OBJECTIVES: Pneumomediastinum (PNM) is a rare complication of mechanical ventilation, but its reported occurrence in patients with acute respiratory distress syndrome secondary to COVID-19 is significant. The objective is to determine the incidence, risk factors, and outcome of PNM in non-ICU hospitalized patients with severe-to-critical COVID-19 pneumonia.

DESIGN: Retrospective observational study.

SETTING: Population-based, single-setting, tertiary-care level COVID treatment center.

PATIENTS: Individuals hospitalized with a diagnosis of COVID-19 pneumonia and severe to critical illness were included. Those hospitalized without respiratory failure, observed for less than 24 hours, or admitted from an ICU were excluded.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: All patients underwent a complete clinical assessment and chest CT scan, and were followed up from hospitalization to discharge or death. The outcome was the number of cases of PNM, defined as the presence of free air in the mediastinal tissues diagnosed by chest CT scan, in non-ICU hospitalized patients and the subsequent risk of intubation and mortality. PNM occurred in 48 out of 331 participants. The incidence was 14.5% (95% CI, 10.9–18.8%). A CT-Scan Severity score greater than 15 was positively associated with PNM (odds ratio [OR], 4.09; \( p = 0.002 \)) and was observed in 35.2% of the participants (95% CI, 26.2–44.9%). Noninvasive ventilation was also positively associated with PNM (OR, 4.46; \( p = 0.005 \)), but there was no positive association with airway pressures. Fifty patients (15%) were intubated, and 88 (27%) died. Both the risk for intubation and mortality were higher in patients with PNM, with a hazard ratio of 3.72 (\( p < 0.001 \)) and 3.27 (\( p < 0.001 \)), respectively.

CONCLUSIONS: Non-ICU hospitalized patients with COVID-19 have a high incidence of PNM, increasing the risk for intubation and mortality three- to four-fold, particularly in those with extensive lung damage. These findings help define the risk and outcome of PNM in severe-to-critical COVID-19 pneumonia in a non-ICU setting.

KEY WORDS: COVID-19; noninvasive ventilation; pneumomediastinum; positive-pressure ventilation

Pneumothorax (PNX) and pneumomediastinum (PNM) are recognized complications of mechanical ventilation, with barotrauma being the main causative mechanism (1–7). With the use of protective ventilation following the acute respiratory distress syndrome (ARDS) network trial (8), the incidence of PNX and PNM in mechanically ventilated patients has become rare. However, ARDS secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a notable exception with the reported frequency

*See also p. 145.

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ranging from 9% to 32% with invasive mechanical ventilation (IMV) (9–15). The incidence of PNM in patients undergoing noninvasive mechanical ventilation (NIV) or using high-flow nasal cannula (HFNC) is extremely rare. Patients with COVID-19 pneumonia, however, demonstrate a higher incidence of PNM while on NIV or HFNC (16–24), and even on low-flow oxygen therapy (LFOT). These findings suggest the presence of other pathophysiological mechanisms. We hypothesized that the higher incidence of PNM in COVID-19 pneumonia is the result of elevated baseline lung injury. Further, we expected PNM to worsen patients’ prognosis, increasing the risk for intubation and mortality.

This study aimed at investigating the incidence, clinical risk factors, and outcomes of PNM in non-ICU hospitalized patients with severe-to-critical COVID-19 pneumonia in a tertiary-care center.

**MATERIALS AND METHODS**

**Study Design, Setting, and Participants**

We retrospectively analyzed data from a cohort of SARS-CoV-2 patients consecutively admitted to the COVID center of the Campus Bio-Medico University and Teaching Hospital in Rome, Italy, between October 2020 and June 2021 (second Italian pandemic wave). Patients were prospectively followed up from hospitalization to discharge or death, whichever came first. All data were extracted from the electronic patient registry. This study conforms to the Helsinki Declaration and was approved by the local Ethical Committee (Comitato Etico Fondazione Policlinico Campus Bio-Medico; study title: PNEUMOMED-19; protocol: PAR 11.22 OSS; approval date: January 25, 2022).

