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Systematic Review / Meta-analysis

Pulmonary barotrauma in COVID-19: A systematic review and meta-analysis

Dhan Bahadur Shrestha[a,*], Yub Raj Sedhai[b,**], Pravash Budhathoki[c], Ayush Adhikari[d], Nisheem Pokharel[e], Richa Dhakal[f], Satyasuna Kafle[g], Wasey Ali Yadullahi Mir[a], Roshan Acharya[h], Markos G. Kashiouris[i], Mark S. Parker[j]

[a] Department of Internal Medicine, Mount Sinai Hospital, Chicago, IL, USA
[b] Department of Internal Medicine, Division of Hospital Medicine, Virginia Commonwealth University, School of Medicine, Richmond, VA, USA
[c] Department of Internal Medicine, BronxCare Health System, Bronx, NY, USA
[d] Department of Anesthesia and Critical Care, TU Teaching Hospital, Kathmandu, Nepal
[e] Department of Internal Medicine, KIST Medical College, Lalitpur, Nepal
[f] Department of Internal Medicine, Kathmandu Medical College, Kathmandu, Nepal
[g] Department of Intensive Care Unit, Bhaktapur Hospital, Bhaktapur, Nepal
[h] Department of Internal Medicine, Cape Fear Valley Medical Center, Fayetteville, NC, USA
[i] Department of Internal Medicine, Pulmonary and Critical Care, Virginia Commonwealth University, School of Medicine, Richmond, VA, USA
[j] Department of Radiology, Division of Thoracic Imaging, Virginia Commonwealth University, School of Medicine, Richmond, VA, USA

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ABSTRACT

Background: An ever-increasing number of studies have reported an increased incidence of spontaneous pulmonary barotrauma such as pneumothorax, pneumomediastinum, and subcutaneous emphysema in patients with COVID-19. We conducted this systematic review and meta-analysis to assess the value and significance of the available data.

Methods: A thorough systematic search was conducted to identify studies of barotrauma in hospitalized patients with COVID-19. Data analysis of case reports was done using a statistical package for the social sciences (SPSS) version 22, and meta-analysis was performed using CMA-3.

Results: We identified a total of 4488 studies after thorough database searching.118 case reports and series, and 15 observational studies were included in the qualitative analysis. Fifteen studies were included in the quantitative analysis. The observational studies reported barotrauma in 4.2% (2.4–7.3%) among hospitalized patients; 15.6% (11–21.8%) among critically ill patients; and 18.4% (13–25.3%) in patients receiving invasive mechanical ventilation, showing a linear relationship of barotrauma with the severity of the disease. In addition, barotrauma was associated with a longer length of hospital stay, more extended ICU stay, and higher in-hospital mortality. Also, a slightly higher odds of barotrauma was seen in COVID-19 ARDS compared with non-COVID-19 ARDS.

Conclusion: COVID-19 pneumonia is associated with a higher incidence of barotrauma. It presents unique challenges for invasive and non-invasive ventilation management. Further studies are required to unravel the underlying pathophysiology and develop safer management strategies.

1. Introduction

Pulmonary barotrauma refers to the spontaneous rupture of alveoli and the subsequent release or dissection of air into the various extra alveolar spaces resulting in pneumothorax, pneumomediastinum, pulmonary interstitial emphysema, pneumatocele or air cyst formation, subcutaneous emphysema, pneumopericardium, and or pneumoperitoneum. An increasing number of barotrauma cases have been

; COVID-19, Coronavirus Disease 2019; IMV, Invasive Mechanical Ventilation; ARDS, Acute Respiratory Distress Syndrome; NIPPV, Non-invasive Positive Pressure Ventilation; ICU, Intensive Care Unit.

* Corresponding author. Department of Internal Medicine, Mount Sinai Hospital, Chicago, IL, USA.
** Corresponding author. Department of Internal Medicine, Virginia Commonwealth, University, School of Medicine, Richmond, USA.
E-mail addresses: medhan75@gmail.com (D.B. Shrestha), YubRaj.Sedhai@vcuhealth.org (Y.R. Sedhai).

