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Air leak with COVID-19 – A meta-summary

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Abstract

Introduction: There are various reports of air leaks with coronavirus disease 2019 (COVID-19). We undertook a systematic review of all published case reports and series to analyse the types of air leaks in COVID-19 and their outcomes.

Methods: The literature search from PubMed, Science Direct, and Google Scholar databases was performed from the start of the pandemic till 31 March 2021. The inclusion criteria were case reports or series on (1) laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, (2) with the individual patient details, and (3) reported diagnosis of one or more air leak syndrome (pneumothorax, subcutaneous emphysema, pneumomediastinum, pneumoperitoneum, pneumopericardium).

Results: A total of 105 studies with 188 patients were included in the final analysis. The median age was 56.02 (SD 15.53) years, 80% males, 11% had previous respiratory disease, and 8% were smokers. Severe or critical COVID-19 was present in 50.6% of the patients. Pneumothorax (68%) was the most common type of air leak. Most patients (56.7%) required intervention with lower mortality (29.1% vs. 44.1%, $p = 0.07$) and intercostal drain (95.9%) was the preferred interventional management. More than half of the patients developed air leak on spontaneous breathing. The mortality was significantly higher in patients who developed air leak with positive pressure ventilation (49%, $p < 0.001$) and required escalation of respiratory support (39%, $p = 0.006$).

Conclusion: Air leak in COVID-19 can occur spontaneously without positive pressure ventilation, higher transpulmonary pressures, and other risk factors like previous respiratory disease or smoking. The mortality is significantly higher if associated with positive pressure ventilation and escalation of respiratory support.

Keywords

Pneumothorax in COVID-19, barotrauma, pneumomediastinum, subcutaneous emphysema, SARS-CoV-2, pneumoperitoneum, spontaneous pneumothorax

Introduction

The surge of patients with coronavirus disease 2019 (COVID-19) remains unabated, globally inundating healthcare systems. The respiratory system is the primary target of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The common pulmonary manifestations of COVID-19 include cough, dyspnoea, sputum production, pneumonia, respiratory failure, and acute respiratory distress syndrome (ARDS).[1,2] ARDS is the common pathophysiology of severe COVID-19 requiring respiratory support and hospital or intensive care unit (ICU) admission.[2,3] The overall case fatality rate with COVID-19 is 2–3% but may increase to 43% (29%–58%) in patients requiring invasive mechanical ventilation (IMV).[3] Despite concerns, there is no significant difference reported between COVID-19-related ARDS or non-COVID-19 ARDS.[4,5]

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Air leak is an unusual pulmonary complication reported with COVID-19. Air leak is defined as leakage of air from an air-containing space (like lung) into a potential space like a pleural cavity.[6] There are various reports of air leak (like pneumothorax, pneumomediastinum, pneumoperitoneum, pneumopericardium or subcutaneous emphysema) in patients with COVID-19-related ARDS (online Appendix A: References of included studies). However, some of the patients who developed air leak were on respiratory support with positive pressure ventilation (PPV). Barotrauma in patients of ARDS requiring IMV is a known risk factor for air leak. The incidence of air leak with COVID-19-related ARDS on IMV was reported to be seven times higher than that for non-COVID-19 ARDS and associated with higher mortality despite the use of lung-protective ventilation.[7,8] Spontaneous air leaks are defined as leaks without any specific underlying cause like the use of PPV, trauma, or any iatrogenic intervention. There are various case reports on spontaneous air leak syndrome in COVID-19 (online Appendix A). Spontaneous pneumothorax or pneumomediastinum is reported rarely with other viral pneumonia-causing epidemics (e.g. influenza or SARS).[9–14] We performed a systematic review and meta-summary of the case reports and case series to analyse the types of air leaks in patients with COVID-19 and their outcomes.

