MAYO CLINIC

ORIGINAL ARTICLE

Pneumothorax and Pneumomediastinum in COVID-19 Suggest a Pneumocystic Pathology

Aayla K. Jamil, MBBS, MPH; Amit Alam, MD; Ronnie M. Youssef, MD; Joost Felius, PhD; Johanna S. van Zyl, PhD; and Robert L. Gottlieb, MD, PhD

Abstract

Objective: To determine whether the apparent excess incidence of pneumothorax and pneumomediastinum in patients with coronavirus disease 2019 (COVID-19) is explained adequately by iatrogenic causes vs reflecting sequelae of severe acute respiratory syndrome coronavirus 2 infection.

Patients and Methods: We retrospectively reviewed patients within our health care system from March 15, 2020, through May 31, 2020, who had a diagnosis of pneumothorax or pneumomediastinum during hospitalization for confirmed COVID-19 infection with attention to timing of pneumothorax and pneumomediastinum; presence, laterality, and placement, or attempts at central lines; and presence of mechanical ventilation before the event.

Results: We report clinical data and outcomes from 9 hospitalized patients with COVID-19 who developed pneumothorax and/or pneumomediastinum among more than 1200 hospitalized patients admitted within our hospital system early in the pandemic. Many events were inexplicable by iatrogenic needle injury, including 1 spontaneous case without central line access or mechanical ventilation. One occurred before central line placement, 2 in patients with only a peripherally inserted central line, and 1 contralateral to a classic central line. Three of these 9 patients died of complications of COVID-19 during their hospital stay.

Conclusion: With COVID-19 affecting the peripheral lung pneumocytes, patients are vulnerable to develop pneumothorax or pneumomediastinum irrespective of their central line access site. We hypothesize that COVID-19 hyperinflammation, coupled with the viral tropism that includes avid involvement of peripheral lung pneumocytes, induces a predisposition to peripheral bronchoalveolar communication and consequent viral hyperinflammatory-triggered pneumothorax and pneumomediastinum.

 ■ Mayo Clin Proc Inn Qual Out 2021;5(5):827-834

A surge in complications of mechanical ventilation associated with the coronavirus disease 2019 (COVID-19) pandemic is anticipated because of a corresponding spike in routine complications of positive pressure ventilation, increased ventilatory days, and critical care delivery. However, we and others have independently observed hospitalizations associated with pneumothoraces and pneumomediastinum that appeared incompletely or inadequately explained by the more typical barotrauma or iatrogenic causes including central venous line insertions.[1,2]

Pneumothorax is a condition of partial or complete lung collapse due to air in the pleural cavity and is typically detected and measured using radiographic methods, ultrasound, or computerized tomography scan. A pneumothorax can be primary spontaneous with no underlying lung disease as seen with genetic predisposition, secondary spontaneous due to underlying parenchymal lung diseases, or nonspontaneous due to iatrogenic and traumatic factors. In primary and secondary spontaneous pneumothorax, air may originate from bronchoalveolar communication with the pleural space, whereas in nonspontaneous pneumothorax due to penetrating trauma or medical interventions, air is entrained either from the exterior or from an induced bronchoalveolar connection to the pleural

From the Baylor Scott & White Research Institute, Dallas, TX (A.K.J., A.A., J.F., J.S.V.Z., R.L.G.); College of Medicine, Texas A&M Health Science Center, Dallas, TX (A.K.J., A.A., R.M.Y., J.F., J.S.V.Z., R.L.G.); Center for Advanced Heart and Lung Disease, Baylor University Medical Center, Dallas, TX (A.A., R.L.G.); and Department of Internal Medicine, TCU and UNTHSC School of Medicine, Fort Worth, TX (R.L.G.).

space. Small asymptomatic cases may self-resorb, whereas those with mild symptoms may have needle aspiration performed. Those with marked symptoms require percutaneous chest tube or invasive tube thoracostomy, and recurrent pneumothoraces may require obliteration of the pleural space via pleurodesis using medical and surgical techniques.[3] A similar condition, in which air is trapped in the mediastinum, is termed *pneumomediastinum*.

The inflammatory nature of COVID-19 causes pneumonitis, which frequently includes the peripheral juxtapleural alveoli. This might predispose the patient to various modes of alveolar-pleural communication or perhaps a microcystic process (in contrast to the macrocystic process of pneumatocoeles observed after *Pneumocystis jirovecii* pneumonia).