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reported with COVID-19 pneumonia in hospitalized patients. Some studies have correlated COVID-19 related barotrauma with a longer length of hospitalization, longer ICU stay, and higher mortality [1]. Barotrauma has been reported among COVID-19 patients requiring invasive mechanical ventilation (IMV), non-invasive positive pressure ventilation (NIPPV), and other forms of respiratory support ranging from supplemental oxygenation by nasal cannula to heated high flow nasal cannula [1–3]. Risk factors, pathophysiology, and clinical implications of barotrauma in patients with COVID-19 are not well understood. Thus, to fully evaluate the available data, we sought to perform this systematic review and meta-analysis. We have included studies (case reports, case series, cohort, and case-control studies) from the onset of the COVID-19 pandemic from December 31, 2019, up until May 4, 2021.

2. Methods

We used Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for the systematic review of available literature [4]. The study protocol was registered in the International prospective register of systematic reviews (PROSPERO) with ID: CRD42021261038 [5]. The completed PRISMA 2020 checklist is uploaded for review purposes with manuscript submission. Additionally, the quality of the systematic review is self-assessed using AMSTAR 2 criteria and submitted [6].

2.1. Literature search

Electronic databases including PubMed, PubMed Central, Embase, and Scopus were used to search relevant articles published until May 4, 2021, using the following MeSH terms and appropriate Boolean operators as ((emphysema) AND (COVID-19)) OR ((barotrauma[MeSH Terms])) AND (SARS COV-2[MeSH Terms])). Electronic search details are available in supplementary file 1.

2.2. Selection of studies

2.2.1. Type of studies

We included case reports, case series, cohort studies, and case-control studies. Patients included in the studies fulfilled the following criteria; (1) more than 17 years of age, (2) confirmed diagnosis of COVID-19 based on a positive reverse transcriptase polymerase chain reaction (RT-PCR) nasopharyngeal swab (3) and spontaneous pneumothorax, pneumomediastinum, pneumopericardium, pneumoperitoneum, hydropneumothorax, or subcutaneous emphysema either at their initial presentation or during treatment of COVID-19 pneumonia. Editorials, comments, viewpoints, systematic reviews, meta-analyses, and articles lacking full text and adequate data were excluded.

2.2.2. Outcome measures

The primary outcome of interest was the incidence and type of barotrauma event. The secondary outcomes of interest were the impact of barotrauma on the clinical outcome in terms of hospitalization, length of ICU stay, and hospital mortality. Further, we compared the incidence of barotrauma between COVID-19 ARDS vs. Non-COVID-19 ARDS (i.e., ARDS from other etiologies).

2.2.3. Data extraction and management

All the stages of data extraction were done according to the PRISMA guideline. The first two authors individually screened published articles based on inclusion and exclusion criteria using Covidence [7]. Discrepancies were resolved by mutual consent obtained from the third author. Data were extracted onto a standardized form designed in Microsoft Excel to collect the pertinent information, including the first author, type of study, site of study, year of publication, age, gender, associated comorbidities, the incidence of barotrauma, type of barotrauma, cause of barotrauma, treatment modality for barotrauma, and clinical outcomes in terms of length of hospitalization, length of ICU stay, and in-hospital mortality. The sample size, mean age, percentage of male and female, associated comorbidities, type of barotrauma, and the clinical outcomes were included for the cohort studies. Further analysis of data from case reports was done in Statistical Package for the Social Sciences (SPSS) version 22. For meta-analysis of observational studies, comprehensive meta-analysis version-2 (CMA-3) was used.

2.2.4. Risk of bias (quality) assessment

The quality of individual articles was evaluated using the Joanna Briggs Institute (JBI) [8] critical appraisal for cohort studies, case-control studies, and case series (Supplementary file 1, Tables 1–3) [1,2,8–20].

2.2.5. Strategy for data synthesis

The handling of data and combining results of the studies was done using proportion and the Random effect model using CMA-3 software. Additionally, data from the case reports were summarized, and descriptive analysis was done using Statistical Package for the Social Sciences (SPSS) version 22.

3. Results

A total of 4488 studies were identified after thorough database searching, and 1304 duplicates were removed. Title and abstracts of 3184 studies were screened, and 2892 irrelevant studies were excluded. Full-text eligibility of 292 studies was assessed, and 159 studies were excluded for definite reasons. A total of 118 case reports and series and 15 observational studies were included in the qualitative analysis, and 15 studies were included in the quantitative analysis. The following information is depicted in the PRISMA flow diagram (Fig. 1).

