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.

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Letter to the Editor

Five severe COVID-19 pneumonia patients treated with triple combination therapy with lopinavir/ritonavir, hydroxychloroquine, and interferon β-1b

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide, resulting in a pandemic [1]. Since there is no proven effective treatment for severe COVID-19, combining antiviral and anti-inflammatory agents may be an alternative to improve patient outcomes [2]. Here, we report five patients with severe COVID-19 pneumonia who improved with triple combination therapy, with lopinavir/ritonavir (LPV/r), hydroxychloroquine, and interferon β-1b. Low-dose, short term corticosteroids were also used to reduce excessive inflammation. The clinical courses of the patients are summarized in Fig. 1.

Patient 1, a 64-year-old man from Daegu, the main cluster of the COVID-19 outbreak in South Korea, was diagnosed with COVID-19 on March 5. He was admitted to a local hospital for fever and mild dyspnea on March 10, and was transferred to Gyeongsang National University Changwon Hospital (GNUCH) on March 12. At that time, his body temperature was 38°C, respiratory rate was 33 breathes per minute. A chest x-ray showed bilateral reticulonodular opacities across the mid- to lower lung fields. Oxygen therapy via high flow nasal cannula (HFNC) was started. The triple antiviral combination was administered for 13 days and methylprednisolone (0.5 mg/kg/day) was prescribed during the first 4 days. Since then, his symptoms were gradually improved. He was discharged on April 11.

Patient 2 was a 68-year-old man from Daegu and was diagnosed with COVID-19 on March 7. Despite starting LPV/r after hospitalization, his symptoms worsened, and he was transferred to GNUCH on March 13. On admission, his body temperature was 36.6°C, respiratory rate was 23 breathes per minute, and SpO_2 was 95% under 5 L/minute oxygen via nasal cannula. A chest x-ray showed diffuse ground glass opacities in both lung fields. The triple antiviral combination was started immediately. As the oxygen demand continued to increase, HFNC was started and methylprednisolone (0.5 mg/kg/day) was used for 3 days from March 16. Since then, his clinical course stabilized and the oxygen supply was stopped on March 23.

Patient 3 was a 74-year-old man diagnosed with COVID-19 in Daegu on March 7 presenting with 6 days of fever, cough, and dyspnea. He was transferred to GNUCH on March 10. On admission, his temperature was 38.3°C, respiratory rate 25 breaths per minute, and oxygenation saturation 98% under 4 L/min oxygen flow via nasal cannula. A chest x-ray revealed bilateral infiltrations, and triple antiviral combination was started immediately. The antivirals were stopped sequentially as the patient's symptoms improved quickly.

Patient 4 was a 39-year-old man diagnosed with COVID-19 on March 24 after a trip to Thailand and the Philippines. He had influenza-like symptoms from March 18. He was transferred to GNUCH on March 27. On admission, his temperature was 38.3°C, respiratory rate 32 breaths per minute. The ferritin level was 2596 ng/mL and interleukin-6 575.5 pg/mL. As the diagnosis of pneumonia was made, the triple antiviral combination and levofloxacin were started. HFNC was applied and methylprednisolone (1 mg/kg/day) were started because his clinical features were consistent with moderate acute respiratory distress syndrome (ARDS). However, his oxygenation had deteriorated and mechanical ventilator care started on March 30. As his clinical course worsened and the PaO_2/FiO_2 fell to 95, the methylprednisolone was increased to 2 mg/kg/day for 3 days along with other management for ARDS. Since then, his symptoms were gradually improved. He was discharged on April 30.

Patient 5 was a 54-year-old woman from Daegu and was diagnosed with COVID-19 on March 30. She was transferred to GNUCH on March 31. Despite the triple antiviral combination, her fever continued, and the oxygen demand increased for the first week. HFNC was applied, and methylprednisolone (0.5 mg/kg/day) was administered on April 8. While maintaining triple combination treatments, her symptoms and oxygen demand gradually improved. The oxygen was stopped on April 15 and she was discharged on May 1.

The symptoms of the patients were improved on median 11 days (range, 7-15 days) after their admission. However, they were hospitalized for median 32 days (range, 16-41 days) until they met the discharge criteria, 2 consecutive negative RT-PCR results for SARS-CoV-2. Virus was detected intermittently with a high cycle threshold (Ct) value at the end of the treatment period. Further work is required on whether detection of a small amount of viral RNA after improvement of patients indicates infectivity [3]. In this case series, three patients deteriorated initially during the treatment of triple antivirals, and rapid improvements of their clinical parameters were observed after use of methylprednisolone without an increase in viral load. This finding is in line with some studies reported a mortality benefit or prevention of disease progression in corticosteroid groups [4,5]. The triple combinations were temporarily stopped in two cases (patient 4 and 5) because of increasing liver enzyme levels, and one patient (patient 4) developed a skin rash at the end of treatment. Most adverse events were not severe and the medications could be maintained with symptomatic control. In conclusion, our case series suggests that triple antiviral combination therapy is a possible option for some severe COVID-19 pneumonia cases. More well-designed studies are required to demonstrate the efficacy and safety of this combination therapy.

