# Comparison of the Clinical Course of COVID-19 Pneumonia and Acute Respiratory Distress Syndrome in 2 Passengers from the Cruise Ship Diamond Princess in February 2020

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**Case series**
**Patients:** Male, 72-year-old • Male, 70-year-old
**Final Diagnosis:** Acute respiratory distress syndrome (ARDS) • COVID-19 • COVID-19 pneumonia
**Symptoms:** Cough • fever • malaise • nausea • respiratory distress • vomiting
**Medication:** —
**Clinical Procedure:** —
**Specialty:** Critical Care Medicine • Infectious Diseases • Radiology

**Objective:** Rare disease
**Background:** Patients with coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 can rapidly progress to acute respiratory distress syndrome (ARDS). Because clinical diagnosis of ARDS includes several diseases, understanding the characteristics of COVID-19-related ARDS is necessary for precise treatment. We report 2 patients with ARDS due to COVID-19-associated pneumonia.
**Case Report:** Case 1 involved a 72-year-old Japanese man who presented with respiratory distress and fever. Computed tomography (CT) revealed subpleural ground-glass opacities (GGOs) and consolidation. Six days after symptom onset, reverse transcription-polymerase chain reaction (RT-PCR) testing confirmed the diagnosis of COVID-19-associated pneumonia. He was intubated and received veno-venous extracorporeal membrane oxygenation (ECMO) 8 days after symptom onset. Follow-up CT revealed large diffuse areas with a crazy-paving pattern and consolidation, which indicated progression of COVID-19-associated pneumonia. Following treatment with antiviral medications and supportive measures, the patient was weaned off ECMO after 20 days.
Case 2 involved a 70-year-old Asian man residing in Canada who presented with cough, malaise, nausea, vomiting, and fever. COVID-19-associated pneumonia was diagnosed based on a positive result from RT-PCR testing. The patient was then transferred to the intensive care unit and intubated 8 days after symptom onset. Follow-up CT showed that while the initial subpleural GGOs had improved, diffuse GGOs appeared, similar to those observed upon diffuse alveolar damage. He was administered systemic steroid therapy for ARDS and extubated after 6 days.
**Conclusions:** Because the pattern of symptom exacerbation in COVID-19-associated pneumonia cases seems inconsistent, individual treatment management, especially the CT-based treatment strategy, is crucial.

**MeSH Keywords:** Coronavirus • Extracorporeal Membrane Oxygenation • Pneumonia, Viral • Respiratory Distress Syndrome, Adult • COVID-19

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# Background

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China, in December 2019, and has since spread globally. As of July 17, 2020, COVID-19 has been reported in 13,616,593 patients, resulting in 585,727 deaths in 216 countries and regions [1]. In Japan, the disease outbreak was particularly challenging on the Diamond Princess cruise ship carrying 3700 crew members and passengers, of which 712 were diagnosed with COVID-19 and 13 died [1]. COVID-19 mainly affects the respiratory system, and some patients quickly develop hypoxia and acute respiratory distress syndrome (ARDS). Because COVID-19-related ARDS can be fatal and includes several diseases, understanding its clinical characteristics is valuable for precise treatment [2,3]. Thus, to provide insights into the disease condition, we compared the different clinical courses and imaging findings of 2 patients from the Diamond Princess cruise ship who had ARDS due to COVID-19-associated pneumonia.

# Case Reports

Two patients from Diamond Princess with COVID-19-associated pneumonia were admitted to our hospital, Saiseikai Yokohamashi Tobu Hospital, in Yokohama, Japan. The chest computed tomography (CT) scans of the patients are shown in Figures 1 and 2.

