Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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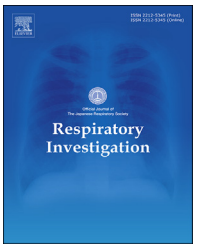

Letter to the Editor

An increasing rate of pneumomediastinum in non-intubated COVID-19 patients: The role of steroids and a possible radiological predictor

We read with great interest the article by Tacconi et al., recently published in *Respiratory Investigation*. In their work, the authors described the differences in the incidence and outcome of spontaneous pneumomediastinum (PMD) in patients with coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome (ARDS) between the first two pandemic waves. The authors found a higher incidence during the second wave at a quasi-significant level ($p = 0.05$) and a clearly significantly higher incidence when restricting the population to non-invasively ventilated or spontaneously breathing patients ($p = 0.031$) [1].

Our team has recently published a study assessing the differences in the incidence of pneumothorax (PNX)/PMD in non-invasively ventilated COVID-19 ARDS patients between the first and the second Italian waves. We identified only one PNX/PMD case in the first wave, while we identified 13 cases in the second wave ($p < 0.005$) [2].

We are pleased to read that another research group confirmed our findings. It is still unclear whether this difference originates from a different pattern of the disease or a difference in the management of the patients. As the only major differences in the clinical management at our institution between the two waves were the extensive use of dexamethasone and avoidance of hydroxychloroquine in the second wave, we hypothesized that steroid-induced lung frailty might be involved in a higher incidence of PNX/PMD [3]. A higher proportion of steroid use among patients who developed PNX/PMD has been identified also by other colleagues [4,5], although the difference has disappeared after the adjustment for respiratory severity at admission [5]. Notably, several authors have underlined that a large number of COVID-19 patients receive steroids despite a lack of indication [6] and potential harm [7,8].

Data from Tacconi et al. have also confirmed that the development of PMD/PNX is associated with higher in-hospital mortality [1]. A similar finding has been reported by Chopra et al. (63% with PNX vs. 49% without; $p = 0.04$) [9].

These data are in line with those identified in our recent systematic review, which confirms a 61.6% pooled estimate for mortality in COVID-19 patients who develop barotrauma [10,11]. Of note, we observed that the overall rate of barotrauma is more frequent in COVID-19 patients, with 14.7% of the patients having at least one barotrauma event (pooled estimates, 16.1%; 95% confidence interval [CI], 11.8%–20.4%), whilst in non-COVID-19 ARDS patients, barotrauma occurred in 31/493 patients (6.3%; pooled estimates, 5.7%; 95% CI, −2.1%–13.5%) [10].

It is possible that the higher incidence of barotrauma in COVID-19 ARDS patients depends on the specific pathogenesis of the disease, with microvascular thrombosis enhancing virus-induced direct damage to pneumocytes and thereby increasing the risk of lung frailty [12]. Altered respiratory mechanics with excessive respiratory drive and the development of dangerous transpulmonary pressures in spontaneously breathing patients may be responsible for the higher rate of PMD/PNX observed also in spontaneously breathing COVID-19 patients [13]. Similar pathogenesis occurring during asthma exacerbations has been suggested for some cases of PMD [14]. Indeed, we recently identified Macklin-like radiological sign (i.e., collection of air along peripheral bronchovascular sheaths detected using chest computed tomography [CT] scan [15]) as a strong predictor for the development of PNX/PMD within the next 8–12 days in COVID-19 ARDS patients [16,17]. The high effectiveness, accuracy, sensitivity, and specificity of the Macklin-like radiological signs as a predictor of PNX/PMD have been further validated by Paternoster et al. (sensitivity, 100% [95% CI: 89.1%–100%]; specificity, 99.85% [95% CI: 99.2%–100%]; accuracy, 99.8% [95% CI: 99.2%–100%]) [18].

Detection of Macklin-like radiological sign on the baseline chest CT scan in patients with respiratory failure may be used to identify patients at high risk for barotrauma and select patients for advanced management strategies, including ultraprotective ventilation [19] or early use of extracorporeal membrane oxygenation without invasive ventilation [20]. However, these hypotheses require further investigation.

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IRB approval

This letter does not involve a study enrolling patients. Accordingly, approval by the Institutional Ethics Committee was not required.

Conflict of interest

The authors have no conflict of interest to declare.

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