary to COVID-19.

Treatment

Upon diagnosis with severe COVID-19, the patient was admitted to our intensive care unit and placed immediately on noninvasive ventilation (NIV) (inspiratory positive airway pressure (IPAP), 12 cmH₂O; expiratory positive airway pressure (EPAP), 6 cmH₂O; FiO₂ 60%). Additionally, he was prescribed the following bundle pharmacotherapy: lopinavir/ritonavir antiviral tablets (500 mg/12 h) with α-interferon (5.0 × 10⁶ U/12 h, atomized inhalation), thymosin α1 (1.6 mg/day, subcutaneous injection), and low-molecular-weight heparin (4.0 kIU/day, subcutaneous injection).

While on NIV, the patient’s respiratory function became increasingly distressed. When his PaO₂/FiO₂ ratio declined to only 116 mmHg after 120 min on NIV, he was intubated and placed on mechanical ventilation.

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**Table 1. Case patient’s inflammatory marker data summary.**

| Marker       | February 3  | February 4  | February 5  | February 6  | February 7  | February 8  | February 9  | February 10 |
|--------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| WBCC         | 7.0         | 11.13       | 10.71       | 10.82       | 8.02        | 6.53        | 7.32        | 8.54        |
| N%           | 75.6        | 87          | 88.9        | 88.6        | 82.7        | 80.4        | 85.7        | 82.7        |
| N            | 5.29        | 9.69        | 9.52        | 9.59        | 6.63        | 5.25        | 6.27        | 7.06        |
| L%           | 19.6        | 9.8         | 7.3         | 7           | 10.7        | 12.7        | 8.7         | 8.3         |
| L            | 1.37        | 1.09        | 0.78        | 0.76        | 0.86        | 0.83        | 0.64        | 0.71        |
| Procalcitonin| 0.227       | 0.575       | 0.386       | 0.246       | 0.131       | 0.123       | 0.092       | 0.056       |
| CRP          | —*         | 133.41      | 69.31       | 36.5        | 24.44       | 14.92       | 11.37       | 6.8         |

*Although we did not obtain a CRP datum on Feb 3, the referring hospital recorded a CRP of 119.3 1 day prior.

**Figure 1.** Pretreatment (left) and posttreatment (right) chest CT.
ventilation (MV) in assisted control-volume control mode (tidal volume, 420 mL; positive end-expiratory pressure, 10 cmH\textsubscript{2}O, 20 breaths/min, FiO\textsubscript{2} 50%). The classification of his COVID-19 was adjusted from severe to critical. A chest CT scan performed shortly after intubation showed bilateral ground-glass lung changes and extensive consolidation, mostly in the right lower lung (Figure 1). After the CT scan, he was placed in a prone position for 12 h. Subsequently, we observed a gradual improvement in his PaO\textsubscript{2}/FiO\textsubscript{2} ratio, which reached 158 and 190 mmHg by 1:00 and 7:00 pm, respectively, on February 4, 2020. Subsequently, he was placed in the prone position 12 h/day for the next 4 days.

On day 2 of MV (Feb 4th), the patient produced a moderate amount of thick, white sputum. Although he did not have a fever, we observed troubling changes in his inflammatory blood markers. As shown in Table 1, his WBCC had increased by about 63% from 1 day prior, his procalcitonin levels had more than doubled, and his CRP levels had increased moderately relative to 2 days prior. Thus, we suspected a secondary bacterial infection and antibiotic (ceftriaxone, 2.0 g/day) was administered to him.

The patient was sustained on enteral feeding (1750 mL/day of 1750 kcal, 25 kcal/kg). To minimize reflux aspiration risk, the feeding solution was delivered via a nasal jejunal tube at a rate of 100 mL/h while the patient lay in a supine position and at a rate of 50 mL/h during the hours he lay in a prone position. To ensure patient safety while he was in a prone position, a nurse was dedicated to attending to him (1:1 care).

Over the next several days, we observed reductions in the patient’s sputum amount as well as in his inflammation marker levels (Table 1). By February 9th, 6 days after admission, the patient had a PaO\textsubscript{2}/FiO\textsubscript{2} ratio that remained consistently near or above 300 mmHg and a follow-up chest CT (Figure 1) showed that his previously noted bilateral lung changes had been mostly absorbed. Thus, we began to wean the patient off MV with a gradual reduction in the MV settings, sedation level, and analgesia level. The patient was extubated at 10:00 am on February 10th, and transitioned immediately to NIV (IPAP 12 cmH\textsubscript{2}O, EPAP 6 cmH\textsubscript{2}O, FiO\textsubscript{2} 40%). An arterial blood gas panel performed on a sample collected 2 h after extubation showed a PaO\textsubscript{2}/FiO\textsubscript{2} ratio of 387. The patient was able to breathe effortlessly and reported feeling well. The following day (February 11th), he was transitioned from NIV to high-flow nasal cannulae (40 L/min, FiO\textsubscript{2} 40%). Then, on February 12th, he was transferred from our intensive care unit to the common ward.