## Case 1

Case 1 involved a 72-year-old Japanese man who presented with respiratory distress, which started from February 4, and fever, which developed 4 days after symptom onset. The patient had boarded the Diamond Princess on January 20, 2020. He was transported to our hospital on February 11 (the first day of illness), and vital signs upon initial examination were as follows: heart rate, 112 bpm; respiratory rate, 24 breaths/min; blood pressure, 154/100 mmHg; body temperature, 38.8°C; and oxygen saturation ($SpO_2$) 94% (6 L/min of oxygen via a face mask). He had a prior medical history of untreated diabetes and a tobacco use history of 60 pack-years. A CT examination revealed a mosaic-like pattern comprising multiple ground-glass opacities (GGOs) in both lungs (Figure 1A), suggesting COVID-19-associated pneumonia. The patient was transferred to the intensive care unit and administered ceftriaxone 2.0 g (intravenously, once daily) and azithromycin 0.5 g (intravenously, once daily) for suspected co-infection. On the third day, the patient tested positive for SARS-CoV-2 by reverse transcription-polymerase chain reaction (RT-PCR) testing from nasopharyngeal swabs, which confirmed the diagnosis of COVID-19-associated pneumonia. The testing was

performed with LightMix® Modular SARS-CoV for use on the LightCycler® 480 System II.

On the fifth day, adequate $SpO_2$ was no longer maintained, and the patient underwent tracheal intubation and mechanical ventilation. However, because ventilation remained insufficient after increasing the respiratory settings ($FiO_2$ 1.0; plateau pressure 30 $cmH_2O$; positive end-expiratory pressure 16 $cmH_2O$), the settings had to be adjusted for severe ARDS with a $PaO_2/FiO_2$ ratio <100. Veno-venous extracorporeal membrane oxygenation (VV ECMO) was initiated on the same day. CT scans performed after VV ECMO initiation revealed large diffuse areas with a crazy-paving pattern mixed with consolidation on the peripheral side in both lungs, which indicated progression of COVID-19-associated pneumonia (Figure 1B). From the sixth day, 400 mg/100 mg lopinavir/ritonavir was administered twice daily. On the 18th day, the follow-up CT showed exacerbation of consolidation on both dorsal sides due to atelectasis and unchanged GGOs on the ventral side (Figure 1C). Up to this point, the respiratory settings were maintained at lung rest ($FiO_2$ <0.4; peak inspiratory pressure <25 $cmH_2O$; positive end-expiratory pressure <10 $cmH_2O$), and dry-side hydration management was carried out under deep sedation. Since tidal volume started to increase under the same lung rest settings on approximately 19th day, VV ECMO flow and sweep gas were gradually reduced. On the 25th day, the patient was successfully weaned from VV ECMO, and on the 29th, the follow-up CT showed that consolidation and GGOs were mostly resolved (Figure 1D). The patient was weaned off the ventilator on the 30th day. On the 71st day, he was discharged from the hospital without sequelae.