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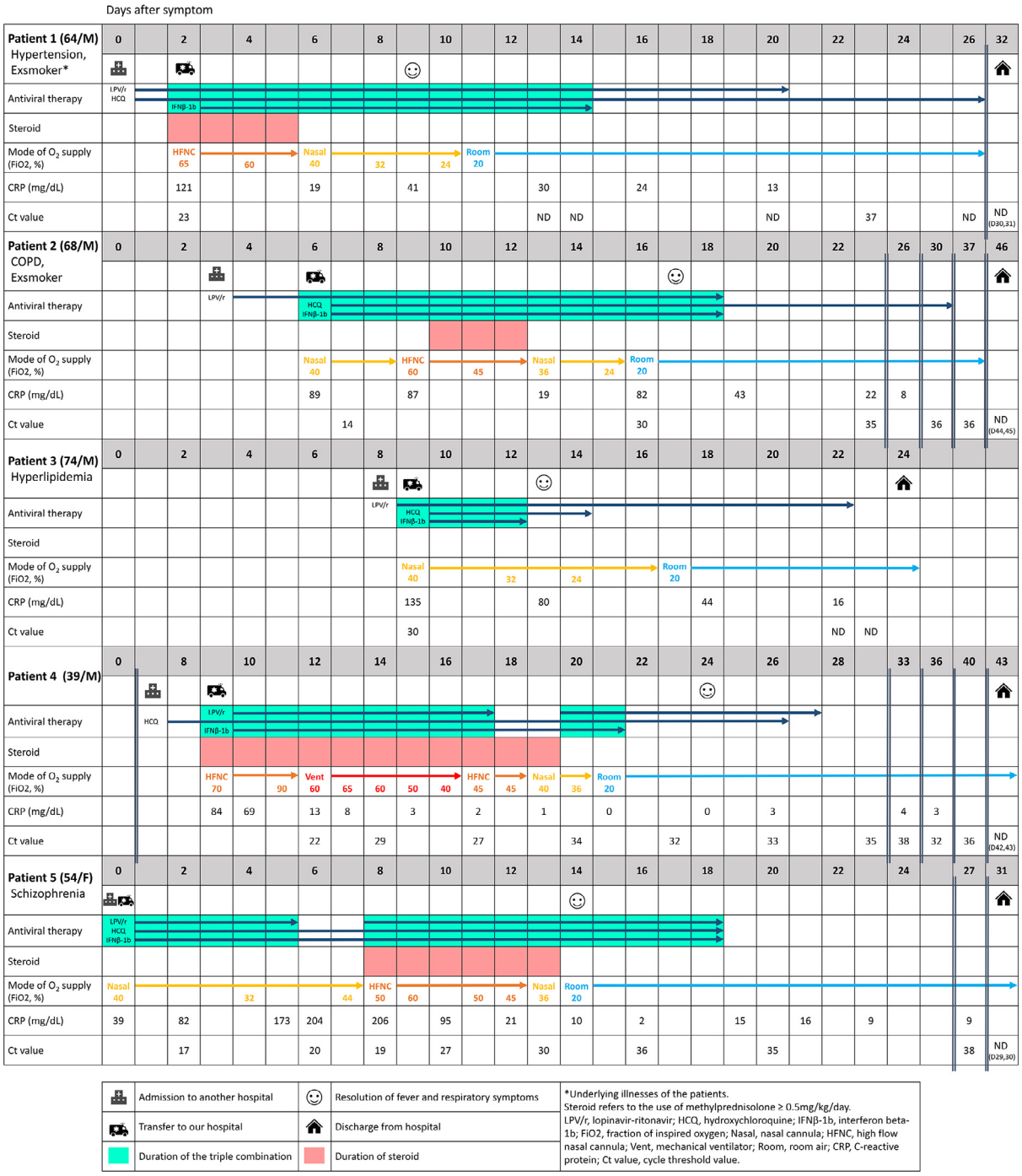

Fig. 1. Clinical characteristics for individual patients included in the case series.

Declarations

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Competing Interests: We have no conflicts of interest to declare.

Ethical Approval: The GNUCH Institutional Review Board approved this study (2020-04-014).

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