Material and methods

We performed a systematic search for this meta-summary from PubMed, Science Direct, and Google Scholar databases from the inception of the pandemic of COVID-19 till 31 March 2021. The search terms used were "pneumomediastinum" OR "pneumothorax" OR "surgical emphysema" OR "subcutaneous emphysema" OR "barotrauma" OR "air leak" AND COVID-19. The inclusion criteria were clinical studies on (1) laboratory-confirmed SARS-CoV-2 infection, (2) case reports or case series with individual patient details, and (3) reported diagnosis of one or more air leak syndrome (pneumothorax, subcutaneous emphysema, pneumomediastinum, pneumoperitoneum, pneumopericardium, barotrauma). Further, it was filtered for the literature published in the English language and on adult (>18 years) humans. The authors screened all the search results to include only the relevant literature for air leak syndrome. Duplicate articles from different search databases were excluded. Eligible studies were further reviewed by all the authors for final inclusion based on the availability of individual patient's data. (Figure 1) We included case reports and case series to understand baseline demographics, respiratory support at the time of air leak, and their impact on the outcome. All the case reports and case series were evaluated, and the data were extracted for patient's demographics, the severity of COVID-19, type of air leak, symptoms and respiratory support at the time of the event, method of diagnosis, intervention performed for air leak and outcomes. A datasheet for evaluation was further prepared. The World Health Organization classification on severity assessment of COVID-19 was used.[15]

Statistical analysis

The prepared datasheet was evaluated by Excel, Microsoft office 2019. Categorical variables were presented as frequency and percentage. Mean (standard deviation (SD)) or median (interquartile range (IQR)) was used for continuous variables. Qualitative correlation statistics were analysed by Chi-square test and Fisher's exact test. A p-value of <0.05 was deemed significant.

Results

The primary search of the literature resulted in 126 studies from 905 articles, as per the eligibility criteria, relevant to the topic under investigation and excluding duplication. Finally, 105 studies and 188 patients that met all three inclusion criteria were included (Figure 1). The studies were of poor to fair quality due to a high risk of selection bias. Most of the case reports or series were from Europe (39.6%) and North America (28.3%). (Figure 2) The demographics, clinical characteristics, type of air leak, diagnosis, respiratory support and intervention performed are presented in Table 1. The median age of the patients was 56.02 (SD 15.53) years, and 80% were males (Table 1). The distribution of patients based on the severity of COVID-19 were mild (15.1%), moderate (33.1%), severe (36.7%), and critical (13.9%). The history of respiratory disease was present in only 11% of the patients, with chronic obstructive pulmonary disease (COPD) (5%) and asthma (4%) being reported mostly. The common symptoms reported during air leak were worsening of respiratory condition (increasing respiratory rate, breathlessness and hypoxia) (59%), respiratory distress (28%), chest pain (23%), abnormal swelling of face and chest (14%), and intractable cough (10%). The duration of air leak from the hospital admission was a median of five (IQR-13) days (Figure 3).

More than half (56.6%) of the patients who developed air leak, were not on PPV. Twenty-eight percent developed air leak while on IMV, 7% were on non-invasive ventilation (NIV), and 11% on high flow nasal cannula. The common types of air leaks reported

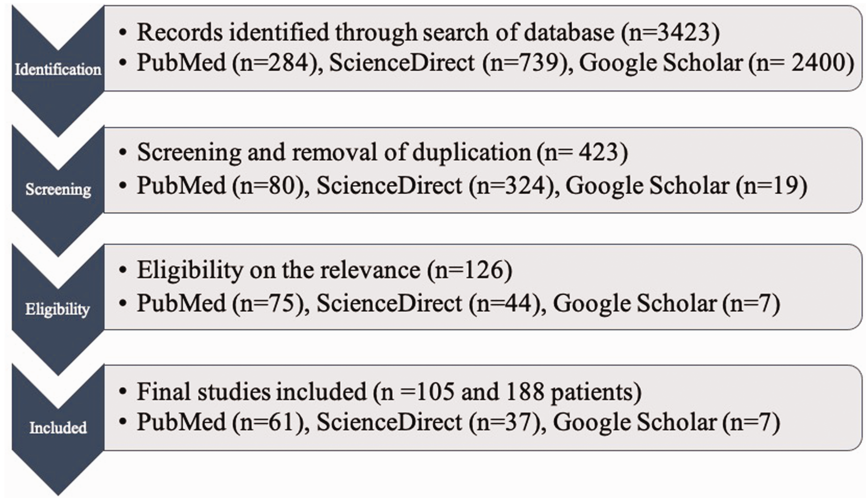

Figure 1. PRISMA flow diagram of the selected literature for the meta summary of air leak.

