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A meta-analysis on incidence of barotrauma in patients with COVID-19 ARDS undergoing invasive mechanical ventilation

To the Editor

Barotrauma is a common complication in patients with Acute Respiratory Distress Syndrome (ARDS) undergoing Invasive Mechanical Ventilation (IMV) [1]. It usually occurs due to overdistension of the injured lungs, and/or severity of the underlying disease [2]. Recent studies have shown that the incidence of barotrauma is further increased in mechanically ventilated COVID-19 Induced ARDS (CARDS) patients [3] we sought to evaluate the incidence, clinical outcomes, and characteristics of barotrauma among COVID-19 patients receiving invasive and non-invasive positive pressure ventilation. METHODOLOGY: This retrospective cohort study included adult patients diagnosed with COVID-19 pneumonia and requiring oxygen support or positive airway pressure for ARDS who presented to our tertiary-care center from March through November, 2020. RESULTS: A total of 353 patients met our inclusion criteria, of which 232 patients who required heated high-flow nasal cannula, continuous or bilevel positive airway pressure were assigned to non-invasive group. The remaining 121 patients required invasive mechanical ventilation and were assigned to invasive group. Of the total 353 patients, 32 patients (65.6% males]. However, due to a small number of researches, there is no conclusive evidence supporting this claim. Therefore, the primary objective of this meta-analysis is to evaluate the incidence of barotrauma in CARDS patients receiving IMV compared to a Non-COVID ARDS cohort.

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic review and meta-analyses (PRISMA) guidelines [4]. To perform this study, an electronic literature search of PubMed, Cochrane CENTRAL and Embase was conducted in June 2021 using the following terminologies and their MESH terms: Barotrauma, ARDS, COVID-19 and Mechanical Ventilation. Additionally, bibliographies of related articles and conference proceedings for indexed abstracts were also reviewed. No language restrictions were set in our search.

Included studies comprised of ARDS patients with positive real-time Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) assays for COVID-19 infection and reported the risk of barotrauma in both COVID and Non-COVID cohorts undergoing IMV. In these studies, barotrauma was defined as pneumothorax, pneumomediastinum, subcutaneous emphysema, and/or pneumopericardium. We excluded studies in which patients were not receiving IMV or had developed barotrauma due to iatrogenic cause. Retrieved studies were first imported onto EndNote Version 21 for removal of duplicates. Thereafter, they were filtered on the basis of their titles and abstracts, and for the remaining studies, full text was studied. The baseline study characteristics were extracted onto a standardized collection table by two independent reviewers (HFS and AS), and a third reviewer (SOJ) was consulted in case of any discrepancies. Risk of bias in the included studies was analyzed using the Newcastle-Ottawa Scale [5].

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Table 1. Forest plot assessing the incidence of barotrauma in Covid-19 vs. non Covid-19 patients

Study, Country	Year	Study Design	Total Patients (N)	Gender Distribution (Male)	Mean Age (Year)	Incidence of Barotrauma (N)	
						In Covid-19 Patients	In Non-Covid-19 ARDS Patients
Lemmers et al., Italy	2020	Retrospective cohort	332	239	69	23	3
McGuinness et al., USA	2021	Retrospective cohort	1082	698	63	196	49
E. Christoph et al.,	2021	Retrospective cohort	643	–	59	43	56

Statistical analysis was conducted using Review Manager [version 5.4; The Cochrane Collaboration, 2020]. To analyze the studies, Odds Ratio (OR) and 95% confidence intervals (CI) were calculated, by pooling the studies using a random effects model. This model was used keeping in view the heterogeneity in the studies and patient characteristics. Higgins I^2 was used to determine the heterogeneity between the studies.

Three studies [6–8] clinical and imaging data of patients seen between March 1, 2020, and April 6, 2020, who tested positive for COVID-19 and experienced barotrauma associated with invasive mechanical ventilation, were compared with patients without COVID-19 infection during the same period. Historical comparison was made to barotrauma rates of patients with acute respiratory distress syndrome from February 1, 2016, to February 1, 2020, at the authors' institution. Comparison of patient groups was performed using categoric or continuous statistical testing as appropriate, with multivariable regression analysis. Patient survival was assessed using Kaplan-Meier curves analysis. Results A total of 601 patients with COVID-19 infection underwent invasive mechanical ventilation (mean age, 63 years ± 15 [standard deviation]; 71% men met our inclusion criteria. 1997 patients (992 in CARDS group and 1005 in Non-Covid ARDS group) were thereby included in this meta-analysis, with mean age of participants being 63.67. (Figure 1). Our pooled analysis shows that the incidence of barotrauma is significantly higher in CARDS patients compared with Non-Covid ARDS patients receiving IMV (OR = 0.33, 95% CI = 0.13–0.83, p = 0.0001, I^2 = 89%) (Table 1). Two out of three of our included studies were of good quality judged by their score of 7 or more on the Newcastle Ottawa scale.

Our meta-analysis suggests that patients infected with CARDS undergoing IMV have an increased risk of developing barotrauma as compared to patients with ARDS due to other etiologies. This association strongly reflects that SARS CoV-2 infection presents with an atypical form of ARDS.9 Numerous studies have been conducted to explain the pathogenesis of barotrauma in CARDS patients, however the exact etiology remains to be established. Factors such as an exaggerated immune response caused by the virus [10], prolonged intubation times11 and lack of a consensus on the management strategy for different phenotypes of CARDS; namely L and H12CA admitted from March 15-June 20, 2020. PATIENTS. 77 patients with COVID-19 pneumonia. 75 patients met inclusion criteria. RESULTS. 21% of patients with severe COVID-19 sustained barotrauma (33% of patients receiving IMV, 8% of patients receiving (NIV, have been implicated at large.

