The incidence, clinical characteristics, and outcomes of pneumothorax in hospitalized COVID-19 patients: A systematic review

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ABSTRACT

Background: Pneumothorax has been frequently described as a complication of COVID-19 infections.

Objective: In this systematic review, we describe the incidence, clinical characteristics, and outcomes of COVID-19-related pneumothorax.

Methods: Studies were identified through MEDLINE, Pubmed, and Google Scholar databases using keywords of "COVID-19," "SARS-CoV-2," "pneumothorax," "pneumomediastinum," and "barotrauma" from January 1st, 2020 to January 30th, 2021.

Results: Among the nine observational studies, the incidence of pneumothorax is low at 0.3% in hospitalized COVID-19 patients. However, the incidence of pneumothorax increases to 12.8−23.8% in those requiring invasive mechanical ventilation (IMV) with a high mortality rate up to 100%. COVID-19-related pneumothorax tends to be unilateral and right-sided. Age, pre-existing lung diseases, and active smoking status are not shown to be risk factors. The time to pneumothorax diagnosis is around 9.0−19.6 days from admission and 5.4 days after IMV initiation. COVID-19-related pneumothoraces are associated with prolonged hospitalization, increased likelihood of ICU admission and death, especially among the elderly.

Conclusion: COVID-19-related pneumothorax likely signify greater disease severity. With the high variability of COVID-19-related pneumothorax incidence described, a well-designed study is required to better assess the significance of COVID-19-related pneumothorax.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is known to cause coronavirus disease 2019 (COVID-19), resulting in the ongoing global pandemic.[1] COVID-19 presents with a wide variety of respiratory complications that range from self-limiting upper respiratory tract infection to acute respiratory failure from acute respiratory distress syndrome (ARDS) and pleural diseases such as pleural effusion and pneumothorax.[2] Pneumothorax is a common complication of invasive mechanical ventilation (IMV) in critically ill patients, with reported incidence up to 15%.[3] Additionally, the overall incidence of hospitalized COVID-19 patients requiring IMV is around 17 to 42% with increasing frequency in non-survivors (57−59%) compared to survivors (1−15%).[4,5] Generally, critically ill patients with pneumothorax experienced a 2-fold increase in the risk of ICU and hospital mortality than those without pneumothorax.[6−8] Among those who develop pneumothoraces, the mortality and recovery rate

are poor in the setting of IMV, septic shock, and the evidence of tension physiology compared to those with procedure-related pneumothorax.[9] The significance of pneumothorax in COVID-19 infections, initially limited to several case reports/series, has been increasingly described and analyzed in multiple observational studies during the ongoing pandemic. A postmortem examination of 91 deceased COVID-19 patients observed that ARDS was responsible for 80.2% of death, followed by cardiac injury (34.1%), hepatic and renal injury (31.9%), and pneumothorax (1.1%).[10] The purpose of our systematic review is to discuss the incidence, characteristics, and outcomes of pneumothorax in patients with COVID-19 infections based on the current evidence available in the medical literature.

Methods

This systematic review was conducted and presented in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Ethical approval and informed consent were not required for this study as it was a systematic review of previously published studies.

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Search

A literature search was performed through MEDLINE, Pubmed, and Google Scholar databases using keywords of "coronavirus disease 2019 (COVID-19)," "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)," "pneumothorax," "pneumomediastinum," and "barotrauma" from January 1st, 2020 to January 30th, 2021. All specified keywords were combined using the "OR" operator and "AND" operator for searching the literature. Moreover, to detect additional studies, any cited references were reviewed to identify relevant literature that met our inclusion criteria.

Inclusion criteria

Articles that met the following criteria were included in our study: 1) studies that described pneumothorax on chest imaging [using either chest radiography or chest computed tomography (CT)] in hospitalized adults and children due to COVID-19 infections; 2) observational studies, including cohort, case-control, and cross-sectional studies; 3) studies written in English language; 4) studies in which diagnosis of COVID-19 infections was made via real-time reverse transcription-polymerase chain reaction (RT-PCR) from nasopharyngeal or oropharyngeal swab; 5) published between January 1st, 2020 to January 30th, 2021 in a peer-review journal; and 6) studies addressing at least one of the following issues: a) incidence, b) risk factors, c) onset, and/or d) outcome of COVID-19-related pneumothorax.

Exclusion criteria

The exclusion criteria were specified as follows: 1) studies with less than 40 patients (defined as case series) and/or case reports; 2) studies that only reported signs of barotraumas such as pneumomediastinum and subcutaneous emphysema in the absence of pneumothorax in hospitalized COVID-19 patients; and 3) studies describing iatrogenic causes (e.g., from central venous catheter insertion) of pneumothorax in COVID-19 patients.

Data collection

Two researchers (W.C. and B.S.) independently screened the titles and abstracts, and reviewed the full texts of articles to identify studies that evaluated the incidence, risk factors, onset, and outcomes of pneumothorax in patients with COVID-19 infections. Any disagreements were resolved by discussion or with a third researcher (K.H.). The extracted data from full texts of included studies was added into a standardized Excel (Microsoft Corporation) form. All included studies were analyzed for: study design (e.g., retrospective or prospective; cross-sectional, case-control, or cohort; single- or multi-center); study type (clinical or radiologic characteristic); month/year; country; number of patients; patient type (hospitalized or intensive care unit [ICU]); incidence of pneumothorax; age of the patient (e.g., mean +/- standard deviation or median [interquartile range]); gender; the location of pneumothorax; chest tube requirement; co-existing pneumomediastinum; time to pneumothorax development from initial admission; co-existing lung diseases; smoking status; IMV; mortality; and requirement of ECMO support were presented in Table 1. In Table 4, information obtained were ventilator parameters (peak inspiratory pressure, plateau pressure, positive end-expiratory pressure [PEEP], tidal volume [TV]), baseline (respiratory rate [RR], partial pressure of oxygen/fraction of inspired oxygen [PaO2/FiO2], partial pressure of carbon dioxide [PaCO2]) and hospitalization respiratory variables (peak respiratory rate, lowest PaO2/FiO2, highest PaCO2), among COVID-19 patients requiring IMV. We also included observational studies (40 and more patients) that described pneumothoraces among patients with severe acute respiratory syndrome

(SARS) and middle east respiratory syndrome (MERS) infections that were available in the current literature for comparison (Table 3).