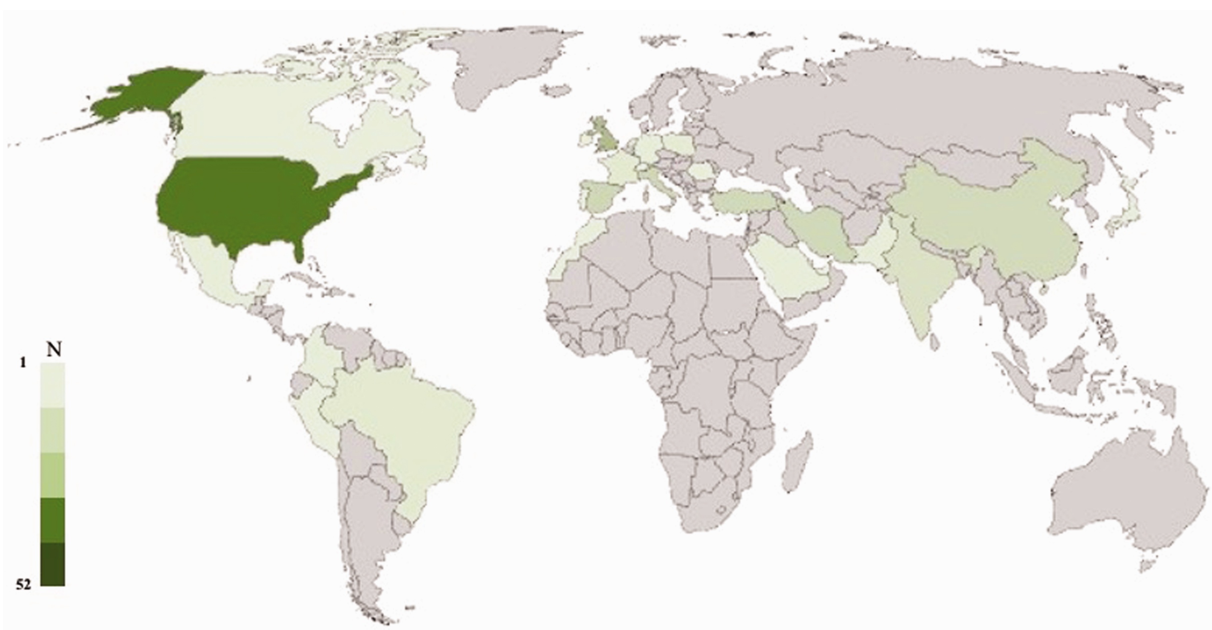

Figure 2. Geographical distribution of the patients reported with air leaks.
N: number of patients.

were pneumothorax (68%), pneumomediastinum (47%), and subcutaneous emphysema (34%) (Figure 3).

The initial diagnosis was based on clinical assessment (27%) or chest X-ray (43%). Computed tomography (CT) thorax was used as the initial diagnostic modality in 22% of the patients and for confirmation in 36% of the patients with air leak. The most common interventional management for air leak was the insertion of an intercostal drain (ICD), unilaterally (42%) or bilaterally (7%). The patients who were managed conservatively without any intervention had higher mortality (44.1% vs. 29.1%, $p = 0.07$), but it was statistically non-significant. Fifty-eight (31%) patients died after an air leak, with a median duration of 11 (IQR-14.5) days after the event (Figure 3). There was a significant association between the escalation of respiratory support after air leak and mortality ($p = 0.006$). There was also significantly higher mortality ($p < 0.001$) in patients who developed air leak while on PPV (55%) versus those who were spontaneously breathing (23%).

Table 1. Clinical features, respiratory support, intervention performed, and outcome of the patients with air leak.

