Article

Prognosis of Spontaneous Pneumothorax/Pneumomediastinum in Coronavirus Disease 2019: The CoBiF Score

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**Highlights:**

- Pneumothorax/pneumomediastinum developed without positive pressure ventilation among COVID-19 patients had high fatality.
- Presence of comorbidity, bilateral pneumothorax, and fever were related with in-hospital mortality among COVID-19 associated spontaneous pneumothorax/pneumomediastinum patients.
- The CoBiF score (Co = comorbidity, Bi = bilateral pneumothorax, F = fever) well-predicted the early mortality of these patients.

**What is the implication of the main finding?**

- The CoBiF score was validated in multinational cohorts, and it could improve early recognition and treatment of COVID-19 pneumothorax.

**Abstract:**

Objectives: Pneumothorax and pneumomediastinum are associated with high mortality in invasively ventilated coronavirus disease 2019 (COVID-19) patients; however, the mortality rates among non-intubated patients remain unknown. We aimed to analyze the clinical features of COVID-19-associated pneumothorax/pneumomediastinum in non-intubated patients and identify risk factors for mortality.

Methods: We searched PubMed, Scopus, and Embase from January 2020 to December 2021. We performed a pooled analysis of 151 patients with no invasive mechanical ventilation history from 17 case series and 87 case reports. Subsequently, we developed a novel scoring system to predict in-hospital mortality; the system was further validated in multinational cohorts from ten countries (n = 133).

Results: Clinical scenarios included pneumothorax/pneumomediastinum at presentation (n = 68), pneumothorax/pneumomediastinum onset during hospitalization (n = 65), and pneumothorax/pneumomediastinum development after recent COVID-19 treatment (n = 18). Significant differences were not observed in clinical outcomes between patients with pneumomediastinum and pneumothorax (±pneumomediastinum). The overall mortality rate of pneumothorax/pneumomediastinum was 23.2%. Risk factor analysis revealed that comorbidities bilateral pneumothorax and fever at pneumothorax/pneumomediastinum presentation were predictors for mortality. In the new scoring system, i.e., the CoBiF system, the area under the curve which was used to assess the predictability of mortality was 0.887. External validation results were also promising (area under the curve: 0.709).

Conclusions: The presence of comorbidity bilateral pneumothorax and fever on presentation are significantly associated with poor prognosis in COVID-19 patients with spontaneous pneumothorax/pneumomediastinum. The CoBiF score can predict mortality in clinical settings as well as simplify the identification and appropriate management of patients at high risk.

**Keywords:** pneumothorax; pneumomediastinum; coronavirus disease; coronavirus disease 2019; prediction model

1. Introduction

During the coronavirus disease 2019 (COVID-19) pandemic, complications such as pneumothorax (PNx) and pneumomediastinum (PMEx) frequently occurred, both independently and more commonly in conjunction with each other [1]. PNx, which was observed...
previously in severe acute respiratory syndrome coronavirus infection and the Middle East respiratory syndrome, is significantly associated with poor prognosis [2,3]. PNx was also observed among patients with COVID-19, with an estimated incidence of 0.56–4.2%, which increased among patients requiring intensive care [1,4,5]. PNx and PMEx are adverse predictors of mortality, especially among critically ill patients with COVID-19 [6,7]. In particular, substantially high mortality (13.8–63.0%) from PNx/PMEx has been reported in patients with COVID-19, which is worse than that for PNx/PMEx arising from other respiratory etiologies [5,8].

Despite this correlation between PNx/PMEx and COVID-19, PNx/PMEx occurs after the implementation of invasive mechanical ventilation (IMV) in most cases, implying the possibility of adverse effects attributable to barotrauma or complications of critical care. Furthermore, due to its rarity, the existing literature on spontaneous PNx/PMEx in patients who did not receive IMV mainly includes case reports/series and small retrospective studies. Therefore, the true clinical features of COVID-19-associated spontaneous PNx/PMEx remain relatively unknown. Moreover, despite the high associated mortality, to our knowledge, no scoring system for in-hospital mortality in such patients exists.

Therefore, we aimed to comprehensively review spontaneous PNx/PMEx in COVID-19 patients by pooling individual patient data from previous case reports and case series and developing a novel scoring system to predict in-hospital mortality. Additionally, we evaluated multinational cohorts in collaboration with the International COVID-19 Pneumothorax Working Group (ICP-WG) and externally validated our new scoring system using this external dataset.

2. Patients and Methods

2.1. Search Strategy and Selection Criteria

This systematic review was registered with PROSPERO (CRD42022295621) and performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P, Supplementary Table S1).

Articles on COVID-19 patients with PNx and/or PMEx who had not received IMV prior to PNx/PMEx onset, articles on patients with PNx/PMEx without a history of IMV who had been treated for COVID-19 within the past 3 months, and case reports and case series analyzing sufficient individual patient data were included. Articles reporting PNx/PMEx that developed after IMV or an unclear temporal relationship between the events and those on patients aged <14 years were excluded. Review articles, abstracts, letters to the editor, and articles that did not contain sufficient information on patient characteristics or outcomes were also excluded.

Two investigators (WW and VK) searched PubMed/Medline, Embase, and Scopus up to 21 December 2021. The search terms employed are described in detail in Supplementary Table S2. Discrepancies regarding the inclusion/exclusion of studies were discussed and resolved by consensus among four investigators (WW, VK, JIS, and SL). The initial search yielded 303 studies after the elimination of duplicates. After reviewing the abstracts and full texts of these articles, we identified 104 studies (87 case reports and 17 case series) that met the inclusion criteria (Supplementary Table S3). The PRISMA flow diagram of the selection process is depicted in Supplementary Figure S1.