3.1. Narrative summary

There were ten cohort studies, three case-control studies, and two case series among included studies. In addition, three studies were done in the US and Italy, two studies in Turkey, while there was a single study from the UK, Kuwait, Germany, Iran, India, Spain, and Mexico. Three studies reported outcomes in critically ill patients. Six studies were performed on patients receiving invasive mechanical ventilation. Two studies included patients with varying clinical severity receiving different respiratory support modalities. The detailed narrative summary is presented in Tables 1 and 2.

3.2. Proportion of barotrauma

Among the included studies reporting barotrauma, pooling of the individual study data using random-effect model showed barotrauma in 4.2% (2.4–7.3%); 15.6% (11–21.8%); and 18.4% (13–25.3%) of hospitalized patients, severely ill or critically ill patients, and patients receiving invasive mechanical ventilation, respectively (Fig. 2).

3.3. Types of barotrauma reported

Pneumothorax was the most common form of barotrauma reported at 72.2% (58.2–82.8%); followed by pneumomediastinum at 51.5% (36.1–66.6%), and subcutaneous emphysema reported in 48.4% (29.5–67.7%) (Fig. 3). Among the included studies, three studies also reported 12 cases of pneumopericardium.

3.4. Length of hospitalization

Eight studies reported the length of hospitalization (LoH) [1,9,11,12,14,15,18,21]. LoH was longer in COVID-19 patients in all studies than non-barotrauma COVID-19 patients, except Elsaaran H [12]. Due to

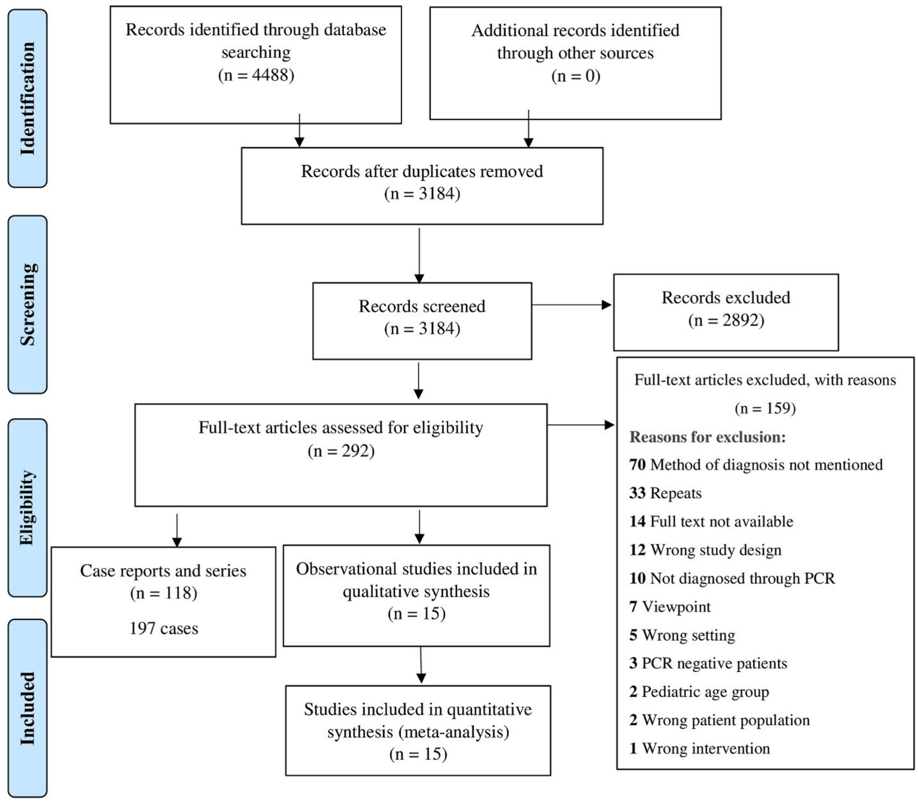

Fig. 1. Prisma flow diagram.

varying severities of patients enrolled in different studies carrying significant biological heterogeneities, the length of hospital stay outcome is not pooled.

3.5. Length of ICU stay

Belletti, Elsaaran, Kahn, and Lemmers reported the ICU length of stay [11,12,14,15]. All four of these studies reported a longer duration of ICU LOS in the barotrauma group.

3.6. Mortality

Thirteen studies reported in-hospital mortality [1,2,9,10,12,14–21]. Total mortality was 58.7% in the barotrauma group compared to 40.6% in the control (non-barotrauma) group.