Variable		N (%)
Previous respiratory illness	Present	19 (11)
	COPD	10 (5)
	Asthma	7 (4)
	ILD	1 (1)
	Tuberculosis	1 (1)
	Lung malignancy	0
	None	116 (62)
History of smoking	Yes	15 (8)
	No	66 (35)
Clinical features at the time of event	Chest pain	44 (23)
	Acute respiratory distress syndrome	52 (28)
	Worsening of respiratory condition	111 (59)
	Cough intractable	18 (10)
	Hemodynamic instability	12 (6)
	Abnormal swelling on face or chest	26 (14)
	Shock	1 (1)
	Not reported	16 (9)
Respiratory support during the event	Oxygen by low flow mask	23 (12)
	Non rebreathing mask	6 (3)
	Non-invasive ventilation	14 (7)
	High-frequency nasal canula	20 (11)
	Invasive mechanical ventilation	52 (28)
	During endotracheal intubation	1 (1%)
	None	59 (31)
Diagnostic modality	Initial diagnosis	Confirmation
Chest X-ray	81 (43%)	25 (13)
Clinical assessment	51 (27%)	3 (2)
Ultrasonography	3 (2%)	2 (1)
CT thorax	41 (22%)	67 (36)
Not given	11 (6%)	
Intervention for air leak	Intercostal drain	
	Unilateral	79 (42)
	Bilateral	14 (7)
	Percutaneous catheter	1 (1)
	Thoracoscopic intervention	4 (2)
	Blowhole skin incision	1 (1)
	Other	5 (5)
	Not reported	18 (10)
Outcome	Mortality	58 (31)
	Not reported	34 (18)
Air leak with use of positive support and outcome	Use of positive pressure(%) Mortality(%)	$P \leq 0.001$
	Yes, 66(43.4%)	36(55%)
	No, 86(56.6%)	19(23%)
Correlation between respiratory support and outcome	Change Number (%)	$P = 0.006$
	Escalation	71(39%)
	De-escalation	18(10%)
	No change	96(51%)
Correlation between treatment strategy and outcome	Strategy Mortality (%)	$P = 0.07$
	Conservative	26 (44.1%)
	Invasive	23 (29.1%)

COPD: chronic obstructive pulmonary disease, ILD: interstitial lung disease, CT: computed tomography.