Quality assessment

Two researchers performed quality assessment using the Newcastle-Ottawa Scale (NOS), containing nine items, for the cohort and case-control studies. In NOS, the total score ranged from 0 to 9 and was categorized into three groups: Low quality "0−3″, moderate quality "4−6″, and high quality "7−9″.[11] For cross-sectional studies, the Prevalence Critical Appraisal Instrument (PCAI), containing 10 items was used, and the total score ranged from 1 to 10.[12] During the quality assessment of the included studies, any disagreements were resolved by discussion or a third researcher.

Results

Study selection

A total of 200 studies were identified in the initial search. After removal of duplicates (n = 80) and those not meeting the inclusion criteria (by title, abstract, and full text: n = 111), nine eligible articles (including five cohorts, two cross-sectional and case-control studies) were included in this review (Fig. 1).

Study characteristics

Table 1 present the characteristics of the included studies. All nine observational studies describing pneumothorax in hospitalized adults or adults and children with COVID-19 infections were retrospective in nature. Out of the nine observational studies, 55.6% (5/9) were retrospective cohort studies, 22.2% (2/9) were case-control studies, and the remaining studies were cross-sectional studies. Among the nine observational studies included in our review, 44.4% (4/9) were performed in the USA, 33.3% (3/9) were performed in China, and the remainder in Spain and the UK. The majority of observational studies [77.8% (7/9)] were clinical studies (primarily discussing the clinical characteristics of COVID-19 patients), and the remaining observational studies by Ding et al. and McGuinness et al. were radiological studies (primarily assessing the radiological features of COVID-19 patients).[2,13] The mean and median age of COVID-19 patients fell between the fifth to seventh decade of life, with a male predominance in the majority of studies. The two case-control studies by McGuinness et al. and Miro et al. had quality scores of seven and six, respectively (Table 2).[13,14] In the five cohort studies, Ekanem et al. and Martinelli et al. had quality scores of eight and seven, respectively.[15,16] However, Cates et al., Ding et al., and Guo et al. had quality scores of five, individually.[2,17,18] Among the two cross-sectional studies by Wang et al. and Zantah et al., quality scores of six were reported.[19,20]

Incidence of COVID-19-related pneumothorax

In hospitalized patients with COVID-19 infections, the overall incidence of pneumothoraces reported in hospitalized COVID-19 patients was 0.3% (242/79,510) in nine observational studies included in our review (Table 1). However, according to a single-center, case-control radiological study by McGuinness et al., which was the only study assessing 601 critically ill COVID-19 patients who required IMV, the incidence of pneumothorax increased up to 12.8%.[13] The largest study included was a multi-center, case-control study by Miro et al. conducted in Spain that described 71,904 COVID-19 patients who were initially assessed in the emergency departments (ED) with a reported incidence of pneumothoraces at 0.06%.[14] No COVID-19 patients required IMV prior to the diagnosis of pneumothorax. The second-largest study was a multi-center, retrospective cohort study by Cates

Table 1
Summary and characteristics of nine observational studies for COVID-19 patients with pneumothoraces.

Author	Study design	Study type	Month, year	Country	Patients (N)	Patient type	Incidence PTX (%)	Age (Y) Mean +/- SD, Median (IQR)	Male, N (%)
COVID-19 Observational Studies									
Cates et al.[17]	Retrospective Cohort, Multi-center	Clinical Characteristics COVID-19	October 2020	USA	3948	Hospitalized, Adults	0.6	70.0 (61−77)	3710 (94)
Ding et al.[2]	Retrospective Cohort, Single-center	Radiologic Characteristics COVID-19	April 2020	China	112	Hospitalized, Adults/Children	3.6	55.8 +/- 16.1	51 (45.5)
Ekanem et al.[15]	Retrospective Cohort, Multi-center	Clinical Characteristics COVID-19	January 2021	USA	1619	Hospitalized, Adults	1.4	60.0 (47.0−67.0)*	18 (81.2)*
Guo et al.[18]	Retrospective Cohort, Multi-center	Clinical Characteristics COVID-19	May 2020	China	105	Hospitalized, Adults	1.0	67.0 (64−74)	48 (45.7)
Martinelli et al.[16]	Retrospective Cohort, Multi-center	Clinical Characteristics COVID-19	November 2020	UK	71	Hospitalized, Adults	84.5	NR	48 (77.4)*
McGuinness et al.[13]	Case-Control, Single-center	Radiologic Characteristics COVID-19	June 2020	USA	601	ICU, Adults	12.8	63.0 +/- 2.0	426 (70.9)
Miro et al.[14]	Case-Control, Multi-center	Clinical Characteristics COVID-19	January 2021	Spain	71,904	Hospitalized, Adults	0.06	66 (47−74)*	29 (72.5)*
Wang et al.[19]	Cross-Sectional, Single-center	Clinical Characteristics COVID-19	October 2020	China	248	Hospitalized, Adults	2.0	64.2 +/- 9.1*	5 (100)*
Zantah et al.[20]	Cross-Sectional, Single-center	Clinical Characteristics COVID-19	September 2020	USA	902	Hospitalized, Adults	0.6	59.5 +/- 14.2*	2 (33.3)*