Herein, we report 9 cases of COVID-19 with pneumothorax and/or pneumomediastinum and find that many of these are out of proportion to any potential iatrogenic needle injury. We assessed unilateral vs bilateral distribution and its relationship to the location or attempts of any central lines, as well as any associated procedural barotrauma.

PATIENTS AND METHODS

We reviewed all inpatient admissions at our institution and its affiliated locations with a diagnosis of COVID-19 by polymerase chain reaction testing established between March 15, 2020 and May 31, 2020, who had documented pneumothorax (identified by Current Procedural Terminology codes 32551-32557) or pneumomediastinum (*International Classification of Diseases, Tenth Revision* code J98.2). Patient demographic characteristics, disease course, pertinent laboratory results, and radiographic images were evaluated. This retrospective noninterventional study was authorized by the Institutional Review Board for Baylor Scott & White Research Institute and qualified for waiver of informed consent.

RESULTS

Of the 1200 medical records reviewed of patients hospitalized for COVID-19, 4 patients had a diagnosis of pneumothorax alone (Figure 1A-C), 2 had a diagnosis of pneumomediastinum alone (Figure 2A), and 3 had both pneumothorax and pneumomediastinum concomitantly (Figure 2B-D). These 9 patients are described here (see Table 1 for demographic characteristics); an additional severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—positive patient, having been in a motor vehicle accident resulting in both traumatic pneumothorax and pneumomediastinum, was excluded from this series. The mean age was 56 years (range, 22-76 years), with 2 women and 7 men.

The chronology of key hospitalization events was reviewed for the timeline of central lines, endotracheal intubation, pneumothorax, and pneumomediastinum (Figure 3). Four patients developed pneumothorax or pneumomediastinum without antecedent central line insertion or access attempt typically associated with a substantial recognized risk of pneumothorax or pneumomediastinum. Saliently, 1 patient developed definitive "spontaneous" pneumothorax absent central venous line access or mechanical ventilation at any time during the admission (Figure 3 and Table 2, patient 4), 1 patient's central line was placed only after the pneumothorax (Figure 3 and Table 2, patient 9), and 2 patients had only peripherally inserted central lines (Figure 3 and Table 2, patients 7 and 8). One patient developed pneumothorax only contralateral to the site of the antecedent central line (Figure 3 and Table 2, patient 3). As anticipated, the events were not always discordant with sites of needle access, with 1 pneumothorax ipsilateral to central line location and 3 patients with unilateral central line access manifested bilateral pneumothorax, pneumomediastinum, or combined pneumothorax and pneumomediastinum, and causality can neither be affirmed nor refuted.

For the 7 patients with an antecedent central line (including the 2 with peripherally inserted central catheter [PICC] lines), the median time between line placement to development of the first pneumothorax or pneumomediastinum was 10 days. Ultrasound guidance was standard for internal and external jugular access, and 6 patients had central line placement on the first attempt while 1 had success on the second attempt.

Four patients (including 3 patients with a pneumomediastinum component) were managed without chest tube placement, whereas 5 patients required chest tube

Mayo Clin Proc Inn Qual Out ■ XXX 2021;5(5):827-834 ■ https://doi.org/10.1016/j.mayocpiqo.2021.05.009
www.mcpiqojournal.org