Individuals included in the study were 18 years old or older with a diagnosis of COVID-19 pneumonia and severe-to-critical illness according to the World Health Organization disease severity classification (25). Diagnosis of COVID-19 infection was confirmed by a positive real-time reverse-transcriptase polymerase chain reaction from a nasopharyngeal swab, whereas COVID-19 pneumonia was diagnosed by a CT scan of the chest, with or without iodine contrast, according to clinical judgment. Individuals hospitalized without respiratory failure, those observed for less than 24 hours and those admitted from the ICU, regardless of whether they had received NIV, IMV, or extracorporeal membrane oxygenation, were excluded.

**Clinical Assessment and Management**

At COVID center admission, all patients underwent a clinical examination, arterial blood gas analysis, routine laboratory tests, and chest CT scan. CT scans were repeated for all patients with worsening symptoms and in most patients who remained hospitalized beyond day 10 irrespective. Patients were treated according to available guidelines; in particular, they all received corticosteroids and anticoagulation with low-molecular-weight heparin. Those presenting within 10 days of symptom onset received an add-on 5-day IV course of remdesivir, if not contraindicated. Only two patients received convalescent plasma. All patients received LFOT. Patients with acute hypoxemic respiratory failure despite LFOT were treated with HFNC, and those with hypercapnic respiratory failure or with HFNC requiring an Fio2 higher than 90% or with very severe hypoxemic respiratory failure but without an indication for endotracheal intubation received NIV. The choice between continuous positive airway pressure (CPAP) or NIV, as well as the choice of interface (i.e., full face mask and helmet), was up to discretion of the clinician and availability of resources. Data collected included demographics, comorbidities, date of symptom onset, date of hospital admission, Pao2/Fio2 ratio (Pao2/Fio2), CT-Scan Severity score index

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**KEY POINTS**

- **Question:** What are the incidence, risk factors, and outcome of pneumomediastinum (PNM) in non-ICU hospitalized patients with severe to critical COVID-19 pneumonia?
- **Findings:** The incidence of PNM is 14.5% and is higher in patients with a CT-scan severity score > 15. Patients with PNM have an HR for intubation of 3.72 and an HR for mortality of 3.27.
- **Meaning:** Patients with severe to critical COVID-19 pneumonia have a high incidence of PNM, particularly those with extensive lung damage. PNM increases the risk for intubation and in-hospital mortality three- to fourfold.

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(CT-SS), laboratory tests results, and prescribed medications. In case of CPAP/NIV, data about positive end-expiratory pressure (PEEP), pressure support, and Fio2 were recorded; data about tidal volume (Vt) and minute ventilation (MV E) were not available. The worst Pao2/Fio2 and the maximum CT-SS for patients who worsened during hospitalization and who underwent a new blood gas analysis and chest CT scan was noted.

CT-Scan Severity Score

CT-SS is a semiquantitative and clinically relevant (26) CT-scan based index used to quantify lung involvement in patients with COVID-19 pneumonia. The lobar involvement is visually quantified by radiologists as less than 25%, 25–49%, 50–75%, or greater than 75%. Lobar extension of pneumonia is scored using a Likert scale ranging from 0 (best) to 4 (worst). The sum of lobar scores gives the CT-SS and ranges from 0 (best) to 20 (worst) (27–29). All CT scans were independently reported by radiologists not participating in the study.

Pneumomediastinum and Outcomes

PNM, defined as the presence of free air in the mediastinal tissues, was diagnosed by chest CT-scan. The presence of PNX or subcutaneous emphysema (SE) was also reported. The date of the diagnosis of PNM was recorded, as well as the date of endotracheal intubation, discharge, or death. No evidence of PNM or PNX was seen on postprocedural radiographs for central line placement.