Author	Location* (%)	Chest Tube* (%)	Pneumomediastinum (%)	Time to PTX (D) Mean +/- SD, Median (IQR)	Lung Disease (%)	Smoking Status (%)	IMV (%)	Mortality (%)	ECMO* (%)
COVID-19 Observational Studies									
Cates et al.[17]	NR	NR	NR	NR	Asthma/ COPD (30.8)	NR	NR	21.0	NR
Ding et al.[2]	NR	NR	NR	10 <	NR	NR	NR	NR	NR
Ekanem et al.[15]	NR	72.7	NR	9.0 (4.0 - 15.0)	Asthma/ COPD (18.2)	13.6*	40.9*	36.4*	9.1
Guo et al.[18]	NR	NR	NR	NR	Unspecified (8.6)	12.4	7.6	2.9	NR
Martinelli et al.[16]	NR	51.6	9.7*	NR	Asthma/ Bronchiectasis/ COPD (30)*	29.0*	45.0*	88.3*	20.0
McGuinness et al.[13]	Right (45.5), Left (40.2), Bilateral (14.3)	NR	10	5.4 (0−41) [IMV]	NR	33.7*	100*	57.0	NR
Miro et al.[14]	Right (81.1), Left (18.9)	72.5	16.2*	NR	Asthma/ COPD (30)	10.0*	NR	NR	NR
Wang et al.[19]	Right (60), Bilateral (40)	60.0	20*	19.6 +/- 10.2	NR	NR	100*	80.0*	20
Zantah et al.[20]	Bilateral (50), Left (33.3), Right (16.7)	100	NR	11 +/- 5.9	ILD (16.7)*	NR	66.7	66.7*	16.7

* Among COVID-19 patients who develop pneumothoraces.

Abbreviations: COPD: chronic obstructive pulmonary disease, ECMO: extracorporeal membrane oxygenation, ICU: intensive care unit, ILD: interstitial lung disease, IMV: invasive mechanical ventilation, IQR: interquartile range, N: number of patients, NR: non-reported, PTX: pneumothorax, SD: standard deviations, Y: years.
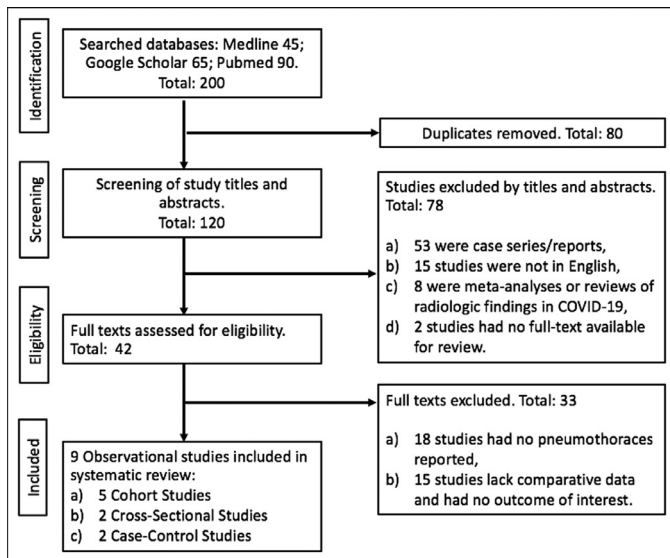
Fig. 1. Flowchart for studies selected in review of COVID-19 patients with pneumothorax.

et al. that assessed 3948 COVID-19 patients treated in the veteran affairs (VA) hospitals across the USA with a reported incidence of pneumothorax at 0.6%.[17] The number of COVID-19 patients requiring IMV was not described, although 36.5% of them required ICU admission. The third-largest study was by Ekanem et al., describing 1619 COVID-19 patients with an incidence of pneumothorax at 1.4%, and 40.9% of COVID-19 patients were mechanically ventilated before the diagnosis of pneumothorax.[15] A single-center study by Wang et al. revealed that although the incidence of pneumothorax was low at 2.0% (5/248) among hospitalized COVID-19 patients, all patients who developed pneumothoraces were critically ill [23.8% (5/21)] and universally required mechanically ventilated (100%).[19]

COVID-19-related pneumothorax characteristics

Five observational studies (Table 1) exclusively described the gender of hospitalized COVID-19 patients who developed pneumothoraces in which most were male [76.7% (102/133)].[14−16,19,20] Among the four observational studies describing the locality of pneumothorax, COVID-19-related pneumothorax was commonly unilateral and predominantly right-sided in 56.9% (74/130) of cases.[13,14,19,20] Moreover, chest tube insertion was required in up to 64.0% (87/136) of COVID-

19 patients who developed pneumothoraces for the management of pneumothoraces according to five observational studies.[14−16,19,20] According to three observational studies, less than 20% of hospitalized COVID-19 patients developed pneumomediastinum concurrently with pneumothoraces (Table 1).[14,16,19]