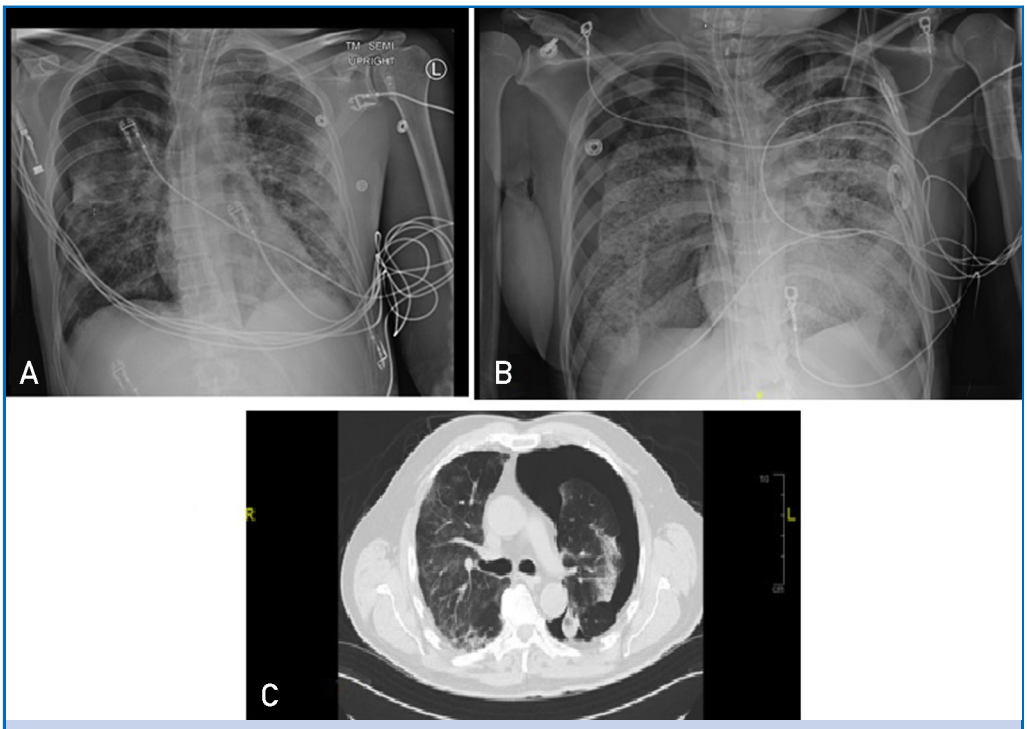

FIGURE 1. Pneumothorax case examples. A, Patient 1 with right moderate apical pneumothorax before chest tube placement. B, Patient 2 with stable left-sided pneumothorax and now large right-sided pneumothorax. C, Patient 4 with left-sided pneumothorax and rightward mediastinal shift; note the peripheral and subpleural nature of the pulmonary infiltrates in both lungs, particularly vigorous focally on the left.

insertion (Table 2). Three patients died during hospitalization. The cause of death was refractory shock resulting from complications of acute respiratory failure due to COVID-19. The remaining patients were discharged home. The average length of hospital stay was 39 days (range, 22-65 days), with an average duration of hospital stay after developing pneumothorax or pneumomediastinum of 24 days (range, 5-48 days).

None of the 9 patients had a documented history of smoking, asthma, or chronic obstructive pulmonary disease. One patient had a history of cancer. Most patients received empirical antibiotics per clinical decision, and peak inflammatory markers were recorded (Supplemental Table, available online at http://www.mcpiqojournal.org). Five patients had heart failure according to chart annotation. Five patients suffered from shock (1 septic shock and the other 4 with cardiogenic shock, none of which were treated with temporary mechanical circulatory support). Of the 4 patients with cardiogenic shock, 3 had heart failure. One patient had acute renal failure requiring dialysis and later died. Eight patients received mechanical ventilation, and 1 patient went on to receive veno-venous extracorporeal membrane oxygenation.

DISCUSSION

These 9 cases suggest an excess increase in pneumothoraces and pneumomediastinum that cannot be attributed to iatrogenesis alone. The utility of this case series is not in the absolute numbers, but rather in the actionable message that this needs to be tracked and followed on a larger scale. As pneumomediastinum is otherwise rare in the nonsurgical patient and because our series included "spontaneous" pneumothorax in a patient without instrumentation or positive pressure ventilation, we believe that this excess may be due to viral pathophysiological effects of