Statistical Analysis

Descriptive statistics were used to report participants’ characteristics. Categorical variables of patients with and without PNM were compared using chi-square test, whereas continuous variables were compared using Student t test or the Wilcoxon rank-sum test, as appropriate. The association between PNM and clinical, laboratory, and radiological variables was visually explored initially and then quantified using logistic regression models, with PNM as independent variable, and results reported using odds ratio (OR), 95% CIs, and p value. The worst Pao2/Fio2 and the maximum CT-SS were used to study their association with PNM at the peak of disease. A multivariable regression model, adjusted for age, sex, and comorbidities, was used to test the independency of the associations found in the univariable logistic regression models.

As patients developing PNM cannot experience death before diagnosis (“immortal time bias”), a time-dependent analysis was performed by dividing the follow-up time of each patient in different time periods (etime1: time from admission to PNM diagnosis; etime2: time from PNM diagnosis to outcome). Survival was estimated using the Kaplan-Meier estimator. The assumption of proportionality of hazards was checked using Schoenfeld residuals. The hazard ratio (HR) of mortality was estimated using a time-varying covariate Cox regression model, adjusting for age, sex, disease severity (CT-SS), and comorbidities. The risk of intubation was estimated with the Aalen-Johansen estimator, considering death as a competing risk. The assumption of proportionality of hazards was again checked using Schoenfeld residuals. The Cox regression model was used to calculate the HR of endotracheal intubation using Fine and Gray model, adjusting for age, sex, disease severity (CT-SS), and comorbidities.

All the analyses were performed using R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria, 2020), using the following packages: “survival,” “survminer,” and “cmprsk.”

RESULTS

Four hundred thirty-three patients with COVID-19 were admitted to our tertiary-care center during the study period, and 331 patients satisfied our predefined inclusion criteria (Fig. 1). The mean age of participants was 66 years (sd, 14), 70% were male, and hypertension was the most common comorbidity (55%). At admission, the mean Pao2/Fio2 was 172 (sd, 93), with 24% having a Pao2/Fio2 < 100, and the mean CT-SS was 11 (sd, 4). At the peak of the disease, the mean Pao2/Fio2 was 134 (sd, 89), and the mean CT-SS was 12 (sd, 5). PNM was diagnosed in 48 (14.5%) patients. It was isolated in 15 (31.3%), associated with SE in 14 (29.2%), associated with PNX in one (2.1%), and associated with both in 18 (37.5%). Of note, among the 33 patients who developed SE, all but one had concomitant PNX or PNM. Tube thoracostomy was performed in the left fifth intercostal space lateral to the anterior axillary line in only one case of PNM where there was a coexisting PNX, and the others were managed conservatively. The median length of
hospitalization was 13 days (interquartile range [IQR], 14). Fifty patients (15%) needed intubation, with a median time from admission to intubation of 8 days (IQR, 7 d), and 88 (27%) died.

No statistically significant difference was observed between the demographic characteristics and comorbidities of patients with or without PNM. Those with PNM had more impaired lung function at admission and at the peak of disease, with a lower mean $\text{PaO}_2/\text{FiO}_2$, a higher mean CT-SS, and a higher use of methylprednisolone (cumulative dose, 1355 mg), dihydrocodeine, and CPAP/NIV. They also showed higher mean levels of d-dimer (4,217 vs 1,926 ng/dL; $p = 0.01$) and C-reactive protein (10.6 vs 6.8 mg/dL; $p = 0.02$). The median hospitalization was longer in participants with PNM (25 vs 11 d; $p < 0.001$). Patients developing PNM had a significantly higher incidence of intubation, but there was no difference in the time from admission to intubation (8 d for both; $p = 0.60$) or in mortality. Further details on population characteristics are provided in e-Table 1 (http://links.lww.com/CCM/H214). Patients developing PNX in addition to PNM did not differ in baseline characteristics from those developing PNM alone, with the exception of a slightly higher CT-SS at the peak of disease (18 vs 16; $p = 0.02$).