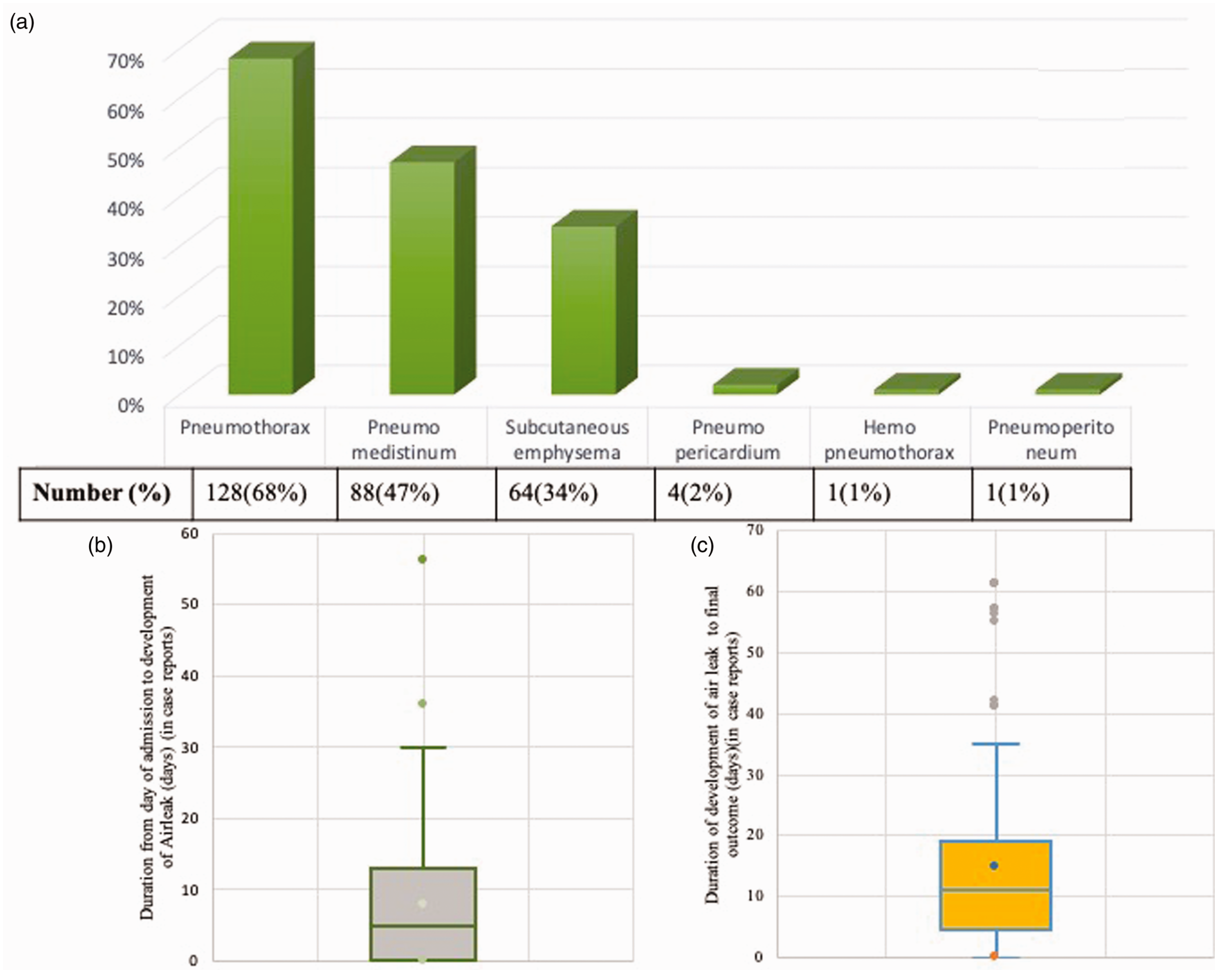

Figure 3. (a) Distribution of patients based on the type of air leak, (b) Box-plot depicting the median number of days from admission to air leak, (c) Box-plot depicting the median number of days from air leak to the final outcome.

Discussion

To the best of our knowledge, this is the first systematic analysis of the studies on air leak with COVID-19. The meta-summary included the largest cohort of patients (n = 188) who developed air leak syndrome with COVID-19. The COVID-19 was severe or critical in 50.6% of the patients at the time of diagnosis. Pneumothorax (68%) was a common type of air leak, 56.7% required intervention, and an ICD (95.9%) preferred interventional management. Almost half of the patients who developed air leak were spontaneously breathing. The mortality was significantly higher in patients who developed air leak with PPV and required escalation of respiratory support due to air leak.

Air leak in hospitalized patients is commonly linked to either iatrogenic intervention or to the use of PPV (non-invasive or invasive mechanical ventilation), also known as pulmonary barotrauma, owing to higher transpulmonary pressure. A higher plateau pressure (a surrogate of transpulmonary pressure) is proposed inciting cause in these patients. A retrospective single-centre case-cohort study reported a higher incidence of pneumomediastinum and subcutaneous emphysema in patients with COVID-19 on IMV despite using lung-protective ventilation.[7] Few other case series found patients with COVID-19 who developed air leaks had a higher need for IMV, longer ICU length of stay, and higher mortality rates when compared to those who have no air leaks.[8,16] The development of air leak in the absence of higher transpulmonary pressure cannot be explained by pulmonary barotrauma alone.

The event of air leak was heralded either with symptoms of respiratory distress (28%) or worsened pre-existing respiratory symptoms (59%) in the majority. The median duration for air leak in our meta-summary was 5 (IQR-13) days, again suggesting an early development of air leak during hospitalization which was unrelated to respiratory support.

The exact pathophysiology of air leak in spontaneously breathing patients with COVID-19 is unclear.

The higher incidence of air leak in COVID-19-related ARDS independent of transpulmonary pressure and various cases of spontaneous air leak without any previous risk factors suggest pathogenesis beyond pulmonary barotrauma. The primary target site of SARS-CoV-2 is angiotensin-converting enzyme-2 (ACE-2) receptors which are mainly expressed in type II pneumocytes besides vascular endothelium, myocardium, proximal tubules of kidneys, and intestines.[17] The ACE-2 has a protective effect on lung inflammation, fibrosis, and pulmonary arterial hypertension, while SARS-CoV-2 interaction with ACE-2 may result in its down-regulation. The lung damage in COVID-19 is the resultant of host-triggered dysregulated immune response causing extensive inflammation and eventual fibrosis.[18] The post-mortem lung histopathology of patients with COVID-19 showed diffuse alveolar damage, hyaline membrane formation, endotheliitis, and vascular microthrombi, similar to other coronaviruses like SARS and MERS.[19] However, fibro-myxoid exudates in the alveoli were excessive with SARS-CoV-2-infected lungs.[19] The inflammation and imbalance of cytokines may cause alveolar or pleural wall damage and rupture during spontaneous breathing induced by swings in transpulmonary pressure (or lung stress), also known as patient self-inflicted lung injury (P-SILI).[20,21] The peripheral distribution of lesions (subpleural consolidations) in COVID-19 and high shear force due to increased respiratory rate or P-SILI may also cause pneumothorax. The other proposed hypothesis for air leak could be the Mecklin effect, causing a large pressure gradient between marginal alveoli and surrounding structures. The marginal alveoli are close to the pulmonary blood vessels, pleura, and bronchioles separated only by an interstitium. The temporary increased intra-alveolar pressure during cough or deep breathing may rupture the damaged marginal alveoli, developing interstitium emphysema which can then traverse through broncho vascular sheath into pericardium, mediastinum, peritoneum, or subcutaneous space.[7,20]