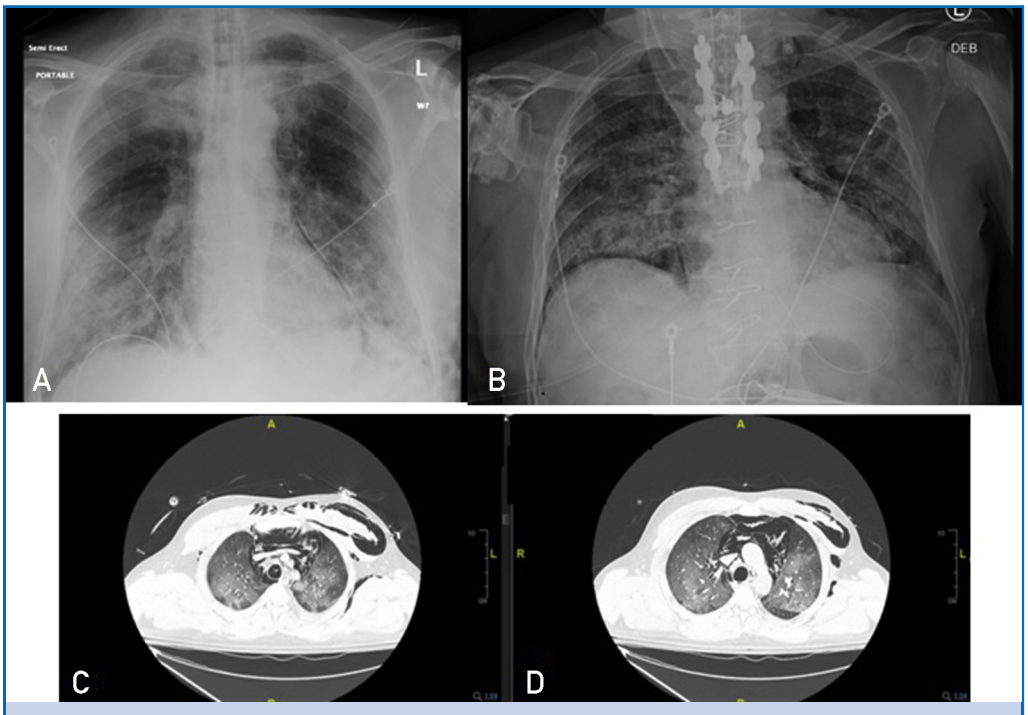

FIGURE 2. Pneumomediastinum case examples. A, Patient 5 with pneumomediastinum without pneumothorax. B, Patient 6 with worsening pneumomediastinum and stable right-sided pneumothorax. C and D, Patient 9 with pneumomediastinum and small left-sided pneumothorax.

COVID-19 on the lung inflammation affecting the peripheral pneumocytes.

It is clear that many of these cases either cannot be (or are extraordinarily unlikely to be) central line-related. One patient neither had a central line placed nor required mechanical ventilation at any time during the admission, despite pneumothorax, and 1 patient had pneumothorax diagnosed before the central line insertion. For the 2 patients who had only a PICC line for central access, a line-related iatrogenic pneumothorax or pneumomediastinum is extraordinarily unlikely. Moreover, although both those PICC lines were on the right side, one patient had a progression to develop pneumomediastinum whereas the other developed a contralateral left pneumothorax (Figure 3, patients 7 and 8). Although both had received mechanical ventilation as a potential confounder, the initiation of mechanical ventilation was not proximate in time.

Sarbecoviruses, such as severe acute respiratory syndrome coronavirus 1 and 2, evade the initial immune response by concealing the RNA genome and tend to infect type I and type II pneumocytes lining the lung alveolar walls.[4] These cells are responsible for gas exchange and lung surfactant release. The virus also causes a severe cytokine response, which, combined with alveolar damage and lung collapse, can cause severe respiratory failure. Fibrin clots are created in the alveoli because of coagulation cascade activation. The severity of hospitalized COVID-19 appears to be the consequence of the immunological response and pathological sequelae rather than by the viral load. These patients often require intubation and ventilation because of lung consolidation and restricted oxygen saturation. Some authors have suggested that the expiratory phase of respiration is mainly affected by sarbecovirus infection with obstructed alveoli.[4] Along with respiratory distress and pneumonia, other associated clinical manifestations that have occurred are pneumothorax and pneumomediastinum, as our case series highlights.

Pneumothorax has been reported as a complication of central venous line insertion with an incidence of 0% to 6.6%, especially

Mayo Clin Proc Inn Qual Out ■ XXX 2021;5(5):827-834 ■ https://doi.org/10.1016/j.mayocpiqo.2021.05.009
www.mcpiqojournal.org

TABLE 1. Patient Demographic Characteristics, Main Findings, and Outcomes[a,b]