Overall, the incidence risk of PNM in our cohort of non-ICU hospitalized patients was 14.5%, (95% CI, 10.9–18.8%), whereas the incidence rate of PNM was 3.5 cases per 100 inpatients/mo (95% CI, 2.6–4.68). The median time from symptom onset to PNM diagnosis was 17 days (IQR, 8 d), whereas the median time from hospital admission to PNM diagnosis was 8 days (IQR, 6 d).

PNM had an exponential association with CT-SS, with no cases observed in patients with CT-SS less than 7, 10 (21%) cases in patients with CT-SS from 7 to 15, and 38 (79%) of cases observed in patients with CT-SS greater than 15 (Fig. 2A). The incidence risk of PNM in patients with CT-SS greater than 15 was significantly higher: 35.2% (95% CI, 26.2–44.9%) versus 4.5% (95% CI, 2–8%).

The minimum and maximum airway pressures recorded in patients on CPAP and NIV were 6 and 27 cm H$_2$O, respectively. The risk of PNM did not increase with higher airway pressures (Fig. 2B). The use of dihydrocodeine, a $\text{PaO}_2/\text{FiO}_2$ less than 100, an increased C-reactive protein, and the cumulative dose of methylprednisolone showed a positive association with PNM. However, only
and CPAP/NIV (adjusted OR, 4.46 [p = 0.005]) were independently associated with PNM (Table 1).

Mortality was higher in patients developing PNM, with a median time from PNM to death of 22 days (95% CI, 15–45) and a sharp increase approximately a week after the diagnosis of PNM (Fig. 3A). The adjusted HR of mortality of PNM was 3.46 (p < 0.001). Age and CT-SS greater than 15, but not PNX, were other independent risk factors for mortality, with an HR of 1.08 (p < 0.001) and 2.36 (p < 0.001), respectively (Table 2). Likewise, the risk for intubation was higher in patients with PNM (Fig. 3B), with an HR of 3.63 (p < 0.001), whereas a CT-SS greater than 15, but not PNX, represented an independent risk factor (Table 2). The interaction between PNM and PNX was not associated with an increased risk of mortality (HR, 2.93; p = 0.32) or intubation (HR, 0.31; p = 0.29). The median time from PNM to intubation in patients developing PNM was 13 days (95% CI, 9–26 d).

DISCUSSION

This study demonstrates that the incidence of PNM in non-ICU hospitalized patients admitted to a
tertiary-care center with severe-to-critical COVID-19 pneumonia is 14.5% and is higher in those patients with a CT-SS greater than 15 and those on NIV/CPAP as opposed to HFNC/LFOT. The presence of PNM increased the risk for intubation and inhospital mortality three- to four-fold.

The incidence of PNM in this study is higher than that in previous studies reported in the literature. Kahn et al (15) reported an incidence of 8% in COVID-19 patients on NIV, whereas Rajdev et al (30) found an incidence of 4.7%. A possible explanation for this apparent discrepancy is the fact that Rajdev et al (30) retrospectively separated their cohorts into a noninvasive ventilation group and an invasive ventilation group. Their reported incidence is from the NIV group that excluded all patients initially on NIV but subsequently requiring IMV. Kahn et al (15) followed a similar study design, distinguishing between the incidence of PNM in patients who never received IMV from those who did, irrespective of the mode of initial management. We opted to report the

Table 2.

| Mortality | Crude HR (95% CI) (p) | Adjusted HR (95% CI) (p) |
|-----------|-----------------------|------------------------|
| Pneumomediastinum | **2.66 (1.65–4.29) (< 0.001)** | **3.27 (2.06–5.20) (< 0.001)** |
| Age (yr) | **1.06 (1.04–1.08) (< 0.001)** | **1.09 (1.06–1.11) (< 0.001)** |
| Sex (M) | **0.88 (0.55–1.40) (0.58)** | **1.35 (0.84–2.18) (0.22)** |
| CT-SS > 15 (vs ≤15) | **2.39 (1.50–3.81) (< 0.001)** | **2.33 (1.41–3.84) (< 0.001)** |