## Case 2

Case 2 involved a 70-year-old Asian man residing in Canada who presented with cough, malaise, nausea, vomiting, and fever, which developed from February 7. The patient had also been a passenger on the Diamond Princess. He was subsequently transferred to our hospital 5 days after the onset of symptoms. Vital signs at the initial examination were as follows: heart rate, 99 bpm; respiratory rate, 16 breaths/min; blood pressure, 160/101 mmHg; body temperature, 38.0°C; and $SpO_2$, 96% (room air). His prior medical history included untreated diabetes. A CT examination revealed bilateral subpleural GGOs suggestive of COVID-19-associated pneumonia (Figure 2A). He was hospitalized in a general care ward; however, although oxygen saturation and respiratory condition were maintained, his oxygen demand gradually increased the next day. Ceftriaxone 2.0 g (intravenously, once daily) and azithromycin 0.5 g (intravenously, once daily) were administered for suspected co-infection from the third day of illness. After a definitive diagnosis of COVID-19-associated pneumonia was reached by positive RT-PCR testing from nasopharyngeal swabs, using LightMix® Modular SARS-CoV with the LightCycler® 480 System
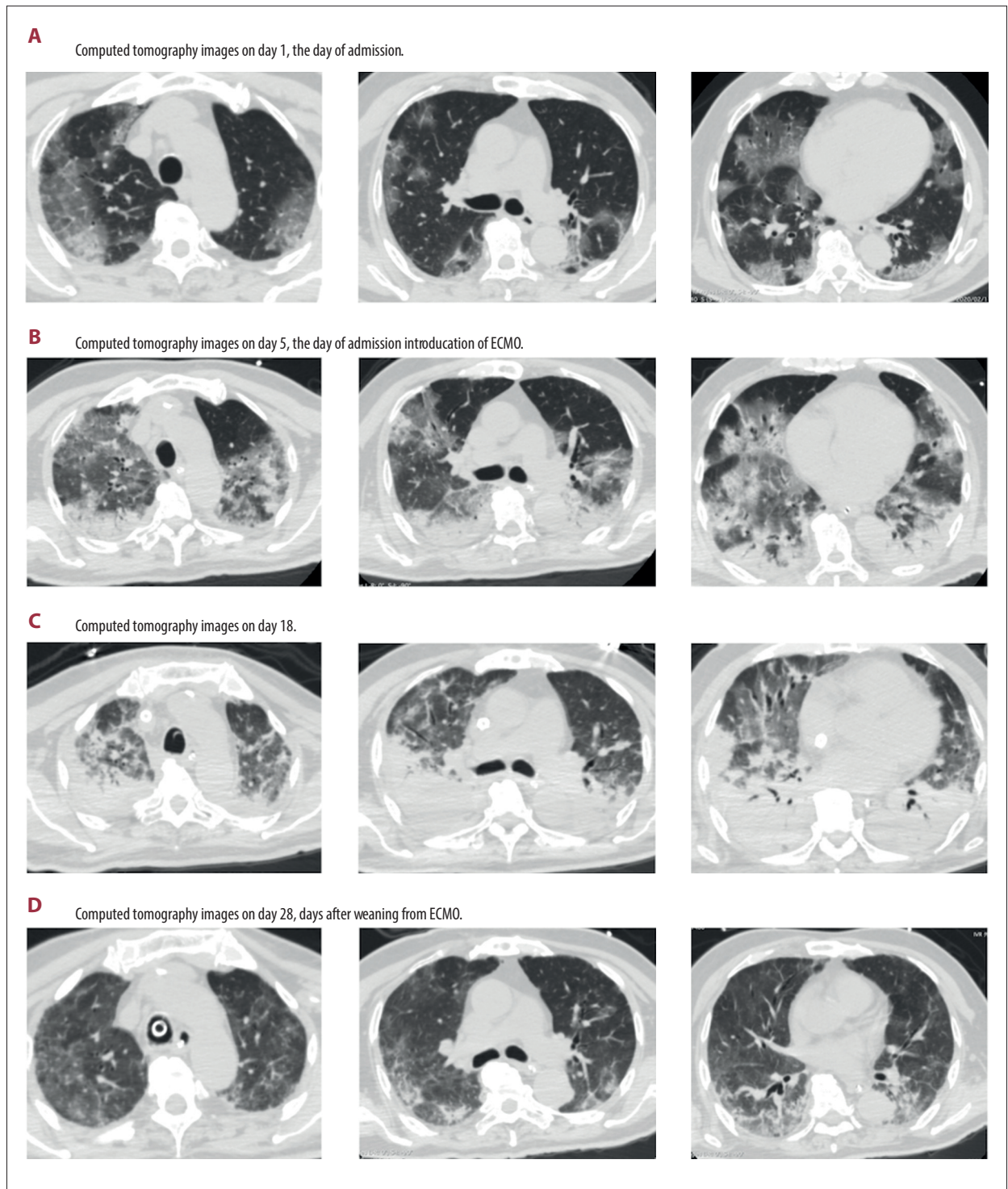
**Figure 1.** Chest computed tomographic images of a 72-year-old patient with severe acute respiratory distress syndrome due to COVID-19-associated pneumonia. (**A**) Images obtained on the day of admission exhibit multiple ground-glass opacities with a mosaic-like pattern in bilateral lungs. (**B**) Images taken on the fifth day, after intubation and introduction of veno-venous extracorporeal membrane oxygenation (VV ECMO), show diffuse large regions with a crazy-paving pattern in both lungs mixed with consolidation on the peripheral side. (**C**) Images taken on the 18th day show exacerbation of consolidation of both dorsal sides due to atelectasis and unchanged ground-glass opacities. (**D**) Images taken on the 28th day, 3 days after weaning off VV ECMO, reveal almost resolved consolidation in both lungs.