Patient no.	Age (y)/ gender	Comorbidities	Baseline creatinine level (mg/dL)	Medical treatment of COVID-19
1	35/M	CHF	1.17	Remdesivir, methylprednisolone
2	23/F	CHF	0.80	Remdesivir, convalescent plasma
3	67/M	CHF, HTN	1.08	Remdesivir, vancomycin, cefepime, ceftriaxone
4	65/M	DM, HLD, HTN	1.49	Blinded sarilumab or placebo, methylprednisolone, ceftriaxone
5	62/M	CHF, DM, HLD, HTN	1.34	Hydroxychloroquine, lopinavir/ritonavir, convalescent plasma, piperacillin/tazobactam
6	76/M	CAD, CHF, DM, HLD, HTN	1.59	Remdesivir, methylprednisolone, convalescent plasma
7	75/M	HLD	0.66	Methylprednisolone, hydroxychloroquine, vancomycin, cefepime, azithromycin
8	69/F	DM, HLD, HTN	1.27	Methylprednisolone, vancomycin, piperacillin/tazobactam, ciprofloxacin, cefepime
9	36/M	None	0.99	Methylprednisolone, hydroxychloroquine, piperacillin/ tazobactam, vancomycin, cefepime

[a]CAD, coronary artery disease; CHF, congestive heart failure; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; F, female; HLD, hyperlipidemia; HTN, hypertension; M, male.
[b]SI conversion factor: To convert to mg/dL values to mmol/L, multiply by 0.0259.

in emergency insertions, using large catheters and multiple needle passes.[2] Most studies have found a predominance with subclavian vein cannulation, while other studies have found internal jugular vein access to be associated with developing pneumothorax.[2,5-7] A Canadian study from 2002 to 2015 found a 1.7% incidence of pneumothorax.[8] In the present study, we found no consistent association between the laterality of the pneumothorax or pneumomediastinum and the central line site in patients with COVID-19, with the condition occurring ipsilateral or contralateral to the central line site, bilateral, or in the absence of a central line.

Pneumothorax and spontaneous pneumomediastinum has been reported to be associated with the original severe acute respiratory syndrome (caused by SARS-CoV-1)[9] as well as COVID-19 (caused by SARS-CoV-2). For example, in a case series of 75 patient hospitalized with SARS-CoV-1, 9 (12%) developed spontaneous pneumomediastinum that similarly appeared to lack correlation to intubation or positive-pressure ventilation. One study reported an incidence of spontaneous pneumothorax in SARS-CoV-1 of 1.7%, with secondary pneumothorax developing in patients receiving mechanical ventilation or having venous catheters placed close to the pleura.[10] These cases were associated with the severity of the inflammatory response to the disease. A study by Chen et al[11] reported pneumothorax in 1% in an early case series of 99 patients with COVID-19. Case reports of COVID-19 patients have documented pneumothorax postintubation as well as the development of mediastinal emphysema and pneumothorax.[12] Pneumothorax may be provoked by barotrauma, but there have been cases of pneumothorax reported in COVID-19 patients without any history of mechanical ventilation[13,14] and our system protocols promote lung protective ventilation. "Spontaneous" cases of pneumothorax and pneumomediastinum in the setting of COVID-19 may be due to the severity of alveolar damage and inflammation and alveolar wall rupture leading to pneumothorax and pneumomediastinum, similar to that reported in SARS-CoV-1.[9] This may further our understanding of the pathophysiologic trigger of spontaneous pneumomediastinum as well,[15] as there appears to be an under-recognized viral predisposition.

We observed patients with COVID-19 developing pneumothorax and/or pneumomediastinum in the absence of barotrauma. When patients with COVID-19 and acute respiratory distress syndrome fail self-proning or