| Endotracheal Intubation | Crude HR (95% CI) (p) | Adjusted HR (95% CI) (p) |
|-------------------------|-----------------------|------------------------|
| Pneumomediastinum | **7.35 (4.20–12.85) (< 0.001)** | **3.72 (2.02–6.83) (< 0.001)** |
| Age (yr) | **0.99 (0.97–1.01) (0.46)** | **1.01 (0.98–1.03) (0.68)** |
| Sex (M) | **3.33 (1.42–7.81) (0.01)** | **3.05 (1.25–7.43) (0.01)** |
| CT-SS > 15 (vs ≤15) | **9.22 (4.32–19.7) (< 0.001)** | **5.77 (2.58–12.89) (< 0.001)** |

CT-SS = Chest CT-Scan Severity score, HR = hazard ratio.
Adjusted HR is calculated considering all the variables in the table and comorbidities (i.e., arterial hypertension, diabetes mellitus, and chronic obstructive pulmonary disease).
incidence of PNM in all patients presenting to our hospital with severe-to-critical COVID-19 and initially managed noninvasively regardless of whether they subsequently required IMV. In point of fact, excluding the number of patients in our cohort who eventually required IMV (n = 50), the incidence of PNM was only 7%. Another contributing factor could be that repeat CT scans were performed for all our patients with worsening symptoms. We subsequently observed an increasing incidence of PNM to a peak at day 14 postsymptom onset. Kahn et al (15) and Rajdev et al (30) do not explicitly mention follow-up CT scans for their cohorts.

As expected, the incidence of PNM varied depending on the type of respiratory support received. In patients requiring LFOT, none had PNM, whereas in those treated with HFNC and CPAP/NIV, the incidence was 8% and 33%, respectively. The risk of PNM was more than four times higher in patients on CPAP/NIV compared with patients on HFNC, confirming that positive-pressure ventilation is a cause of air leakage. Our observation is in line with other reports showing a high incidence despite the use of protective ventilation (9, 10). Of note, eight cases occurred in patients on HFNC. Since HFNC generates a PEEP (3–5 cm H₂O at flows of 30–50 L/min), it is reasonable to assume that even minimum PEEPs might cause air leakage even though the use of HFNC or CPAP with a PEEP less than 7.5 cm H₂O is generally considered protective (31, 32). Further, the incidence of PNM did not increase with higher maximum airway pressures, supporting the hypothesis that positive pressure is not the only trigger for PNM. Lemmers et al (10) reported similar findings with patients developing PNM/SE having comparable airway pressure parameters to patients who did not develop PNM/SE.

According to the Hamman-Macklin mechanism, PNM occurs when peripheral “alveoli” experience rapid and excessive barotrauma (high-pressure gradients from lungs to blood) following an increase in intrathoracic pressure (e.g., Valsalva maneuver and cough) or a decrease in vascular pressure (e.g., pulmonary thromboembolism). Although spontaneous breathing efforts during mechanical ventilation have long been recognized to improve oxygenation and survival (33), recent concerns have emerged highlighting the risk of self-induced lung injury (P-SILI), especially in those with a high respiratory drive (34–36). In patients with spontaneous breathing, the total applied pressure to the respiratory system is the sum of the pressure generated by the respiratory muscles (Pmus) and the pressure generated by the ventilator (Paw). As a result of the combination of Pmus and Paw, transpulmonary pressure increases, leading to lung tissue stress from larger Vts (34). In heterogeneous ARDS lungs, especially in more severe disease, the stress on “alveoli” varies in different parts of the lung (37, 38). Those more compliant and anterior receive the highest Vts, increasing the risk for overdistension and barotrauma. Supporting this hypothesis was the positive association between dihydrocodeine use, a proxy for clinically relevant coughing, and PNM (OR, 2.81; p = 0.09). Further, the positive association between PNM and CT-SS could be explained by increased minute ventilation causing lower negative intrathoracic inspiratory pressures exacerbating P-SILI. Increased minute ventilation in severe lung failure may be unavoidable, but limiting coughing with dihydrocodeine in patients with ARDS secondary to COVID-19 should be considered a means to reduce the risk of PNM. This is particularly so for patients with HFNC or with CPAP/NIV who showed a significantly higher prevalence of cough compared with patients requiring LFOT (11% and 8% vs 3%). Sudden increases in intrathoracic pressure during coughing may result in microscopic alveolar rupture leading to PNM (39), especially in patients with compromised lung parenchyma.