Risk factors for COVID-19-related pneumothorax

According to the nine observational studies, the mean/median age groups of COVID-19 patients were between 55 and 70 years of age. About 66.7% (6/9) of observational studies described the presence of pre-existing lung diseases such as asthma, bronchiectasis, chronic obstructive pulmonary disease (COPD), and interstitial lung disease (ILD) among COVID-19 patients (Table 1). However, most COVID-19 patients and even those diagnosed with pneumothoraces did not have pre-existing lung diseases, with a reported frequency of less than 30%. Moreover, four observational studies revealed that less than 34% of COVID-19 patients diagnosed with pneumothoraces were smokers.[13−16] Two retrospective observational studies (Table 4) assessed the different respiratory variables among mechanically ventilated COVID-19 patients who developed pneumothoraces in which ventilator parameters involving peak inspiratory pressure (range 23.7−24.3 cmH2O), plateau pressure (less than 30 cmH2O), PEEP (range 10.6−10.7 cmH2O), TV [mean 437.5 ml (5.4 ml/kg)] were not elevated.[19,20] However, elevated baseline RR was observed in few studies included. A cross-sectional single-center study by Wang et al. observed that the mean baseline RR for COVID-19 patients diagnosed with pneumothoraces was 25.3 +/- 9.7 breaths per min.[19] A case-control study by Miro et al. reported that the median baseline RR among COVID-19 patients diagnosed with pneumothoraces was 24 (IQR 20−30) breaths per min.[14]

Onset of COVID-19-related pneumothorax

In 55.6% (5/9) of observational studies, the overall time to pneumothorax diagnosis was between 9.0−19.6 days from admission and 5.4 days after IMV (Table 1). A study by Ding et al. describing the radiological characteristics of COVID-19 patients reported that pneumothoraces occur with increasing frequency around ten days and more from the first onset of COVID-19 symptoms.[2]

Outcomes of COVID-19-related pneumothorax

Four observational studies assessed the mortality rate among COVID-19 patients diagnosed with pneumothoraces (Table 1). The overall mortality rate of COVID-19 patients diagnosed with

Table 2
The table shows the results of Newcastle-Ottawa Scale (NOS)[11] performed for seven cohorts and two case-control studies.

Author(s)	Case-Control / Cohort Studies	Selection				Comparability	Outcome / Exposure			Total Of 9 Scores
		1	2	3	4	(**)	1	2	3	
McGuinness et al.[13]	Case-Control	*	N/A	*	*	*	*	*	*	7
Miro et al.[14]	Case-Control	*	*	*	*	*	*	N/A	N/A	6
Cates et al.[17]	Cohort	N/A	N/A	*	*	N/A	*	*	*	5
Ding et al.[2]	Cohort	N/A	N/A	*	*	N/A	*	*	*	5
Ekanem et al.[15]	Cohort	*	*	*	*	*	*	*	*	8
Guo et al.[18]	Cohort	N/A	N/A	*	*	N/A	*	*	*	5
Martinelli et al.[16]	Cohort	*	*	*	*	N/A	*	*	*	7

1. Representatives of the exposed cohorts. / Is the case definition adequate ?.
2. Selection of the non-exposed cohorts. / Representativeness of the cases.
3. Ascertainment of exposure. / Selection of controls.
4. The outcome of interest was not present at the start of the study./ Definition of controls.
a) Assessment of the outcome. / Assessment of the exposure.
b) Enough follow-up for the outcome. / Same method of ascertainment for cases and controls.
c) Adequacy of follow-up. / Non-response rate.
Abbreviations: N/A: non-available.

pneumothoraces was up to 74.2% (69/93).[15,16,19,20] A multi-center, retrospective cohort study by Martinelli et al. reported the highest mortality rate among COVID-19 patients diagnosed with pneumothoraces at 88.3%. Although there was no difference in gender and IMV requirement among survivors and non-survivors, COVID-19 patients with pneumothoraces who were acidotic and aged 70 and older had a higher mortality rate observed during subgroup analysis ($P < 0.05$).[16] A cross-sectional study by Wang et al. reported the second-highest mortality rate among COVID-19 patients diagnosed with pneumothoraces at 80.0%.[19] In addition, the use of extracorporeal membrane oxygenation (ECMO) was reportedly used in a total of 16 COVID-19 patients diagnosed with pneumothoraces based on four observational studies included (Table 1).[15,16,19,20] All COVID-19 patients with pneumothoraces that required ECMO support were intubated and mechanically ventilated. Studies by Martinelli et al. and Wang et al. reported the highest requirement of ECMO support among COVID-19 patients diagnosed with pneumothoraces.[16,19]

Discussion

The incidence of pneumothorax is low at 0.3% among the nine studies included in our review but increases up to 12.8−23.8% in critically ill COVID-19 patients requiring IMV. COVID-19-related pneumothorax, when present, tends to be unilateral and right-sided. Age, pre-existing lung diseases, and active smoking status are not risk factors for developing pneumothoraces. Although COVID-19 patients who developed pneumothoraces have a higher baseline respiratory rate, ventilator parameters (e.g., peak inspiratory pressure, plateau pressure, PEEP, and TV) did not alter their frequency of pneumothorax diagnosis among mechanically ventilated COVID-19 patients. The onset of COVID-19-related pneumothorax is around 9.0−19.6 days from admission and 5.4 days after IMV initiation. COVID-19-related pneumothoraces are associated with prolonged hospitalization, increased likelihood of ICU admission and death, especially among the elderly.