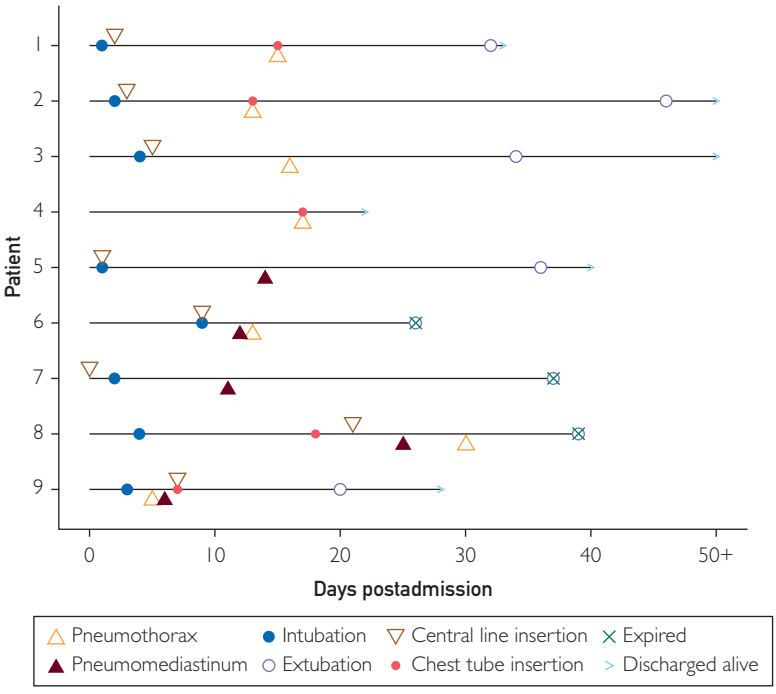

FIGURE 3. Timeline of events.

noninvasive ventilation, care must be taken to maintain lung protective mechanical ventilation with adequately low positive end-expiratory pressure, peek alveolar pressure, and volume-limited ventilation to minimize secondary insult to mitigate this risk of

TABLE 2. Main Findings: Laterality of Pneumothorax, Pneumomediastinum, and Central Line Status and Association With Clinical Severity and Outcomes[a]

Patient no.	Type and laterality	Site of an antecedent central line or attempt	Intubated	Chest tube (postevent)	VV-ECMO	Days from pneumothorax/ pneumomediastinum to discharge or death	Survived to discharge
1	Right apical pneumothorax	Right internal jugular	Yes	Yes	No	15	Yes
2	Bilateral pneumothorax	Right internal jugular	Yes	Yes	Yes	48	Yes
3	Right pneumothorax	Left internal jugular	Yes	No	No	49	Yes
4	Left pneumothorax	None	No	Yes	No	5	Yes
5	Bilateral pneumomediastinum	Left subclavian	Yes	No	No	26	Yes
6	Right pneumothorax, left pneumomediastinum	Right internal jugular	Yes	No	No	17	No
7	Right pneumomediastinum	Right basilic PICC	Yes	No	No	26	No
8	Left pneumothorax, pneumomediastinum	Right basilic PICC	Yes	Yes[c]	No	15	No
9	Left pneumothorax, pneumomediastinum	2 PIV[b]	Yes	Yes	No	23	Yes

[a]PICC, peripherally inserted central catheter; PIV, peripheral intravenous catheter; VV-ECMO, veno-venous extracorporeal membrane oxygenation.
[b]Post pneumothorax received left femoral venous catheter, removed and changed 4 d later to right external jugular vein central line; no technical difficulties described.
[c]Left pneumocath chest tube was placed for pleural effusion 3 d before right basilic PICC line, 7 d before pneumomediastinum, and 12 d before left pneumothorax, and was maintained given events.

Mayo Clin Proc Inn Qual Out ■ XXX 2021;5(5):827-834 ■ https://doi.org/10.1016/j.mayocpiqo.2021.05.009
www.mcpiqojournal.org

barotrauma-induced pneumothorax or pneumomediastinum from developing in patients already predisposed to pneumothorax and pneumomediastinum. When present, central line placement and mechanical ventilation were the only predisposing factors aside from COVID-19 infection to developing pneumothorax or pneumomediastinum. Discordant laterality from needle access and a long median lag time of 10 days from central line placement to the development of pneumothorax in our cohort renders iatrogenic line–related causes at most a minor risk factor. We therefore propose that the disease affecting peripheral pneumocytes may play a role and needs further research. A limitation of this present review is that the number of cases is inadequate for a case-control study to adequately explore ventilator settings as a potential confounder. Nevertheless, we have continued to encounter spontaneous pneumothorax and pneumomediastinum in other patients since this analysis, and we are confident that this is not wholly explained by barotrauma alone.

CONCLUSION

COVID-19 is associated with an intrinsic risk of pneumothorax and pneumomediastinum, and cannot be attributed to iatrogenic causes such as barotrauma or needle-injury alone. Barotrauma does not fully explain all pneumothorax and pneumomediastinum events as some proceeded or occurred in the complete absence of mechanical ventilation. Needle-injury cannot explain all pneumothorax and pneumomediastinum events as some included unilateral pneumothorax contralateral to central line placement, events occurred in the presence of only PICC lines, and even occurred without any central line attempt. We hypothesize that the hyperinflammation of COVID-19, coupled with the viral tropism that includes avid involvement of peripheral lung pneumocytes, induces a predisposition to peripheral bronchoalveolar connection and viral hyperinflammatory-triggered pneumothorax and pneumomediastinum. An admixture of COVID-19–related pneumothoraces and pneumomediastinum that includes both spontaneous and nonspontaneous causes is likely.