Considering that the incidence of barotrauma is further increased in COVID-19 patients undergoing IMV, the need for the evaluation of an effective, standardized and a relatively safer ventilation strategy for this group of patients becomes highly significant. Further evidence-based studies are therefore required to determine the efficacy of the standard approach (high Positive end-expiratory pressure (PEEP) and low tidal volume) for the management of ARDS in these patients, and/or to devise a modified ventilation management plan aimed at optimizing the treatment of CARDS.

To the best of our knowledge, this is the first of its kind meta-analysis that establishes a significant link between the incidence of barotrauma and Covid-19 patients receiving IMV. However, it has several limitations. First, the systematic search brought forth a small number of observational studies, and thus they were unable to fully account for confounding factors. Second, our findings were subjected to significant heterogeneity that could not be explained. Third, the follow-up times for CARDS patients in all of our

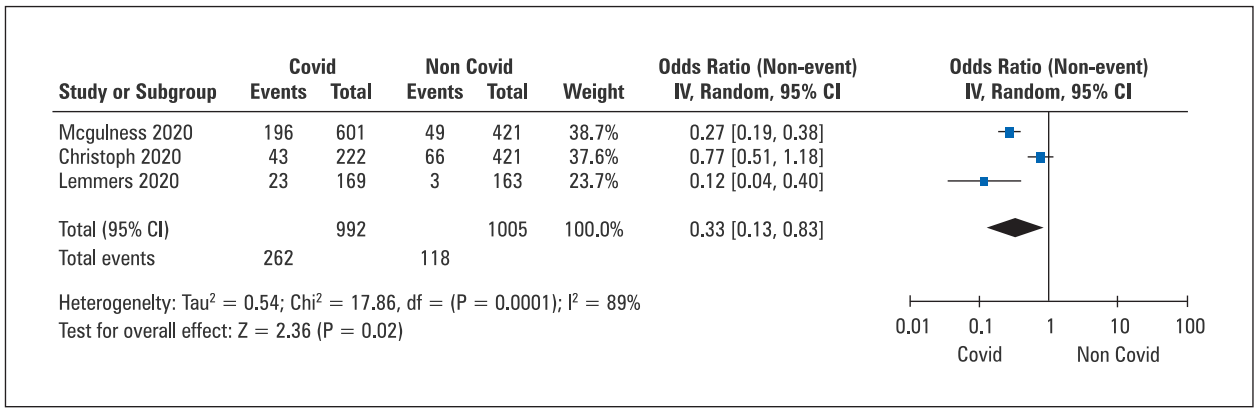

Figure 1. Characteristics of included studies

included studies were less than six months, and therefore could not predict the incidence of a late occurring barotrauma event in this group. Fourth, we could not perform the quality assessment of one of our included studies due to unavailability of complete data.

Conflict of interest

None declared.

References

1. Diaz R, Heller D. Barotrauma And Mechanical Ventilation. StatPearls Publishing 2021.
2. International consensus conferences in intensive care medicine: Ventilator-associated Lung Injury in ARDS. This official conference report was cosponsored by the American Thoracic Society, The European Society of Intensive Care Medicine, and The Societé de Réanimation de Langue Française, and was approved by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med. 1999; 160(6): 2118–2124, doi: 10.1164/ajrccm.160.6.ats16060, indexed in Pubmed: 10588637.
3. Rajdev K, Spanel AJ, McMillan S, et al. Pulmonary barotrauma in COVID-19 patients with ARDS on invasive and non-invasive positive pressure ventilation. J Intensive Care Med. 2021; 36(9): 1013–1017, doi: 10.1177/08850666211019719, indexed in Pubmed: 34013825.
4. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009; 339: b2700, doi: 10.1136/bmj.b2700, indexed in Pubmed: 19622552.
5. Wells G, Shea B, O'Connell D, et al. The newcastle-ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. ; 2014.
6. McGuinness G, Zhan C, Rosenberg N, et al. Increased incidence of barotrauma in patients with COVID-19 on invasive mechanical ventilation. Radiology. 2020; 297(2): E252–E262, doi: 10.1148/radiol.2020202352, indexed in Pubmed: 32614258.
7. Lemmers DHL, Abu Hilal M, Bnà C, et al. Pneumomediastinum and subcutaneous emphysema in COVID-19: barotrauma or lung frailty? ERJ Open Res. 2020; 6(4), doi: 10.1183/23120541.00385-2020, indexed in Pubmed: 33257914.
8. Christoph E, Kay S, Sjoding MW, et al. Barotrauma Among Patients with COVID-19 ARDS Versus Historical ARDS. American Journal of Respiratory and Critical Care Medicine . 2021; 203(A2491), doi: 10.1164/ajrccm-conference.2021.203.1_meetingabstracts.a2491.
9. Li Xu, Ma X. Acute respiratory failure in COVID-19: is it „typical" ARDS? Crit Care. 2020; 24(1): 198, doi: 10.1186/s13054-020-02911-9, indexed in Pubmed: 32375845.
10. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe. 2020; 27(6): 992–1000.e3, doi: 10.1016/j.chom.2020.04.009, indexed in Pubmed: 32320677.
11. Belletti A, Palumbo D, Zangrillo A, et al. Company ' S Public News and Information. 2020.
12. Kahn MR, Watson RL, Thetford JT, et al. High incidence of barotrauma in patients with severe Coronavirus Disease 2019. J Intensive Care Med. 2021; 36(6): 646–654, doi: 10.1177/0885066621989959, indexed in Pubmed: 33722090.