The increase in the overall incidence of COVID-19-related pneumothorax from 0.3% to 12.8% among COVID-19 patients requiring IMV observed in our review could be due to the greater severity of illness. McGuinness et al. was the only study that assessed 601 critically ill COVID-19 patients in which all of them required IMV with a mortality rate up to 57.0% (343/601), signifying a severe course of COVID-19 disease that likely explains the high incidence rate of 12.8% (77/608) observed.[13] Furthermore, the incidence of pneumothoraces was higher in mechanically ventilated COVID-19 patients (12.8% versus 0.5%; $P < 0.001$) than mechanically ventilated non-COVID-19 patients over the same study duration, indicative of severe COVID-19 disease among the enrolled patients. Martinelli et al. reported a high incidence of 84.5% of pneumothoraces in their study of 71 hospitalized COVID-19 patients. This discordance in pneumothorax incidence could be due to the small sample size of the study where 69% (49/71) of COVID-19 patients enrolled were critically ill and required either NIMV, IMV, and ECMO support with a high mortality rate of 88.3% (53/60) among those diagnosed with pneumothoraces.[16] Although 100% of COVID-19 patients who developed pneumothoraces were critically ill and required IMV in the study by Wang et al., many [91.5% (227/248)] COVID-19 patients enrolled did not require ICU admission. When taking into account critically ill COVID-19 patients, 23.8% (5/21) developed pneumothoraces indicating greater disease severity with mortality rates of 80.0% among those diagnosed.[19] These findings demonstrate that COVID-19 disease severity likely plays a vital role in explaining the high incidence of pneumothorax reported, consistent with greater IMV requirements and poor mortality rates observed.

The largest study among VA patients compared 3948 COVID-19 patients with 5,4533 influenza patients over the same timeframe.[17] In that study, a significant higher proportion of COVID-19 patients

developed pneumothoraces (0.6% versus 0.2%; $P < 0.001$) than influenza A patients. According to six observational studies among SARS patients, the incidence of pneumothorax was 3.4% (31/921) [Table 3]. However, two observational studies by Kao et al. and Lew et al. reported a high incidence of pneumothorax at 12.2% and 17.4%, respectively. In both studies, the majority of critically ill COVID-19 patients required IMV and had a high mortality rate up to 41%.[21,22] Furthermore, a case-control study by Chu et al. observed that a more significant proportion of SARS patients with pneumothoraces required IMV (38.5% versus 10.1%; $P = 0.015$).[23] Compared to MERS patients, the high incidence of pneumothoraces at 11.2% (14/125), observed in two observational studies were likely secondary to the severity of illness in which 54.5−70% required IMV and reported mortality rate was high at 52.7−60%.[24,25] Furthermore, a retrospective cohort study by Das et al. assessed mortality among MERS patients where a significant proportion of non-survivors developed pneumothoraces than survivors (47.4% versus 0.0%; $P = 0.001$) that signifies a more severe course of infection.[25]

Although most COVID-19 patients diagnosed with pneumothoraces are male, according to our review, a case-control study by Miro et al. revealed no gender difference (72.5% vs. 51.3%; $P > 0.05$) among those diagnosed pneumothoraces than those without pneumothoraces.[14] Moreover, Miro et al. observed that COVID-19-related pneumothorax was 3.85-fold more likely to occur on the right side among COVID-19 patients and at higher frequency (81.1% versus 52.7%; $P < 0.001$) compared to non-COVID-19 patients.[14] Furthermore, pneumomediastinum has been increasingly described in COVID-19 patients who are not mechanically ventilated or have a concurrent pneumothorax diagnosis.[16,26−30] This radiologic finding was also observed among the observational studies of SARS and case series of influenza A patients who developed pneumothoraces without a concurrent pneumomediastinum diagnosis, regardless of IMV requirement.[22,31−35] Nevertheless, pneumomediastinum may indicate the presence of severe underlying lung pathology. No difference in the incidence of concomitant pneumomediastinum diagnosis between COVID-19 patients with pneumothoraces and non-COVID-19 patients with pneumothoraces (16.2% vs. 3.2%; $P > 0.05$) according to a case-control study by Miro et al.[14] Other occult signs of pneumothorax are subcutaneous emphysema; however, this may not be clinically apparent, especially in the absence of co-existing pneumomediastinum. Up to 56% of hospitalized COVID-19 patients with concomitant pneumomediastinum and pneumothorax developed subcutaneous emphysema as oppose to 30% in those with solely a radiologic finding of pneumothorax.[36]

A multi-center, retrospective cohort study by Guo et al. assessed 105 elderly COVID-19 patients aged between 60 and 74 years old, and those aged 75 years and older observed no difference in the incidence of pneumothoraces.[18] Although chronic lung diseases such as asthma, COPD, and ILD, are known predisposing factors for developing pneumothorax in critically ill patients, even in the absence of IMV, our review did not show any correlation between pre-existing lung diseases and the risk of developing pneumothorax among COVID-19 patients.[37] Miro et al. demonstrated that pre-existing lung diseases in non-mechanically ventilated COVID-19 patients diagnosed with pneumothoraces did not predispose to the development of pneumothorax (30.0% vs. 15.1%; $P > 0.05$).[14] Cates et al. even demonstrated that COVID-19 patients were 3.5-fold more likely to develop pneumothorax than influenza patients despite a greater amount of influenza patients suffering from pre-existing lung diseases (52.5% vs. 30.8%; $P < 0.001$) with lesser ICU admission requirement (17.6% vs. 36.5%; $P < 0.001$).[17] Similar results were noted among critically ill SARS patients by Kao et al. in which no difference in pre-existing lung diseases was noted among those who developed pneumothoraces and those who did not.[21] Two case-control observational studies by McGuinness et al. and Miro et al. reported no association between pneumothorax development in COVID-19 patients

Table 3
Summary and characteristics of six studies for SARS patients and two studies for MERS patients who developed pneumothoraces were also included.