Another mechanism is the progression of the inflammatory phase of illness to cavitating lung disease and formation of micro or macro cysts. The chest tomography (CT) of the thorax in patients with COVID-19 showed mainly ground-glass opacities, vascular engorgement consolidation, and linear opacities.[22] However, a CT scan of few patients with severe COVID-19 also showed cystic spaces or cavitation, with an incidence of 3% in those admitted with pneumonia.[22,23] The transient increased in transpulmonary pressure either due to bout of cough or deep inspiration which may rupture these cystic lesions and progress to air leak traversing along the broncho vascular sheath.

Various case reports are published for air leak in COVID-19 without the use of PPV. In this meta-summary, spontaneous air leak was diagnosed in 86 (56.6%) patients. Other risk factors known for spontaneous pneumothorax include tobacco smoking, illicit drug abuse (like marijuana, cocaine, heroin), previous respiratory illness like COPD, interstitial lung disease, or vigorous inspiratory manoeuvres (like Valsalva). The incidence of previous respiratory disease (11%) or smoking (8%) was seen only in a minority of cases in this meta-summary.

To summarize, SARS-CoV-2 and lung interplay predispose to air leak in few patients independent of the severity of disease or PPV and absence of commonly implicated risk factors like smoking and underlying lung pathology. However, mortality is significantly higher in patients who developed air leak while on PPV, as seen with other small case series, which may be attributed to more severe disease.[8]

A higher number of studies were reported from developed countries of Europe and North America, likely because of reporting bias or significant patient load from these areas. The management of spontaneous air leak, except tension pneumothorax, is not yet standardized. Persistent air leak (PAL), defined as a leak that persists more than five to seven days, were common in patients with COVID-19 (median of 11 days).[24] The treatment of PAL depends on the origin of the air leak. Conventionally, a surgical repair of PAL was considered the gold standard. However, surgical repair may not be feasible in critically ill patients with COVID-19-related ARDS and may increase morbidity or mortality. An ICD for a prolonged duration with an expectant resolution is considered the preferred treatment.[24] Other minimally invasive management options like the use of sealants, Watanabe spigots, metal coils, or alcohol sclerosis of the airways have been tried in other patients with variable success.[24] A recent randomized controlled trial found that conservative management was non-inferior to interventional management for primary spontaneous pneumothorax.[25] The unilateral or bilateral ICD (49%) with expectant management was the preferred intervention for air leak in patients with COVID-19. The underlying severity of disease, worsening respiratory condition and pneumothorax (68%) as primary air leak syndrome could explain this conservative option in most patients. The interventional management with a prolonged ICD in this meta-summary was associated with lower mortality, although it was not statistically significant. The surgical (preferably minimally invasive) option is considered only in patients with PAL despite prolonged ICD and overall surgical or anaesthesia fitness assessment. The time to resolution or mortality was a median of 11 (IQR 14.5) days after the air leak, as seen in the primary spontaneous pneumothorax patients.

Strength and limitations

This is the first meta-summary on published case reports and case series on air leak with COVID-19, with many cases worldwide. We included case series and reports with individual patient's details like demographics, respiratory support, intervention, and outcome. The included studies were only case reports and case series, with a considerable reporting bias, missing data and hence, the results cannot be generalized. The exact incidence of air leak could not be calculated. There were missing data in few case reports and case series, and information bias cannot be excluded because of selective reporting of only spontaneous pneumothorax.

Conclusion

The air leak in COVID-19 can be the cause of acute worsening of respiratory condition. The air leak can develop independently of the severity of disease or PPV and the absence of traditional risk factors like smoking and respiratory disease. The exact pathophysiology of air leak with COVID-19 is unclear, and future histopathological studies may provide a better understanding. The mortality is significantly higher with air leak associated with PPV and in those requiring escalation of respiratory support. The management options include a prolonged ICD or minimally surgical options for PAL who failed expectant treatment. The calculation of true incidence and outcomes of air leak associated with COVID-19 need prospective larger cohort studies.

Declaration of conflicting interests

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Informed consent

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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