**Outcome and follow-up**

While being cared for in the common ward, the patient recovered well and met our hospital criteria for post-COVID-19 discharge: a normal body temperature for ≥3 days, significant alleviation of respiratory symptoms, majority resolution of radiological lung changes, and two consecutive negative respiratory nucleic acid tests with a sampling interval of ≥1 day. The patient was discharged on March 12th.

**Discussion**

Based on an analysis of data recorded as of February 9, 2020—at which time there were 37,287 confirmed cases of SARS-CoV-2 infection in mainland China and 302 confirmed cases outside of China (from 24 countries), with 813 deaths in mainland China—Han and colleagues reported an estimated mortality rate of 2.2%. As of yet, there

| Class  | Imaging   | Symptoms                                      |
|--------|-----------|------------------------------------------------|
| Mild   | Normal    | Mild                                           |
| Moderate | Pneumonia | Fever and/or respiratory symptoms             |
| Severe | Pneumonia | At least one of:                              |
| Critical | Pneumonia | Severe plus at least one of:                   |

- Respiratory distress, RR ≥30 breaths/min
- Resting state oxygen saturation ≤93%
- PaO\textsubscript{2}/FiO\textsubscript{2} ≤300 mmHg
- Respiratory failure requiring MV
- Septic shock
- Organ failure requiring intensive monitoring and care
is no specified gold-standard pharmacotherapy regimen for COVID-19. In the context of this highly transmissible and evolving widespread infectious disease, we offer a summary of our experience with a critical ventilated COVID-19 patient who was cured of the disease.

Early and correct diagnosis is critical for the management of COVID-19 patients. In accordance with the Guidelines for the Diagnosis and Treatment of COVID-19 by the National Health Commission,\(^5\) we diagnosed the patient in the present case with COVID-19 based on the presence of a fever and cough with a normal WBCC/L% and bilateral radiographic lung changes, followed by confirmation of COVID-19 with nucleic acid testing. Because the patient had a poor PaO\(_2\)/FiO\(_2\) ratio requiring MV, his COVID-19 classification was adjusted from severe to critical (Table 2).

Early and accurate evaluation of patients showing symptoms consistent with COVID-19 is important for enabling detection of rapid deterioration to critical COVID-19. In a study of 52 patients with critical COVID-19 treated at Jin Yin-tan hospital in Wuhan, China between late December 2019 and January 26, 2020, it was reported that patients over 65 years of age with comorbidities and ARDS were at increased risk of death from COVID-19.\(^8\) Pre-existing heart disease and lymphocytopenia have also been reported to be prognostic predictors for acute respiratory failure due to COVID-19.\(^9\)–\(^11\) In the present case, we were attentive to our patient’s 30-year history of hypertension and the reduction in his lymphocyte levels over the early days of his treatment, which indicated that he was at risk of potential rapid deterioration.

Beyond early detection, early appropriate respiratory support is critical for optimizing the outcomes of patients with COVID-19. NIV has been shown to allow half of COVID-19 patients to survive without the introduction of MV when they are admitted because of acute respiratory failure. The use of NIV, particularly in overcrowded clinical settings, may preserve resources by delaying or avoiding intubation. However, early identification of patients who do not respond well to NIV is key to preserving their chances of survival.\(^11\) Previously, we kept immunodeficient patients on NIV for multiple days in the early stages of treatment, with the aim of avoiding invasive MV. However, we found that keeping critical COVID-19 patients with significant respiratory distress and hypoxemia on NIV for extended periods of time often leads to oxygen debt, which puts them at greater risk of cellular injury, organ dysfunction, and death.\(^12\) Furthermore, long-term NIV can lead to respiratory muscle fatigue, worsening of inflammatory processes, and subsequent prolonged MV and a poor prognosis. Thus, in the context of respiratory failure and hypoxemia, we limit NIV in patients with a PaO\(_2\)/FiO\(_2\) ratio <200 mmHg to \(\leq\)2 h. If the patient’s condition does not improve within 2 h, we now transition them immediately to MV with the parameters indicated in the Case Report section.