Author	Study Design	Study Type	Month, Year	Country	Patients (N)	Patient Type	Incidence PTX (%)	Age (Y) Mean +/- SD, Median (IQR)	Male, N (%)
SARS Observational Studies									
Choi et al.[61]	Retrospective Cohort, Single-center	Clinical Characteristics SARS	November 2003	China	267	Hospitalized, Adults	2.2	39 (18−96)	104 (39)
Chu et al.[23]	Case-Control, Single-center	Clinical Characteristics SARS	June 2004	China	112	Hospitalized, Adults	4.5	38.8 +/- 12.7	46 (41.1)
Kao et al.[21]	Case-Control, Single-center	Clinical Characteristics SARS	June 2005	China	41	ICU, Adults	12.2	68.8 +/- 18.0*	4 (80)*
Lew et al.[22]	Retrospective Cohort, Single-center	Clinical Characteristics SARS	July 2003	Singapore	46	ICU, Adults	17.4	51 (20−78)	24 (52.2)
Sihoe et al.[35]	Cross-Sectional, Multi-center	Clinical Characteristics SARS	June 2004	China	356	Hospitalized, Adults	1.7	48 +/- 16.7*	4 (66.7)*
Wong et al.[62]	Cross-Sectional, Single-center	Radiologic Characteristics SARS	November 2004	China	99	Hospitalized, Adults	1	39.4 +/- 12.8	NR
MERS Observational Studies									
Das et al.[25]	Retrospective Cohort, Multi-center	Radiologic Characteristics/Outcome MERS	September 2015	Saudi Arabia	55	Hospitalized, Adults/Children	16.4	54.0 +/- 16.0	16 (29)
Saad et al.[24]	Retrospective Cohort, Single-center	Clinical Characteristics MERS	December 2014	Saudi Arabia	70	Hospitalized, Adults	7.1	62 (1−90)	46 (65.7)

Author	Location* (%)	Chest Tube* (%)	Pneumomediastinum (%)	Time to PTX (D) Mean +/- SD, Median (IQR)	Lung Disease (%)	Smoking Status (%)	IMV (%)	Mortality (%)	ECMO (%)
SARS Observational Studies									
Choi et al.[61]	NR	NR	100*	NR	NR	NR	0	12.0	NR
Chu et al.[23]	Bilateral (100)	100	100*	19.6 +/- 4.6	NR	NR	NR	12.5	NR
Kao et al.[21]	NR	NR	NR	8.0 +/- 4.4 [IMV]	Latent Tb (16.7)	NR	100*	41.0	NR
Lew et al.[22]	NR	NR	12.5*	NR	Asthma (4.4)	NR	100	10.1	NR
Sihoe et al.[35]	Bilateral (50), Right (33.3), Left (16.7)	66.7	50*	24.3 +/- 8.1	NR	NR	33.3*	33.3	NR
Wong et al.[62]	NR	NR	NR	NR	NR	NR	NR	NR	NR
MERS Observational Studies									
Das et al.[25]	NR	NR	NR	NR	NR	5.5	100*	34.5	NR
Saad et al.[24]	NR	NR	NR	NR	NR	12.9	60	60.0	NR

Abbreviations: ECMO: extracorporeal membrane oxygenation, ICU: intensive care unit, IMV: invasive mechanical ventilation, IQR: interquartile range, N: number of patients, NR: non-reported, PTX: pneumothorax, SD: standard deviations, TB: tuberculosis, Y: years.

who were smokers.[13,14] Miro et al. even observed that non-smokers were at a 5.5-fold increased risk of developing pneumothoraces. Compared to SARS patients, a case-control study by Chu et al. reported that no difference in smoking status was observed between patients who developed pneumothoraces and those that did not.[23] In light of the poor correlation between pre-existing lung diseases and active smoking status, pneumothorax should be considered a potential complication of hospitalized COVID-19 patients during the assessment of worsening respiratory symptoms even in the absence of pulmonary comorbidities.

In addition, IMV can be a lifesaving intervention in many critically ill COVID-19 patients, and in some cases, IMV was applied before the development of pneumothoraces (Table 1). However, similar to any other invasive interventions, it carries its own risk and complications that can lead to ventilator-induced lung injuries (VILI) such as volutrauma and barotrauma, especially in ARDS patients due to the overdistension of normal non-dependent lung regions with relatively higher compliance than dependent lung regions.[20,38] Although only two observational studies in our review described the respiratory variables involving peak inspiratory pressure, plateau pressure, PEEP, and TV among mechanically ventilated COVID-19 patients, these variables were not elevated.[19,20] A case series by Udi et al. observed that COVID-19 patients who developed barotrauma (e.g., pneumothorax, pneumomediastinum, and subcutaneous emphysema) had lower ventilator variables of peak inspiratory pressure, plateau pressure, and TV than those who did not develop barotrauma.[26] In a similar fashion, another case series by Abdallat et al. noted that critically ill COVID-19 patients receiving IMV experience a higher rate of barotrauma at a PEEP of 10−15 cmH20 as opposed to a PEEP of 15 cmH20 and more.[30] Several prospective studies by Anzueto et al., Boussarsar et al., and Weg et al. assessing critically ill non-COVID-19 patients with ARDS demonstrated that high peak inspiratory pressure, plateau pressure, and PEEP did not increase the risk of developing barotraumas despite prolonged ICU length of stay and shorten ventilator-free days.[6,39,40] Similarly, ARDS Network study showed a decrease in mortality of critically ill ARDS patients without affecting the incidence of barotraumas during low tidal volume ventilation.[41] Therefore, barotrauma in the form of pneumothorax is likely related to underlying lung disease severity than lung compliance and ventilator settings. Moreover, it is possible that tachypnea on admission signifies an increase in the respiratory effort to compensate for lung disease of greater severity and greater risk of developing auto-positive endexpiratory pressure (auto-PEEP) from insufficient expiratory time, contributing to pneumothorax development. This likely explains the high RR observed by Miro et al. that is associated with a 5.37-fold increased risk of developing pneumothoraces.[14] Compared to SARS patients, a case-control study by Kao et al. demonstrated that those who developed pneumothorax had higher respiratory rate on admission and more pronounced hypoxia with lower PaO2/FiO2 ratio and higher PaCO2 during hospitalization.[21] Furthermore, in that study, a high PaCO2 and lower PaO2/FiO2 ratio during hospitalization were suggested to indicate an increase in dead space and shunting from ventilation-perfusion mismatch, and diffusion impairment from severe respiratory disease that predisposes to the development of pneumothoraces. However, these parameters (lowest PaO2/FiO2 ratio and higher PaCO2) were not measured during the hospitalization of COVID-19 patients included in our review as all observational studies included were retrospective in nature (Table 4). Current guidelines recommend a low TV of 4−8 ml/kg (ideally 6 ml/kg) during IMV for management of critically ill COVID-19 patients. However, conflicting consensus exists on the use of a high PEEP strategy due to the low lung recruitment observed in COVID-19-induced ARDS.[42−44]