**A** Computed tomography images on day 1, the day of admission.

**B** Computed tomography images on day 4, the day of intubation.

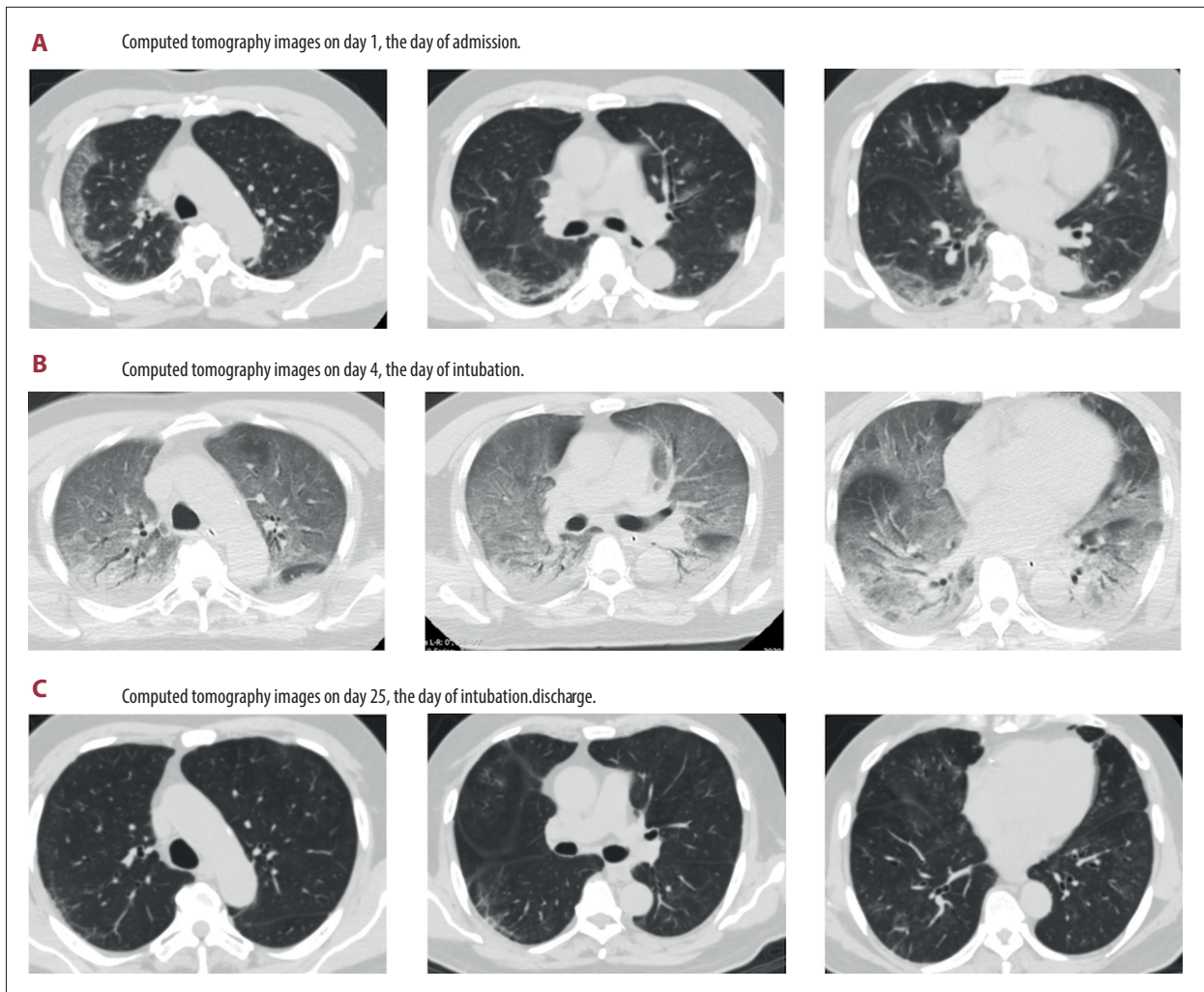**C** Computed tomography images on day 25, the day of intubation.discharge.