After initiation of MV, the patient should be placed in a prone position for 12–14 h/day. It was shown previously in H1N1-infected patients with severe ARDS that starting prone-position MV early and applying it for an adequate duration improves oxygenation.\(^13\) Prone positioning is a beneficial strategy in patients with ARDS because it improves alveolar recruitment and the ventilation/perfusion ratio while reducing lung strain, resulting in improved oxygenation, reduced lung injury, and reduced mortality risk.\(^14\) In the present case, we placed our patient in a prone position for 12 h/day for 5 days at the commencement of MV, and observed steady improvement in his PaO\(_2\)/FiO\(_2\) followed by a prompt recovery and good outcome.

Pharmacologically, we administered a bundle therapy that included an antiviral cocktail (lopinavir/ritonavir plus \(\alpha\)-interferon), an immunity enhancer (thymosin \(\alpha\)1), and an anti-coagulant to prevent thrombosis (heparin). Meanwhile, close monitoring enabled us to recognize and treat a secondary bacterial infection expeditiously based on the recognition of increased sputum and inflammatory marker changes. The importance of being on guard for nosocomial infections cannot be overstated in this context given that they would prolong MV duration, which increases the likelihood of a poor outcome. Indeed, it has been reported that as many as 13.5% admitted patients acquire a nosocomial infection.\(^8\) Thus, it is important that there is adequate staffing together with excellent hand hygiene and environment management practices to limit the spread of nosocomial infections, particularly among patients requiring MV.

**Conclusion**

In conclusion, our patient responded well to the combination of timely evaluation, early invasive
MV incorporating early prone positioning, and a multi-pronged pharmacotherapy regime and had a good outcome. We recommend that this treatment plan be considered for patients with critical COVID-19.

Author contributions

MP was a major contributor in writing the manuscript. YL and XM collected information. RL, WL, and MW analyzed and interpreted the patient data. WC helped with the writing of the manuscript. KJ revised the article. All of the authors approved the final manuscript before submission.

Declaration of conflicting interests

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Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

ORCID iDs

Weiling Cao https://orcid.org/0000-0002-9077-7918
Ming Wu https://orcid.org/0000-0002-0800-5506

References

1. Jiang S, Du L and Shi Z (2020) An emerging coronavirus causing pneumonia outbreak in Wuhan, China: Calling for developing therapeutic and prophylactic strategies. Emerging Microbes & Infection 9(1): 275–277.
2. Chan JF, Yuan S, Kok KH et al. (2020) A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: A study of a family cluster. The Lancet 395(10223): 514–523.
3. Bogoch II, Watts A, Thomas-Bachli A et al. (2020) Potential for global spread of a novel coronavirus from China. Journal of Travel Medicine 27(2): taaa011.
4. Hui DS, Azhar EI, Madani TA et al. (2020) The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—the latest 2019 novel coronavirus outbreak in Wuhan, China. International Journal of Infectious Diseases 91: 264–266.
5. Lin L and Li TS (2020) Interpretation of guidelines for the diagnosis and treatment of novel coronavirus (2019-nCoV) infection by the National Health Commission (trial version 5). Zhonghua Yi Xue Za Zhi 100: E001.
6. Wang D, Hu B, Hu C et al. (2020) Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 323(11): 1061–1069.
7. Han Q, Lin Q, Jin S et al. (2020) Coronavirus 2019-nCoV: A brief perspective from the front line. Journal of Infectiology 80(4): 373–377.
8. Yang X, Yu Y, Xu J et al. (2020) Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respiratory Medicine 8(5): 475–481.
9. Guan WJ, Ni ZY, Hu Y et al. (2020) China medical treatment expert group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. New England Journal of Medicine 382(18): 1708–1720.
10. Nuñez-Gil IJJ, Fernández-Ortiz A, Eid CM et al. (2021) Underlying heart diseases and acute COVID-19 outcomes. Cardiology Journal 28(2): 202–214.
11. Bertaina M, Nuñez-Gil IJ, Franchin L et al. (2021) Non-invasive ventilation for SARS-CoV-2 acute respiratory failure: A subanalysis from the HOPE COVID-19 registry. Emergency Medicine Journal 38(5): 359–365.
12. Rivers EP, Yataco AC, Jaehne AK et al. (2015) Oxygen extraction and perfusion markers in severe sepsis and septic shock: Diagnostic, therapeutic and outcome implications. Current Opinion in Critical Care 21(5): 381–387.
13. Sahoo JN, Gurjar M, Mohanty K et al. (2019) Prone ventilation in H1N1 virus-associated severe acute respiratory distress syndrome: A case series. International Journal of Critical Illness and Injury Science 9(4): 182–186.
14. Gordon A, Rabold E, Thirumala R et al. (2019) Prone positioning in ARDS. Critical Care Nursing Quarterly 42(4): 371–375.