Coronavirus disease 2019 (COVID-19) is a public health emergency caused by severe acute respiratory syndrome virus coronavirus 2 and is increasing globally, particularly in Indonesia.¹ Most COVID-19 cases present mild symptoms with a low case fatality rate (CFR) of 2.3%. Meanwhile, cases with severe clinical manifestations, such as respiratory failure, septic shock, and multiple organ dysfunction syndrome, have a high CFR of 50%.² Studies have reported that 9–11% of patients with COVID-19 required intensive care unit (ICU) admission. Of these critically ill patients, 99% required respiratory support, with 88% requiring mechanical ventilation and 11% non-invasive ventilation. CFR among these patients was 26%.³⁴ Only a few studies have reported pneumothorax as a radiologic manifestation of COVID-19 pneumonia and iatrogenic pneumothorax related to mechanical ventilation, which are associated with increased morbidity and mortality.⁵⁻⁷ We report four cases of pneumothorax in critical ICU-hospitalized patients with COVID-19.

CASE 1

A 48-year-old man was admitted to the hospital with persistent fever, cough, and dyspnea for 8 days. He had a history of controlled hypertension, mild defect of the heart septum, but no history of pneumothorax, chest trauma, or underlying lung disease. He was initially in the happy hypoxemia condition, wherein he appeared clinically sound and only complained of mild dyspnea despite a peripheral oxygen saturation (SpO₂) of 77% in room air. His chest computed tomography (CT) scan showed ground-glass opacity (GGO) and multifocal crazy paving pattern in bilateral lungs, predominantly along the

ABSTRACT
Coronavirus disease 2019 (COVID-19) is a public health emergency caused by SARS-CoV-2. A few studies reported pneumothorax in patients with COVID-19. Pneumothorax is associated with an increased morbidity and mortality. Hence, it should be considered during the treatment and follow-up of patients with COVID-19. Herein, we reported four cases of pneumothorax in critical COVID-19 patients hospitalized in the ICU and treated with a mechanical ventilation. All patients were diagnosed with COVID-19, type 1 respiratory failure, and acute respiratory distress syndrome. All patients developed pneumothorax during mechanical ventilation, although the ventilator settings were set to lung-protective strategy.

KEYWORDS COVID-19, disseminated intravascular coagulation, hypoxia, respiratory distress syndrome
lung periphery and paraseptal emphysema in the first left lung segment (Figure 1, a and b). His laboratory examination showed lymphopenia and increased levels of neutrophils, D-dimer, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). His blood gas analysis (BGA) showed a pO\textsubscript{2} of 57 mmHg, pCO\textsubscript{2} of 29 mmHg, and HCO\textsubscript{3} of 22.4 mmol/l. The reverse transcription polymerase chain reaction (RT-PCR) test yielded a positive result for COVID-19 infection, establishing the diagnosis of COVID-19 with type 1 respiratory failure and acute respiratory distress syndrome (ARDS). He was immediately admitted into the ICU and given oxygen therapy through a non-rebreathing mask (NRM) then a high-flow nasal cannula (HFNC). As the dyspnea got worsened, he was intubated and given mechanical ventilation. The ventilator settings on the day he developed pneumothorax (range during hospitalization) were as follows: a pressure control of 14 (14–18) cmH\textsubscript{2}O, peak inspiratory pressure (PIP) of 35 (35) cmH\textsubscript{2}O, positive end-expiratory pressure (PEEP) of 10 (6–10) cmH\textsubscript{2}O, tidal volume of 6 ml/kg predicted body weight (PBW), respiratory rate (RR) of 25 (20–25) x/min, and the fraction of inspired oxygen (FiO\textsubscript{2}) of 60% (35–60%). He developed right lung hydropneumothorax and atelectasis on hospitalization day-14 (Figure 1c).