3.7. Barotrauma in COVID-19 ARDS vs. Non-COVID-19 ARDS

Only two studies reported the incidence of barotrauma among COVID-19 ARDS and non-COVID-19 ARDS patients. However, pooling the data using a random-effect model showed a slightly higher barotrauma odds ratio in COVID-19 ARDS than non-COVID-19 (OR, 3.31; CI, 0.66–16.65, I^2: 83.95%) (Supplementary file 1, Fig. 1).

3.8. Descriptive summary of the case reports and case series

Data from 118 case reports and series including 197 COVID-19 patients were included in this descriptive analysis. Among 197 cases; 83.2% (n, 164) were male, 69% (n, 136) cases with pneumothorax (82; unilateral, 40; bilateral, and 14 with no mention of laterality). Right-sided pneumothoraces (n = 55) was more commonly reported than left-sided pneumothorax (n = 26) (Fig. 4). Among pneumothorax cases, tension pneumothorax was present in 19 cases. Similarly, pneumomediastinum were reported in 49.7% (n, 98), subcutaneous emphysema in 37.1% (n, 73), and pneumoperitoneum in 6.1% (n, 12) cases (Supplementary file 1, Fig. 2). 57.4% (n, 113) required a formal chest tube placement. 2.5% of patients (n, 5) required needle thoracostomy in the setting of tension pneumothorax. 35.5% (n, 70) were treated conservatively and did not require invasive treatment. It is worthwhile noting that more than half of the patients developed barotrauma in the setting of the invasive mechanical ventilation (IMV) support (52.8%, n = 104), while 42.6% (n, 84) patients developed without IMV use.

4. Discussion

Herein we report a comprehensive meta-analysis on the incidence, type of barotrauma, and its impact on clinical outcomes among patients with COVID-19 pneumonia. We have included 118 case reports, case series, and 15 observational studies.

Pneumothorax and pneumomediastinum have been previously associated with coronavirus pneumonia during the SARS epidemic of 2002–2004 [22]. The incidence of barotrauma during the 2002–2004 epidemic varied from 5 to 34% [23–25]. Barotrauma has been increasingly recognized and reported from the onset of the COVID-19 pandemic [26–28]. One of the reasons for the higher incidence could be attributed to the broader use of chest computed tomography (CT) and its sensitivity to detect extra-alveolar gas collections [29]. We observed a linear association of increased barotrauma incidence with increasing disease severity observed as 4.2% (2.4–7.3%) among hospitalized patients, 15.6% (11–21.8%) among critically ill patients in ICU, and 18.4% (13–25.3%) among patients receiving invasive mechanical ventilation.

A higher incidence of barotrauma was observed in COVID-19 ARDS than non-COVID-19 ARDS in some studies, despite the use of lung-protective ventilation strategy in both groups [30]. The findings of our meta-analysis substantiated the conclusions of the individual studies regarding the increased occurrence of barotrauma in COVID-19 ARDS. Conventionally, barotrauma has been associated with high transpulmonary pressure, especially high tidal volume and high positive

Table 1
Narrative summary of the included observational studies.