**Figure 2.** Chest computed tomographic images of a 70-year-old patient with moderate acute respiratory distress syndrome due to COVID-19-associated pneumonia. (**A**) Chest computed tomographic images obtained on the day of admission revealed bilateral subpleural ground-glass opacities. (**B**) Images taken on the fourth day after intubation show initial shrinking of ground-glass opacity shadows and their subsequent spreading. The shadows resemble those in diffuse alveolar damage. (**C**) Images taken on the 25th day before discharge reveal the absence of ground-glass opacities.

II, the patient was transferred to the intensive care unit and intubated on the fourth day due to deterioration in $SpO_2$. The $PaO_2/FIO_2$ ratio after intubation was approximately 180, which was diagnosed as moderate ARDS. A postintubation CT scan revealed that while the initial subpleural GGOs had improved, diffuse GGOs, suggestive of diffuse alveolar damage, appeared (Figure 2B). Because the disease course seemed different from that of typical COVID-19-associated pneumonia, the patient was started with anti-inflammatory steroid therapy (methyl-prednisolone, 1 mg/kg/d) for the early phase of ARDS, after which his respiratory condition and X-ray-detected infiltration shadow gradually improved. On the sixth day, 400 mg/100 mg lopinavir/ritonavir was administered twice daily. He was extubated on the 10th day and discharged from the intensive care unit on the 16th day. He was subsequently discharged from the hospital without any sequelae on the 25th day. CT scans before discharge revealed that the GGOs in both lungs had almost completely disappeared (Figure 2C).

## Discussion

We present 2 cases of ARDS arising from COVID-19-associated pneumonia that required intensive care at our hospital. While the patterns of symptom exacerbation are clearly very different between the 2 cases based on the comparison of their CT imaging findings, the factors contributing to these differences are less clear. Therefore, treatment management according to the needs of individual patients, especially when it is CT-oriented, might be valuable.

ARDS and COVID-19-associated pneumonia are known to show variable imaging patterns that impede the understanding of clinical features [2–4]. Lung changes on CT are not specific for COVID-19 pneumonia and can be found in other forms of viral pneumonia, such as influenza virus pneumonia, which is why confirmation of SARS-CoV-2 infection is required to make an accurate diagnosis [5]. Thus, CT might be used to assess the pattern of change in imaging and the effectiveness of treatment rather than to make a definitive diagnosis [5,6]. Imaging findings in mild cases of COVID-19-associated pneumonia generally follow a 4-stage pattern: an early stage characterized by the appearance of subpleural GGO; a progressive stage characterized by the spreading of GGO bilaterally across multiple lobes, the crazy-paving pattern, or consolidation; a peak stage during which shadow infiltration increases; and an absorption stage [6]. In Case 1, the changes observed on the CT scans corresponded to the exacerbation pattern of COVID-19-associated pneumonia. However, in Case 2, the appearance of diffuse GGOs indicated diffuse alveolar damage, suggesting that this patient's course was different from that of typical COVID-19-associated pneumonia. According to the Berlin Criteria, clinical diagnosis of ARDS includes several diseases. Among them, diffuse alveolar damage is histopathologically confirmed in only half of the patients who fulfilled the clinical criteria [7]. Given that little is known about COVID-19-related ARDS, the exacerbation pattern seen in Case 2 might help determine the treatment strategy.