The pathophysiologic changes of COVID-19 infections that revolve around dysregulation of immune response with high inflammatory markers may play a role in developing pneumothorax and pneumomediastinum independent of ventilator-induced barotrauma (e.g.,

Table 4
Comparison of respiratory variables among mechanically ventilated COVID-19 and SARS patients who developed pneumothoraces.

Author	Average Ventilator Parameters				Baseline Mean			Hospitalization		
	Peak Inspiratory Pressure (cmH2O)	Plateau Pressure (cmH2O)	PEEP (cmH2O)	TV, ml (TV/kg, ml)	RR (breaths per min)	PaO2/FiO2	PaCO2 (mmHg)	Peak RR (breaths per min)	Lowest PaO2/FiO2	Highest PaCO2 (mmHg)
COVID-19 Observational Studies										
Wang et al.[19]	23.7 +/- 1.2	30.0 >	10.7 +/- 1.9	NR (5.4 +/- 0.3)	25.3 +/- 9.7	143.7 +/- 35.0	56.5 +/- 17.6	NR	NR	NR
Zantah et al.[20]	24.3 +/- 3.1	20.3 +/- 3.1	10.6 +/- 1.1	437.5 +/- 21.7 (NR)	NR	162.8 +/- 48.4	NR	NR	NR	NR
SARS Observational Studies										
Kao et al.[21]	33.8 +/- 3.8	20.8 +/- 1.8	8.2 +/- 2.0	733.8 +/- 154.0 (12.5 +/- 3.3)	36.0 +/- 5.1	272.6 +/- 140.8	49.4 +/- 23.0	40.8 +/- 7.1	65.8 +/- 24.3	80.1 +/- 12.3

Abbreviations: PEEP: positive end-expiratory pressure, TV: tidal volume, ml: milliliters, RR: respiratory rate, PaO2/FiO2: partial pressure of oxygen/fraction of inspired oxygen, PaCO2: partial pressure of carbon dioxide.

pneumothorax and pneumomediastinum).[20,45,46] These are likely related to the lung histopathological development of diffuse alveolar damage seen in autopsies of deceased COVID-19 patients that weakens the alveolar walls and gives rise to dilated, cystic and bullous airspaces (pneumatocele) in the lung parenchyma that rupture during intense coughing (sudden rise in intrathoracic pressure) or when receiving positive pressure ventilation causing leakage of air into the pleura resulting in pneumothorax and/or traveling along the bronchovascular bundles (Macklin effect)/interstitium into the mediastinum (pneumomediastinum) with or without disrupting the mediastinal parietal pleural.[16,26,35,47−49] In those receiving IMV during the time of development of pneumothoraces, this can simply reflect that the gas exchange was severely compromised in the more critically-affected lungs and that the alveoli were more readily prone to rupture even in response to a minor increase in thoracic pressure.[19,36] Several studies have even noted incidental radiologic findings of cystic lung changes, including bulla before the development of pneumothorax in hospitalized patients with COVID-19 infections that is not present on admission and likely associated with the resorptive process of consolidation.[19,47,50−53] Similar findings are noted in observational studies of patients with influenza A pneumonia and SARS, known to cause diffuse alveolar inflammation with cysts formation regardless of IMV requirement with only inciting event for pneumothorax is forceful coughing episodes.[35,54−56] Observational study by Gattinoni et al. observed that the number of bullae detected in the dependent lung regions on high-resolution chest CT was significantly higher in critically ill patients who developed pneumothoraces, and among those with ARDS and required prolong IMV.[8] The utility of follow-up chest imaging to evaluate for the atypical complication of bulla and associated pneumothorax formation during COVID-19 infections needs to be better studied.