Figure 1. Chest CT scan and CXR of the COVID-19 cases. Case-1 (a, b, c), coronal (a) and axial (b) views of the chest CT scan on admission showing GGO and multifocal crazy paving pattern (arrow), CXR on day-14 (c) showing right lung hydropneumothorax and atelectasis (arrow); case-2 (d, e, f), chest CT scan on admission (d, e) showing GGO and multifocal crazy paving pattern (arrow), CXR on day-10 (f) showing left lung pneumothorax (arrow); case-3 (g, h, i), CT scan on admission (g, h) showing multifocal GGO (arrow), CXR on day-8 (i) showing right lung pneumothorax (arrow); case-4 (j, k, l), CXR on admission (j) showing opacities involving both lungs (arrow), CXR on day-20 (k) showing right lung pneumothorax (arrow), chest CT image on day-21 (l) showing right lung pneumothorax (asterisk) and GGO (arrow). COVID-19=coronavirus disease 2019; CT=computed tomography; CXR=chest X-ray; GGO=ground-glass opacity
Hence, we inserted a water seal drainage (WSD) and performed bronchoscopy and tracheostomy. On the follow-up, he developed disseminated intravascular coagulation (ISTH score of 5 without fibrinogen measurement), and bronchoscopy was performed twice. On day-18 of hospitalization, an improvement was observed, and a ventilator was weaned. The WSD was placed for 12 days until the pneumothorax had resolved. He was discharged on day-41 without residual pneumothorax.

**CASE 2**

A 46-year-old man was admitted to the hospital for fever, sore throat, cough, and dyspnea for a day. He had a history of uncontrolled type-2 diabetes and no history of pneumothorax, chest trauma, or underlying lung disease. He initially presented with happy hypoxemia (SpO₂ of 88% in room air). His chest CT scan showed GGO and multifocal crazy paving pattern in bilateral lungs with peripheral distribution and multifocal paratracheal lymphadenopathy (Figure 1, d and e). His laboratory examination showed low hemoglobin, white blood cell, and platelet counts; and increased ESR, serum glutamic pyruvic transaminase, serum creatinine, and random blood glucose levels. His pO₂ was 77 mmHg, pCO₂ was 25.7 mmHg, and HCO₃⁻ was 15 mmol/l. He was confirmed as COVID-19 with type 1 respiratory failure, ARDS, and acute kidney injury. He was transferred to the ICU and was intubated since there was inadequate response to NRM or HFNC. The mechanical ventilation setting was a pressure control of 16 cmH₂O, PIP of 35 cmH₂O, PEEP of 10 cmH₂O, tidal volume of 6 ml/kg PBW, RR of 30 x/min, and FiO₂ of 80%. Figure 1f shows the left pneumothorax developed on day-10 of hospitalization. A WSD was hence inserted. He underwent hemodialysis due to uremia and developed septic shock, pressure ulcer grade II, and anemia. On day-18 of hospitalization, tracheostomy was performed because of prolonged intubation. Pneumothorax resolved after 19 days of WSD insertion; however, he continued to remain critical in the ICU due to renal failure and passed away a month later due to multiple organ failures.

**CASE 3**

A 58-year-old man was admitted to the hospital for fever, cough, and dyspnea for 4 days. His medical history was controlled hypertension; however, he had no history of pneumothorax, chest trauma, or underlying lung disease. His chest CT scan showed multifocal GGO involving both lungs with dominant subpleural distribution (Figure 1, g and h). His laboratory examination showed an increased white blood cells, neutrophil counts, aspartate aminotransferase, D-dimer levels, a neutrophil-lymphocyte ratio of 21.5. His BGA showed a pO₂ of 94.5 mmHg, pCO₂ of 27.3 mmHg, HCO₃⁻ of 19.9 mmol/l, SpO₂ of 97.9% on O₂ 15 l/min using NRM. Based on the RT-PCR findings, he was diagnosed COVID-19 with ARDS. Since there was inadequate oxygenation with NRM (pO₂ 49.3 mmHg), he was intubated and applied to mechanical ventilation with the ventilator settings on the day patient developed pneumothorax (range during hospitalization) were as follows: pressure control of 30 (25–30) cmH₂O, a PIP of 35 (35) cmH₂O, PEEP of 15 (10–15) cmH₂O, tidal volume of 6 ml/kg PBW, RR of 30 (25–30) x/min, and FiO₂ of 65% (50–65) was applied. On the follow-up, the renal condition was worsened resulted in uremia (urea level 346.5 mg/dl), a high blood urea nitrogen level of 161.7 mg/dl, a high creatinine level of 5.12 mg/dl, low estimated glomerular filtration rate of 11.5 ml/min/1.73 m², and a high potassium level of 6.4 mmol/l. On hospitalization day-8, he suddenly developed right pneumothorax (Figure 1i). Consequently, a WSD was placed for a day, which resolved the pneumothorax. However, a sudden drop in SpO₂ was seen 2 days after, and chest X-ray revealed recurrent right pneumothorax and increased opacity in both lungs (Figure 1e). He died of bradycardia that developed few hours later.