Author	Type of study	Place of study	Study subjects Characteristics	Total cases	Barotrauma cases	Pneumothorax cases	Pneumomediastinum cases	Subcutaneous emphysema (SE) cases	Pneumopericardium
Belletti A [16] et al., 2021 (all IMV)	Observational Study	Italy	Total: N:116; Barotrauma: 28 Age: Barotrauma (B): 62 (57–70) Other (O): 62 (54–69) Sex: B: Male (23/28) O: Male (75/88) Hypertension: B: 8/28 O: 44/88 DM: B: 5/28 O: 14/88 Active Smoker: B:1/28 O: 2/88 Past Smoker: B:2/28 O: 7/88	116	**28/116** Time from intubation to barotrauma: 14.0 ± 11.0	**22/28 (78.5%)** Chest tube: 18/22 (81.8%) Conservative: 4/22 (18.2%) One chest tube patient additionally required minithoracotomy (4.5%)	**13/28 (46.42%)** Conservative: 12/13 Surgical repair for TEF: 1/13	–	–
Elsaaran H [17] et al., 2021 (critical Admitted COVID)	Retrospective cohort	Kuwait	N: 343; B: 54; O: 289 Age: B: 55.3 (15.0); O: 56.0 (13.3) Sex: Male B: 42/54; O: 243/289 DM: B: 20/54; O: 123/289 HTN: B: 24/54; O:131/289	343	54/343	49/54	8/54	–	2/54
Jones E [18] et al., 2020 (severe COVID)	retrospective cohort	UK	N: 83; B: 8 Age: B: 54.5 (37.8–57.4); O: 57.8 (50.4–65.2) Sex: Male: B: 8/8; O: 53/75 Smoking: B: (2/8); O: 21/28	83	8/83	4/8	7/8	8/8	
Kahn MR [19] et al., 2021 (ICU COVID)	retrospective cohort	USA	Total: 75; B: 16; O: 59 Age: B: 54(15); O: 60 (16) Sex, Female: B: 18/59; O: 2/16 DM: B:9/16; O:34/59 HTN: B: 6/16; O: 30/59 Tobacco Use: B: 2/16; O: 5/59	75	16/75 (Same patients might have presented with multiple types of barotrauma)	9/16	10/16	6/16	4/16
Lemmers DHL [20] et al., 2020 (IMV COVID)	cohort	Italy	Age: B: 64(60–70); O: 67 (59–71) Sex, Male: B:15/23; O: 118/146 DM: B:3/23; O:23/146 HTN: 11/23; O: 79/146	169	23/169	–	–	–	–
Loffi M [21] et al., 2020 (all Admitted)	retrospective cohort	Italy	Age: B: 72(49–80); O: 64 (53–75) Sex, Male; B:5/6; O: 68/96 DM: B: 0/6; O: 11/96 HTN: B: 1/6; O: 37/96 Smoking: B: 2/6; O: 25/96	102	6/102 (pneumo-mediastinum only)	–	6/6	3/6	1/6
McGuinness G [1] et al., 2020 (IMV COVID)	retrospective cohort	USA	Total: 601; B: 89 Age: B: 58(54,61); O: 64 (62,65) Sex: Male: B: 65/89; O: 361/512 Smoking: Never Smoked: 51/89; Past Smoker: 22/89; Current Smoker: 4/89	601	89/601	54/89	59/89	–	14/89
Miro O [2] et al., 2021 (All COVID)	case control	Spain	Total Barotrauma: 40 Age: B: 66(47–74); O: 61 (46–77) Sex, Male: B:29/40; O: 205/400 DM: B: 7/40; O: 74/400	40	40/-	37/40	6/40	6/40	–

(continued on next page)

Table 1 (*continued*)

Author	Type of study	Place of study	Study subjects Characteristics	Total cases	Barotrauma cases	Pneumothorax cases	Pneumomediastinum cases	Subcutaneous emphysema (SE) cases	Pneumopericardium
			HTN: B: 15/40; O: 168/400 Smoking: B: (4/40); O: 26/400						
Ozdemir S [9] et al., 2020 (IMV COVID)	retrospective study	Turkey	N: 107; Barotrauma: 8 Age: B: 61 (53–63.5); O: 60 (51–70) Sex, Male: B:8/8; O: 62/99	107	8/107	8/8	1/8	2/8	–
Ozsoy IE [10] et al., 2021 (Not clear)	retrospective study	Turkey	Total: 70; Barotrauma: 20 Age: B: 57.7 ± 14.1; O: 60.6 ± 13.6 Sex, Male B: 10/20; O: 22/40; DM: B: (7/20); O: 22/40 HTN: B: (5/20); O: 32/40 Smoking B: 4/40 O: 26/400	20	20/- (Same patients might have presented with multiple types of barotrauma)	4/20	20/20	14/20	–
Rodriguez-Arciniega TG [14] et al., 2020	Case control	Mexico	Total: 271 Barotrauma (SPM):9 Age: B:57(CI, 42.8–71.11), O: 59.5 (CI, 58.02–61.77) Sex, Male B: 7/9, O: 165/262 HTN: B: 5/9, O: 154/262 DM: B: 3/9, O: 110/262 Smoking: B: 1/9, O: 36/262	271	9/271 (3.32%) All 9 patients SPM	4/9	9/9	–	–
Swain SK [11] et al., 2020 (IMV)	Retrospective cohort	India	N: 262; Barotrauma: 64 Age: 61 ± 14 Sex: Male: 26 DM: 18 HTN: 22(57.89%)	262	64/262	42/64	32/64	38/64	–
Tofigh AM [12] et al., 2020 (ICU)	Observational study	Iran	Barotrauma: 7 Age: 61.71 ± 14.15 Male: 6/7 DM: 4/7 HTN: 2/7	7	7	7 All cases of B/L pneumothorax All cases B/L chest tubes	–	7	–
Udi J [15] et al., 2020 (All Post-IMV)	Case control	Germany	Total: 20; Barotrauma: 8 Age: B:62 (47–76), O: 61 (38–77) Male; B: 6/8, O: 7/12	20	8/20	5/8 All > chest tube insertion	5/8	2/8	1/8
Wong K [13] et al., 2020 (ICU)	Retrospective cohort	USA	Barotrauma: 75 Age: 62.8 (25–90) Male: 55 (73.3%) HTN: 39/75 DM: 20/75	75	75	75	27/75	–	–