This study also demonstrated an exponential association between PNM and CT-SS. CT-SS was an independent risk factor and the strength of association with PNM was comparable to CPAP/NIV. We hypothesize that diffuse alveolar injury may lower the threshold for alveolar rupture, and the degree of lung involvement would be proportional to the risk for developing PNM.

In this cohort of non-ICU hospitalized patients with severe-to-critical COVID-19 disease, overall mortality was 27%, in line with the literature (40). PNM was associated with a worse prognosis, with an HR for mortality of 3.46 (95% CI, 2.11–5.66; p < 0.001). This result corroborates previous findings that report a higher mortality among mechanically ventilated COVID-19 patients who developed PNM (11, 41). In addition, it demonstrates that PNM is an independent risk factor, not associated with compromised lung parenchyma as quantified by CT-SS or by the presence of PNX. PNM is usually self-limiting and clinically insignificant (42), but particularly in those COVID-19 patients with severe-to-critical disease who cannot be easily weaned off
ventilator, it is an important prognosticator for worsening morbidity/mortality. When PNM increases in size or is located in certain regions of the mediastinum, for instance, the posterior, it leads to a reduction in arterial blood pressure and cardiac index (43, 44) that, together with the impaired ventilation, affect tissue oxygenation and organ functioning, exposing the individual to the risk of secondary complications. This time-dependent process might explain the steep increase seen in mortality several days after PNM diagnosis.

Similar to the literature on ICU patients, this study demonstrated that PNM is associated with a significant increase in median length of hospitalization and a higher chance of intubation, with an HR of 5.77 (95% CI, 2.58–12.89; \( p < 0.001 \)). McGuinness et al (11) report a similar prolonged hospitalization (median, 25 d) in ICU COVID-19 patients on IMV with barotrauma.

The comprehensive clinical assessment and prospectively collected data, the use of CT scan and not chest radiography for PNM diagnosis, the large sample size, and the correction for the “immortal time bias” make the information about PNM in non-ICU hospitalized patients with COVID-19 pneumonia reliable and unique in the literature. The study, however, had some limitations. Not all patients underwent repeat CT scans, which were reserved for patients with worsening symptoms and most, but not all, patients who remained hospitalized beyond day 10. This may have excluded patients who developed PNM without respiratory compromise and those discharged early. Patients classified in the CPAP/NIV group were those who received this treatment although ventilation was not continuous for all the patients and some received HFNC. It was, therefore, not possible to isolate PNM that occurred exclusively during HFNC. Nevertheless, this strengthens the hypothesis that CPAP/NIV is only one of the determinants of PNM and that it can also occur at the lower PEEP generated during HFNC treatment. The lack of data on \( V_t \) and \( MV_{fe} \) prevented us from investigating whether volutrauma might occur despite the use of a protective ventilation. However, previous findings reported that volutrauma is not involved in the genesis of PNM (9). Finally, the lack of pulmonary compliance data did not allow us to investigate the association between different COVID-19 pneumonia phenotypes and the risk for PNM. The lack of information on the premorbid status of lung parenchyma also prevented us from correcting for prior lung disease.

**CONCLUSIONS**

Non-ICU hospitalized patients with severe-to-critical COVID-19 pneumonia have a high incidence of PNM, particularly those with compromised lung parenchyma (CT-SS > 15) and those on NIV/CPAP as opposed to HFNC/LFOT. Patients on HFNC still experienced some risk for developing PNM. PNM increases the risk of intubation and inhospital mortality. Based on these findings, efforts at promoting and improving a timely care of COVID-19 disease are expected to limit the lung damage and, in this way, to prevent the onset of PNM.

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