For the management of COVID-19, many classes of drugs, such as antivirals, antibodies, anti-inflammatory agents, and targeted immunomodulatory therapies, are being developed or evaluated [8]. Other forms of treatment, such as low-dose radiation, convalescent plasma, or mesenchymal stem cells, are also currently under investigation [9,10]. Since June 2020, Remdesivir, a broad-spectrum antiviral drug, and dexamethasone, a potent anti-inflammatory agent, seem to be the most promising [11,12]. Since Remdesivir showed efficient inhibition of viral infection in *in vitro* studies of SARS-CoV-2, it has been studied extensively in retrospective and prospective studies [13]. The first prospective study of Remdesivir, which did not show clinical improvement by day 28 or significant reductions in SARS-CoV-2 RNA loads, was terminated before enrolling enough patients due to a decrease in available COVID-19 patients [14]. However, preliminary results from a double-blind, randomized, placebo-controlled trial of 1063 adults hospitalized with COVID-19 indicates that patients who received Remdesivir had a significantly shorter median recovery time compared with those who received the placebo. In this study, mortality was numerically lower in the Remdesivir group than in the placebo group [11]. During our patients' treatment period, Remdesivir had not been adopted in Japanese medical practice, which led us to the use of lopinavir-ritonavir, which did not show benefit in a randomized, controlled trial afterwards [15].

Recent evidence has shown that the use of corticosteroids reduces mortality at 28 days in patients with COVID-19 pneumonia and ARDS; however, the timing, dose, and contraindications remain controversial [12,16]. Steroid treatment in general ARDS is usually associated with positive results such as reduced mortality rate and extended periods without artificial respiratory support. However, routine use of steroids for the treatment of viral pneumonia, including COVID-19, is not recommended, as mentioned in the World Health Organization consensus statement [17–19]. A systematic review of observational studies of severe acute respiratory syndrome found that this approach did not improve the mortality rate, but instead showed possible harm, such as avascular necrosis, psychosis, and diabetes [20]. Steroids are also known to have anti-inflammatory and immunomodulatory effects that cause delayed antibody production and delayed viral shedding [21]. Meanwhile, a preliminary report on July 18, 2020, from the Randomized Evaluation of COVID-19 Therapy (RECOVERY) study trial showed that patients with severe COVID-19 pneumonia administered 6 mg dexamethasone once daily had significantly lower mortality compared with patients given standard care [12]. Although the National Institutes of Health developed recommendations for the use of the corticosteroid dexamethasone in people with COVID-19, the evidence cannot be considered to be strong; thus, the choice, dosing, duration, and indication of steroids need to be further discussed [10]. Because Case 1 presented as "pure" exacerbation of COVID-19-related pneumonia, we decided not to administer steroids. We opted for steroid treatment in Case 2 because the anti-inflammatory and immunomodulatory effects of steroids in the early phase of ARDS, which is characterized by diffuse alveolar damage, have been reported as clinically significant [22,23]. We again recommend caution in using steroids routinely for treating COVID-19 patients.

Use of ECMO for COVID-19-associated pneumonia is considered a bridge therapy because of the time required before improvement occurs, as in the cases presented. Although ECMO requires extensive resources, including ECMO consoles, disposable equipment, trained staff, and isolation rooms, the use of ECMO for COVID-19 during a pandemic state should be considered cautiously [24]. The Extracorporeal Life Support Organization statement acknowledged that early experience of ECMO in COVID-19 patients in Asia showed notable outcomes; however, the decision to introduce ECMO should depend on local responsibility [25]. In our case, since the cruise ship patients were spread out across multiple hospitals and our hospital had the resources to carry out ECMO, we decided to use ECMO even though the patient was older and had several comorbidities. Thus, as an option for the treatment of severe COVID-19 patients, the use of ECMO should be considered with traditional indications, along with hospital and regional resources.

## Conclusions

This report presented 2 cases of ARDS due to COVID-19-associated pneumonia. These cases exhibited different courses of exacerbation and remission of symptoms based on CT imaging findings; as such, managing treatment appropriately depends on the particulars of each case, especially based on CT findings, as opposed to using a standardized treatment policy. Numerous unknowns remain concerning COVID-19-associated pneumonia, and further reports and analyses are anticipated, particularly for severe cases.

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## Conflict of interest

None.