end-expiratory pressure in ARDS patients [31]. However, Kahn et al. observed no difference in mean airway pressure, positive inspiratory pressure, positive end-expiratory pressure (PEEP), tidal volume, or minute ventilation during 0 or 14 days in patients who sustained barotrauma with those who did not [14]. Thus, we speculate the higher occurrence of barotrauma could be attributed to alveolar viral and inflammatory injury.

COVID-19 induces an elevated level of tumor necrosis factor alfa (TNF-alfa) and Interleukin-6 (IL-6) [32]. In animal models, TNF-alfa has been shown to induce apoptosis-driven alveolar damage [33,34]. Further in the setting of IMV, there is a proportional association between cytokine production, PEEP, and tidal volume [35]. These findings suggest that higher PEEP and higher tidal volume can further enhance the cytokine response worsening alveolar injury predisposing to barotrauma. A linear association between the occurrence of barotrauma and the clinical severity of disease was observed in our meta-analysis. This can be a manifestation of the degree of inflammatory response. Due to the paucity of data among the included studies, we were unable to perform a subgroup analysis of group differences in the incidence of barotrauma among patients receiving NIPPV vs. IMV, or the incidence of barotrauma between different ventilator modes, and settings. In the comprehensive review of case reports and case series, 42.6% of cases in individual cases developed barotrauma without IMV use. Thus, although purely speculative, the higher incidence of barotrauma in COVID-19,

Table 2
Outcomes among COVID-19 with barotrauma.

Author	Hospital LOS	ICU LOS	In-Hospital Mortality	Mortality	Discharged
Belletti A [16] et al., 2021	B: 41.5 (28.0–69.5) O: 28.0 (15.0–44.0)	B: 28.0 (14.5–51.0) O: 12.0 (7.5–21.0)	NR	At F/U for median period of 34.0 (28.0–42.0) days B:17/28 O: 34/88	NR
Elsaaran H [17] et al., 2021	**Mean (SD)** B: 16.4 (8.5) O: 20.1 (14.0)	**Mean (SD)** B: 14.9 (7.8) O: 13.9 (12.1)	B: 38/54 O: 153/289	NR	NR
Jones E [18] et al., 2020	NR	NR	NR	At F/U at three months period B: 5/8 O:34/75	B: 2/8 O:40/75
Kahn MR [19] et al., 2021	B:26(23–45) O: 14 (9–19)	B: 17 (15–30.5) O:7 (3–13)	B:9/16 O: 22/59	At 28-day F/U B:4/16 O: 18/59	B: 4/16 O: 26/59
Lemmers DHL [20] et al., 2020	**Median (IQR)** B:18 (12–28) O: 14(8–23)	**Median (IQR)** B:11(6–21) O: 9(5–18)	B:13/23 O: 73/146	NR	NR
Loffi M [21] et al., 2020	NR	NR	B: 1/6 O: 11/96	NR	B: 5/6 O: 85/96
McGuinness G [1] et al., 2020	**(95% CI)** B: 25(22,28) O: 18 (17,19)	NR	B:47/89 O: 298/512	NR	B:15/89 O: 116/512
Miro O [2] et al., 2021	NR	NR	B:13/40 O: 55/400	NR	NR
Ozdemir S [9] et al., 2020	NR	NR	B:4/8 O: 68/99	NR	NR
Ozsoy IE [10] et al., 2021	**Median (IQR)** B:20.5 (12.3–27.8) O: 9 (8–14)	NR	B: 12/20 O: 2/50	NR	NR
Rodriguez-Arciniega TG [14] et al., 2020	**Mean (SB: 95%CI)** B: 16.8 (13.9: 6.11–27.48) O: 12.06 (6.7: 11.24–12.87)	NR	B: 3/9 O: 96/262	NR	NR
Swain SK [11] et al., 2020	NR	NR	B: 25/38	NR	NR
Tofigh AM [12] et al., 2020	NR	NR	B: 7/7	NR	NR
Udi J [15] et al., 2020	NR	NR	B: 2/8	NR	NR
Wong K [13] et al., 2020	B: 48.7	NR	B: 57/75	NR	18/75