The signal from this formal, initial, retrospective analysis merits additional investigation. Given the global COVID-19 pandemic and the shortened time horizons, we aim to raise awareness among scientists, clinicians, and caretakers to keep pneumothoraces and pneumomediastinum in the differential diagnosis when assessing patients diagnosed with COVID-19.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **COVID-19**, coronavirus disease 2019; **PICC**, peripherally inserted central catheter; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus 2

Grant Support: Study-related expenses have been covered by the not-for-profit research institution.

Potential Competing Interests: The authors report no competing interests.

Correspondence: Address to Robert L. Gottlieb, MD, PhD, Center for Advanced Heart and Lung Disease, Baylor Scott & White Health, 3410 Worth St, Suite 250, Dallas, TX 75246 (robert.gottlieb@bswhealth.org).

ORCID

Aayla K. Jamil: https://orcid.org/0000-0001-9471-3383; Amit Alam: https://orcid.org/0000-0002-3040-3957; Ronnie M. Youssef: https://orcid.org/0000-0002-8460-5810; Johanna S. van Zyl: https://orcid.org/0000-0003-4205-9214; Robert L. Gottlieb: https://orcid.org/0000-0001-8376-8709

REFERENCES

1. Mallick T, Dinesh A, Engdahl R, Sabado M. COVID-19 complicated by spontaneous pneumothorax. *Cureus*. 2020;12(7):e9104.
2. Kaiser CW, Koornick AR, Smith N, Soroff HS. Choice of route for central venous cannulation: subclavian or internal jugular vein? A prospective randomized study. *J Surg Oncol*. 1981;17(4):345-354.
3. Pneumothorax. *Radiopaedia*, https://radiopaedia.org/articles/pneumothorax?lang=us. Accessed May 14, 2020.
4. Gralinski LE, Baric RS. Molecular pathology of emerging coronavirus infections. *J Pathol*. 2015;235(2):185-195.
5. Miller JA, Singireddy S, Maldjian P, Baker SR. A reevaluation of the radiographically detectable complications of percutaneous venous access lines inserted by four subcutaneous approaches. *Am Surg*. 1999;65(2):125-130.
6. Eisen LA, Narasimhan M, Berger JS, Mayo PH, Rosen MJ, Schneider RF. Mechanical complications of central venous catheters. *J Intensive Care Med*. 2006;21(1):40-46.
7. Kusminsky RE. Complications of central venous catheterization. *J Am Coll Surg*. 2007;204(4):681-696.

8. Reeson M, Forster A, van Walraven C. Incidence and trends of central line associated pneumothorax using radiograph report text search versus administrative database codes. *BMJ Qual Saf*. 2018;27(12):982-988.
9. Peiris JS, Chu CM, Cheng VC, et al; HKU/UCH SARS Study Group. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet*. 2003;361(9371):1767-1772.
10. Sihoe AD, Wong RH, Lee AT, et al. Severe acute respiratory syndrome complicated by spontaneous pneumothorax. *Chest*. 2004;125(6):2345-2351.
11. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020; 395(10223):507-513.
12. Khan MI. Post-intubation pneumomediastinum and pneumothorax—background COVID19 pneumonia. Radiopaedia. https://radiopaedia.org/cases/post-intubation-pneumomediastinum-and-pneumothorax-background-covid-19-pneumonia?lang=us. Accessed April 24, 2020.
13. Sun R, Liu H, Wang X. Mediastinal emphysema, giant bulla, and pneumothorax developed during the course of COVID-19 pneumonia. *Korean J Radiol*. 2020;21:541-544.
14. Vega JM, Gordo ML, Tascón AD, Vélez SO. Pneumomediastinum and spontaneous pneumothorax as an extrapulmonary complication of COVID-19 disease. *Emerg Radiol*. 2020;27(6): 727-730.
15. Park SJ, Park JY, Jung J, Park SY. Clinical manifestations of spontaneous pneumomediastinum. *Korean J Thorac Cardiovasc Surg*. 2016;49(4):287-291.