**CASE 4**

A 45-year-old man was admitted to the hospital for fever, cough, and severe dyspnea for 7 days. He had no history of smoking, pneumothorax, chest trauma, or any underlying pulmonary disease. His chest CT scan showed multifocal GGO on both lungs. Moreover, his chest X-ray on admission showed opacities involving both lungs, predominantly on mid-lower lung fields (Figure 1, j and k). His laboratory examination showed elevated white blood cells, neutrophil counts, CRP, and lactate dehydrogenase levels and lymphocytopenia. His BGA showed a pO₂ of 45.4 mmHg, pCO₂ of 30.9 mmHg, HCO₃⁻ of 23 mmol/l, SpO₂ of 93.1% on O₂ 10 l/min using NRM. His RT-PCR assay returned positive for COVID-19; therefore, he was diagnosed COVID-19.
with type 1 respiratory failure and ARDS. He previously had HFNC, but the pO₂ was only 44.7 mmHg. He was subsequently intubated and applied to mechanical ventilation with a pressure control of 15 cmH₂O, PEEP of 10 cmH₂O, tidal volume of 6 ml/kg PBW, RR of 25 x/min, and FiO₂ of 75%. During hospitalization, his D-dimer and liver enzyme levels were increased, indicating a liver injury. He was weaned off the ventilator on day-19 of hospitalization. However, he suddenly developed right lung pneumothorax a day afterwards (Figure 1I). A WSD was inserted and placed for 2 days until pneumothorax was resolved. He was discharged with no residual pneumothorax on day-46 of hospitalization.

DISCUSSION

Pneumothorax was reported in both mechanically ventilated and non-mechanically ventilated COVID-19 patients and associated with an increased morbidity and mortality. Herein, we reported four critical COVID-19 patients diagnosed with COVID-19, type 1 respiratory failure, and acute respiratory distress syndrome treated with mechanical ventilation and developed pneumothorax. Pneumothorax develops because of air leakage into the pleural space that can lead to an impaired oxygenation and ventilation. Pneumothorax is classified into three categories: spontaneous (primary or secondary), traumatic, and iatrogenic. Spontaneous pneumothorax has the highest incidence. Clinical manifestations of pneumothorax include tachycardia, chest pain, tachypnea, hypotension, cyanosis, or altered consciousness. Radiologic modalities: chest radiograph, chest CT, and transthoracic sonography remain the gold standard for diagnosis of pneumothorax. Chest radiograph may indicate a radiolucent hemithorax with a pleural line and absent lung marking. Increasing pressure in the pleural space may lead to tension pneumothorax, which leads to death when untreated. The patients in these case report developed pneumothorax during hospitalization in the ICU on mechanical ventilation owing to ARDS and respiratory failure. The patients did not have a history of pneumothorax or other underlying lung disease, smoking, and structural abnormality predisposing these patients to pneumothorax.