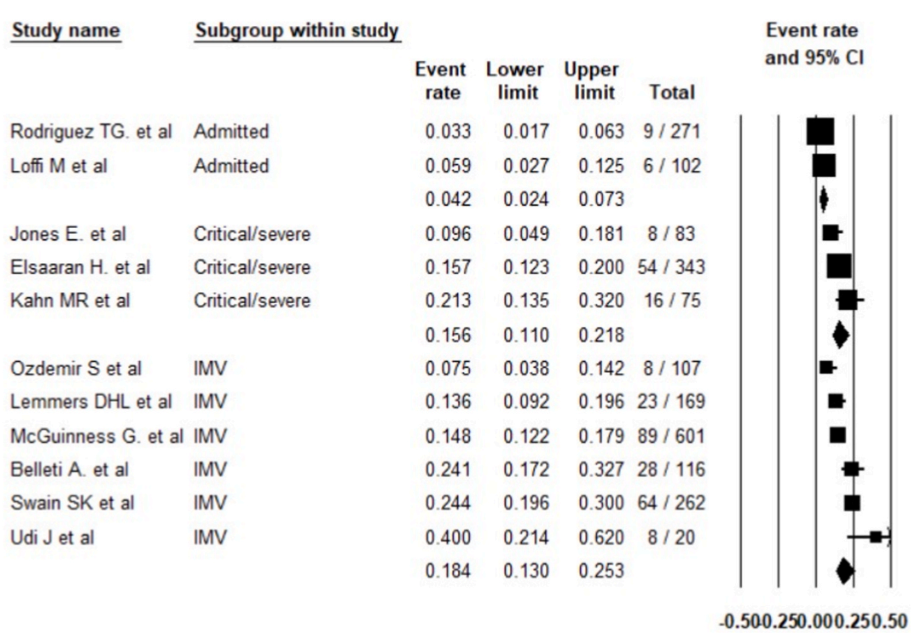

Fig. 2. The proportion of barotrauma among observational studies, random effect model.

even without the use of positive pressure ventilation, could also be a unique manifestation of inflammatory burden, alveolar injury, and its pathophysiologic sequelae. Further studies are warranted to understand the precise pathophysiology.

Spontaneous barotrauma was associated with a longer length of hospitalization, more prolonged ICU stays, and increased mortality. Also, cumulative analysis of case reports showed that more than half of pneumothoraces required formal chest tube placement. In addition, a