The overall time to pneumothorax diagnosis was shown to be between 9.0−19.6 days from admission and 5.4 days after IMV (Table 1). Moreover, an observational study of COVID-19 patients by Abdallat et al. observed that the majority of pneumothoraces occur within 15.0 days from IMV.[30] Compared to SARS-related pneumothorax, the time to diagnosis from admission was between 19.6−24.3 days from admission and 8.0 days after IMV.[23,34,35] A large prospective study in critically ill non-COVID-19 patients reported that the median time to development of pneumothorax was five (IQR 3−10) days from admission and four (IQR 2−8) days following IMV initiation with an increasing incidence of 1.4% on day 5, 2.1% on day 10, and 3.0% on day 30.[7] Similarly, among critically ill non-COVID-19 patients requiring IMV for moderate-to-severe ARDS, the incidence of pneumothorax increases significantly at 30% for early ARDS (IMV for up to a week), 46% for intermediate ARDS (IMV between 1 and 2 week), and up to 87% in late ARDS (IMV 2 weeks and more).[8] The onset of pneumothorax that occurs after admission suggest a sustained period of lung inflammation with extensive parenchymal injury and likely a severe course of COVID-19 infection. The typical radiologic findings in COVID-19 patients are inflammation of the lung parenchyma that predominantly affects the peripheries that will progress and eventually involve the overlying pleura that possibly explain the late onset of pneumothorax.[52,57,58] In a similar fashion, these findings also explain the delayed onset of other pleural diseases such as pleural effusions that are frequently observed ten days and more from the start of COVID-19 symptoms.[2]

Three observational studies by Ekaneem et al., McGuinness et al., and Miro et al. reported of prolonged length of hospitalization (21.5−25.0 days vs. 11.0−18.0 days; P < 0.001) among COVID-19 patients diagnosed with pneumothorax versus those without pneumothorax.[13−15] Additionally, according to Miro et al., COVID-19 patients with pneumothoraces had 12.9, 4.2, and 15.7-folds increased in the risk of ICU admission, prolonged hospitalization, and higher in-hospital mortality than those without pneumothoraces.[14] Previously, the use of ECMO in COVID-19 patients diagnosed with pneumothoraces was limited to several case series. A case series by Jang et al. was the only study that assessed the clinical course of 19 critically ill COVID-19 patients who required IMV and ECMO with a reported incidence of pneumothorax up to 15.8%.[59] A different case series by Udi et al. observed that the requirement of ECMO was no different between COVID-19 patients with barotrauma as opposed to those without barotrauma.[26] In our review, only a minority of COVID-19 patients diagnosed with pneumothoraces required ECMO (Table 1). At this time, we cannot determine the relationship and outcomes of COVID-19 patients with pneumothoraces who needed ECMO support based on the limited evidence in our review. However, two multi-center, retrospective cohort studies by Ekanem et al. and Martinelli et al. showed no improvement in survival among mechanically ventilated COVID-19 patients with pneumothoraces despite ECMO support.[15,16]

Our review has several limitations. First, the available data on pneumothoraces in COVID-19 infections is often limited due to the highly variable frequency reported across many observational studies included compared to other common CT chest findings (Table 1). This can be explained by the inconsistent use of chest imaging in which almost all diagnoses of COVID-19-related pneumothoraces are made with the utilization of CT chest in the observational studies included as opposed to the use of chest radiographs. A delay in diagnosing pneumothoraces may occur as CT chests are more sensitive in diagnosing pneumothorax than chest radiographs. This highlights the importance of routine chest imaging in ensuring a prompt diagnosis of this uncommon entity in COVID-19 infections that is understandably limited to reduce provider and radiology technician exposure to COVID-19 patients. Moreover, depending on the area of practice and existing hospital protocols, physicians may have a very low threshold of ordering chest imaging during the current pandemic when any respiratory symptoms arise that may contribute to the early diagnosis of pneumothorax. Second, some mildly symptomatic COVID-19 patients with undiagnosed pneumothorax could have been advised to remain at home during the outbreak due to the fear of further COVID-19 transmission during hospitalization and exhaustion of the current healthcare system. Third, studies that we reviewed and excluded were published in non-English language (Fig. 1) that would have affected the generalizability of our study, in view of the ongoing worldwide pandemic since we (the authors) were not well versed in other languages. Fourth, in several observational studies, pneumothoraces were observed to be a bystander (minor secondary outcome) result or identified incidentally during subgroup analysis while assessing the many characteristics, risk factors, and outcomes of hospitalized COVID-19 patients which explains their low score.[2,17,18,20,60] Fifth, as the majority of studies included were retrospective (Table 1), real-time data such as ventilator parameters were likely difficult to obtain and limited to few studies as described in Table 4. Lastly, premature death associated with COVID-19 infections may be an independent confounding factor for the development of delayed pneumothoraces, leading to an unintended underestimation of the actual risk in deceased COVID-19 patients.[15,16]

Conclusion

The overall incidence of Covid-19-related pneumothorax is low at 0.3% but increases to 12.8−23.8% in those who are critically ill and require IMV. COVID-19-related pneumothorax is commonly unilateral and right-sided. The onset is around 9.0−19.6 days from admission and 5.4 days after IMV. COVID-19-related pneumothorax is likely a sequela of COVID-19 disease progression due to the inflammatory insult from COVID-19-induce immune dysfunction and increase in respiratory effort that may inflict changes within the lung parenchyma. COVID-19-related pneumothoraces are associated with prolonged hospitalization, increased likelihood of ICU admission and death, especially among the elderly. With increasing incidence

observed among those requiring IMV, COVID-19-related pneumothorax signifies a severe course of infection. As our clinical understanding of COVID-19 continues to expand, it is crucial for healthcare providers to recognize this uncommon presentation of COVID-19 infections in which a causal relationship between COVID-19 and pneumothorax cannot be concluded from our review as it is limited by many variables as described above. Therefore, we hope that more well-designed studies will be performed to describe the incidence, risk factors, onset, and outcomes in COVID-19 patients with pneumothoraces.

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Author contribution

All authors had access to the data and were involved in writing the manuscript.

Declaration of competing interest

None.

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