Two hypotheses likely explain the mechanism of pneumothorax formation in these patients. First, through diffuse alveolar injury and fibrotic parenchyma that render the alveoli susceptible to rupturing. COVID-19 infection may directly cause secondary spontaneous pneumothorax. Previous studies by Aydin et al⁸ and Sun et al⁹ reported that patients with COVID-19 presented with pneumothorax on admission and before mechanical ventilation. Furthermore, similarly to severe acute respiratory distress syndrome, severe strain during persistent cough may cause a sudden increase in alveolar pressure, which could in turn lead to alveolar rupture and air leakage resulting in interstitial emphysema and pneumothorax. In ARDS, subpleural and intrapulmonary air cysts may develop, and their rupture may cause pneumothorax.⁷ Second, iatrogenic pneumothorax due to mechanical ventilation could be the underlying cause. Our patients developed pneumothorax during ventilator support. This phenomenon is rare, especially in the intubated COVID-19 patients. Iatrogenic pneumothorax is reported in up to 15% of patients on ventilator support. It rarely develops in the intubated patients with normal lungs and develops mostly in patients with an underlying lung disease (e.g. chronic obstructive pulmonary disease, ARDS, and so forth), such as these patients.⁵ The development of pneumothorax related to mechanical ventilation (PRMV) in a patient is affected by the underlying lung disease and ventilatory setting, with the underlying lung disease contributes significantly. The risk of PRMV is increased in the lungs with low compliance. Primary phenotypes of COVID-19 pneumonia are divided into type L (low elastance, high compliance, low V/Q ratio, low lung weight, low recruitability), and type H (high elastance, low compliance, high right-to-left shunt, high lung weight, and high recruitability). Patients with the type L phenotype may remain without major symptoms for a period, which may resolve or worsen and evolve into type H.¹⁰ In our case report, the patients had developed type H COVID-19 pneumonia; therefore, their lungs had low compliance. The dependent lung regions tend to collapse resulting in derecruitment. In independent lung regions that are subjected to high pressure overinflation inflated by high PEEP and recruited collapsed region, alveolar rupture may occur, especially in fibrotic and hypoelastic lungs.⁶ Ventilatory settings that are reportedly associated with an increased risk of PRMV are PIP >50 cmH₂O, a high PEEP, and a high tidal volume. Implementation of protective lung strategies is strongly associated with a decreased incidence of
pneumothorax, an improved 28-day survival, and a higher rate of weaning from mechanical ventilation in patients with ARDS than conventional ventilation.⁷ Lung-protective strategy for patients with severe COVID-19 with ARDS, such as our patients, was based on maintenance of a low tidal volume of 4–8 ml/kg PBW, plateau pressure <30 cmH₂O, a PEEP of at least 8 cmH₂O which can be gradually up-titrated, a driving pressure of ≤15 cmH₂O, and target PO₂ of at least 60 mmHg and SpO₂ of 90–94%. ¹⁰,¹¹ The high alveolar recruitment and aeration in this strategy were intended to minimize shear stress in the lung tissue during inspiration.⁷ Our patients developed pneumothorax on an average of 9.25 days (6–13 days) after mechanical ventilation treatment. We had implemented the lung-protective strategies, which resulted in lower PRMV incidence. Therefore, we hypothesized that the underlying lung disease contributed primarily to the development of PRMV in these cases rather than the ventilatory setting. A limitation of our study was that we could not compare findings with patients without mechanical ventilation treatment to ascertain that pneumothorax was not ventilation related, as all the patients required mechanical ventilation. However, previous studies by Aydin et al⁸ and Sun et al⁹ have shown that patients with COVID-19 might develop pneumothorax before receiving mechanical ventilation. Hence, our study showed that the lung-protective strategy was not completely successful in preventing PRMV in critical COVID-19 pneumonia. The resolution of pneumothorax among our patients occurred on an average of 8.25 days (1–19 days) after WSD insertion; hence, our study showed that pneumothorax in critical COVID-19 pneumonia can be resolved rapidly with the usual pneumothorax management strategy.

Positive-pressure ventilation can exacerbate air leak and prevent pleural healing, causing an increase in the size and severity of the existing pneumothorax. Hence, tube thoracostomy with WSD placement is required in PRMV, given the high risk of tension pneumothorax. However, a persistent air leak or lung expansion failure may be the indications for early thoracic surgical consultation and low tidal volume two-lung ventilation thoracoscopy.⁶ The reported success rate of tube thoracostomy in PRMV is 68.6%, defined as no residual air is seen in the follow-up chest radiograph and no major complications.⁷ Patients with PRMV have a significantly higher mortality rate (>2-fold, ranging from 46% to 77%) and significantly longer ICU and hospital stays than those without PRMV.⁷ The CFR among COVID-19 patients with respiratory failure and requiring ICU admission was high, given these patients are in a critical condition because of ARDS, respiratory failure, and other complications such as pneumothorax.¹⁰ However, in our study, only two patients survived with our treatment strategies and fully recovered without sequelae.

Conflict of Interest
The authors affirm no conflict of interest in this study.

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