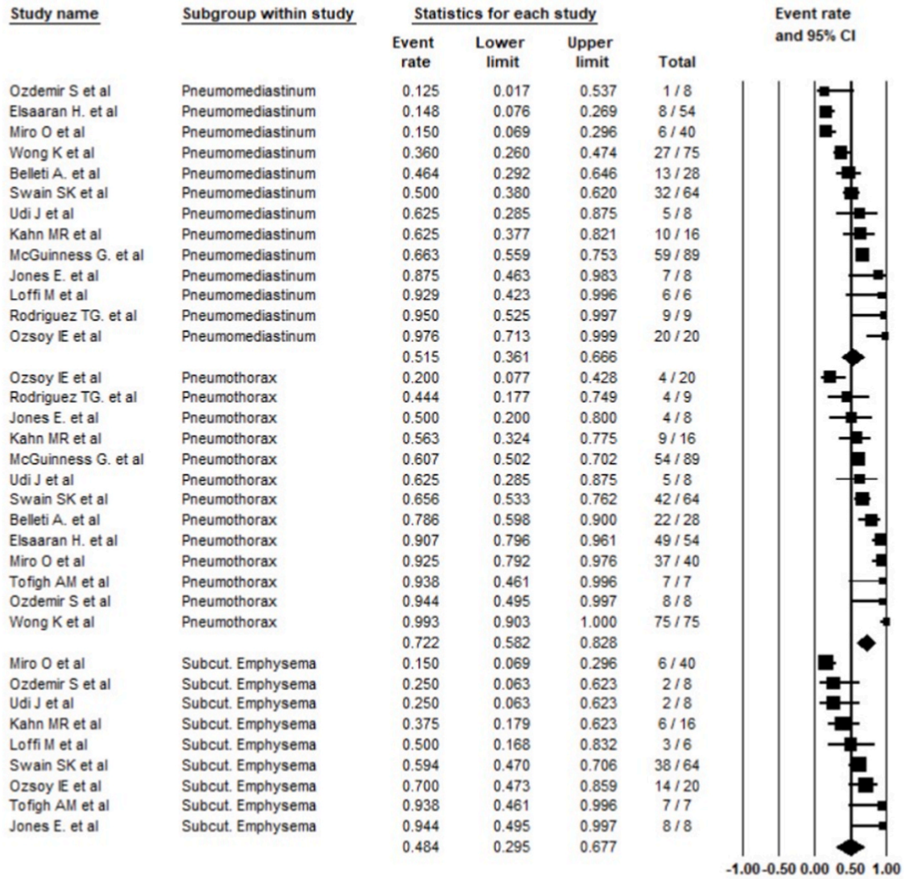

Fig. 3. Common types of barotrauma reported, random effect model.

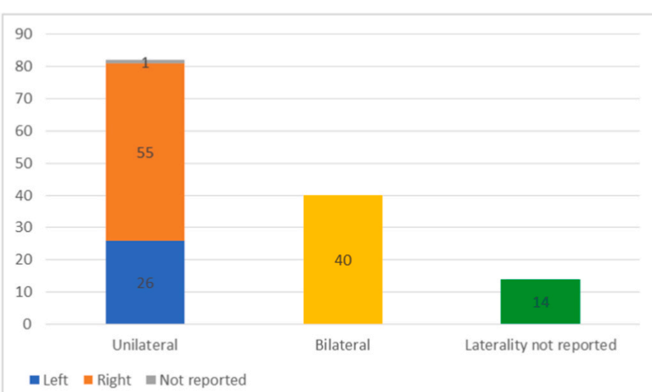

Fig. 4. Laterality of pneumothorax in case studies.

small subgroup of patients developed tension pneumothorax requiring emergent needle thoracostomy. Thus, pneumothoraces with COVID-19 subjected patients undergoing invasive procedures, including emergent life-saving procedures like needle thoracostomy. Hence, clinicians should be well aware of the higher risk of barotrauma in patients with COVID-19, even without positive pressure ventilation use. In addition, spontaneous barotrauma should be considered high in the differential in COVID-19 patients with an acute decline in clinical status.

5. Limitations

Our meta-analysis has several limitations, including a small number of retrospective cohort and case-control studies. There is also significant heterogeneity in the study designs and demographics. The included observational studies have their inherent limitations. Baseline characteristics, mechanical ventilator settings, assessment of organ dysfunction, and clinical outcomes were not individually reported across studies. Reported clinical outcomes in the included studies could be affected by several confounding variables [36]. Further, a higher detection of barotrauma could result from increased use of chest CT during the pandemic. It would have been clinically valuable to compare the incidence of barotrauma between chest radiography and chest CT and different ventilator modes and settings. However, it could not be performed due to the lack of data in the included studies. The presence of comorbidities primarily and severity of organ dysfunction could have significantly influenced the clinical outcomes [36].

6. Conclusion

The incidence of barotrauma in COVID-19 ARDS was higher than ARDS from other etiologies. Barotrauma was seen in COVID-19 among patients receiving IMV, NIPPV, and supplemental oxygenation by other non-invasive modalities. The pathophysiology of viral pneumonia is complex and poorly understood. It is still unrecognized if there are inherently unique mechanisms to COVID-19, which predisposes patients to an exaggerated inflammatory response resulting in alveolar injury that affects respiratory mechanics, resulting in barotrauma at a higher rate than other viral pneumonia. Barotrauma in COVID-19 patients was associated with a longer length of hospitalization, more extended ICU stay, and higher mortality. Further in-vitro and in-vivo studies are required to understand the pathophysiology and develop safer ventilation and treatment strategies in COVID-19 pneumonia.

7. Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data analyzed during the current study are available within manuscript and supplementary files.

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Authors' contributions

DBS, and YRS contributed to the concept and design, analysis, and interpretation of data. DBS, PB, AA, NP, RD, and SK contributed to the literature search, data extraction, review, and initial manuscript drafting. YRS, WAYM, RA, MGK, guided and supervised in different stages and contributed in the interpretation of data, revising the manuscript for important intellectual content and approval of the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.103221.

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