We extracted data on patient demographics, clinical characteristics of PNx/PMEx, COVID-19-associated treatments, radiologic findings, treatments, and clinical outcomes from each eligible case report and case series. Since few studies reported the laboratory findings at presentation, which were not consistent between studies, they were not included in this analysis.

2.2. Data Collection

We recorded the first author, publication year, and country of origin for each eligible case report or case series and collected information on demographic and clinical characteristics, including sex, age, comorbidities, smoking history, COVID-19-specific medical
treatments, symptoms, location of PNx/PMEx, existence of tension PNx or subcutaneous emphysema, chest computed tomography (CT) findings, treatments, duration of hospitalization, intensive care unit (ICU) admission, outcomes, and mortality.

3. Statistical Analysis

Data on continuous variables (age, oxygen saturation, and duration of hospitalization) are presented as median and interquartile ranges after determining the normality of the distribution. Differences in these variables were compared using the Mann–Whitney U test. Fisher’s exact test was performed to compare categorical variables [9]. We performed logistic regression to determine the predictive factors for in-hospital mortality; logistic regression was considered suitable for analysis as all deaths occurred within 2 months of hospitalization. Variables with \( p \)-values < 0.05 in univariate analysis were entered into multivariate analysis, and the variables were selected by backward elimination with a two-tailed \( p \)-value of <0.05. The scoring system for in-hospital mortality was devised based on significant factors as follows:

3.1. Step 1: Development and Internal Validation of the CoBiF Scoring System

Significant variables for in-hospital mortality \( (p < 0.05) \) in the multivariate logistic regression analysis were used to create the CoBiF scoring system. This scoring system was constructed using binary variables to ensure application ease. The score for each variable was measured based on its odds ratio (OR) and regression coefficient. Two variables (comorbidities and bilateral PNx) had similar magnitude for predicting the outcome (score for each: 1), whereas a third variable (fever at PNx/PMEx presentation) had a greater weight (score: 2). The summation of the three scores was used for the prediction model (score 0–4). If the value of any of these three parameters was missing, they were not included in the measurement of predictability. The discriminative power of the CoBiF model was assessed by plotting a receiver operating characteristic curve and calculating the area under the curve (AUC). Bias-corrected AUC was measured for internal validation, and the Mantel–Haenszel chi-square test was performed for calibration.

3.2. Step 2: External Validation

We developed an independent dataset with the same inclusion/exclusion criteria for external validation. First, authors who published retrospective studies in 2022 were approached, and their data were included [10–13]. Second, authors who reported COVID-19-related PNx/PMEx were contacted and encouraged to share data. This was performed by the ICP-WG. Finally, we gathered approved information on 133 patients from 10 countries. Thereafter, the performance of the CoBiF scoring model was assessed by computing the AUC.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 25.0 (SPSS Inc., IBM Corporation, Armonk, NY, USA) and R version 4.0.4 (R Core Team, Vienna, Austria) and were supervised by a medical statistician (HSL).

4. Results

4.1. Demographics and Clinical Characteristics

The patient characteristics and specific COVID-19 treatments are outlined in Table 1. The study population included 151 patients, of whom >80% were men (128/151, 84.8%), and approximately 60% (58.2%, 88/151) were aged <60 years. In total, 54.4% (80/147) of patients had underlying medical conditions, such as hypertension (27.3%), diabetes (11.9%), obesity (11.9%), and other respiratory diseases (11.2%) (Table 1).
| Factor                                      | Total       | PMEx | PNx ± PMEx | p-Value |
|---------------------------------------------|-------------|------|------------|---------|
| Age, years                                  | 56.0 [40.5, 67.5] | 54.0 [38.0, 64.5] | 57.5 [41.0, 68.0] | 0.340   |
| Sex                                         | 0.462       |      |            |         |
| Female                                      | 23 (15.2)   | 8/43 (18.6) | 15/108 (13.9) |         |
| Male                                        | 128 (84.8)  | 35/43 (81.4) | 93/108 (86.1) |         |
| Comorbidity                                |             |      |            |         |
| Comorbidity present                        | 80/147 (54.4) | 26/41 (63.4) | 54/106 (50.9) | 0.199   |
| Obesity                                    | 17/143 (11.9) | 9/40 (22.5) | 8/103 (7.8) | 0.021   |
| Diabetes mellitus                          | 17/143 (11.9) | 5/40 (12.5) | 12/103 (11.7) | 1       |
| Hypertension                                | 39/143 (27.3) | 10/40 (25.0) | 29/103 (28.2) | 0.835   |
| Respiratory disease                        | 16/143 (11.2) | 3/40 (7.5) | 13/103 (12.6) | 0.557   |
| COVID-19-targeted treatments                |             |      |            |         |
| Steroid                                    | 68/116 (58.6) | 25/35 (71.4) | 43/81 (53.1) | 0.100   |
| Convalescent plasma                        | 7/87 (8.0) | 0/29 (0.0) | 7/58 (12.1) | 0.090   |
| Intravenous immunoglobulin                 | 4/90 (4.4) | 2/30 (6.7) | 2/60 (3.3) | 0.598   |
| Lopinavir/ritonavir                        | 10/90 (11.1) | 4/30 (13.3) | 6/60 (10.0) | 0.726   |
| Remdesivir                                  | 19/92 (20.7) | 7/30 (23.3) | 12/62 (19.4) | 0.784   |
| Tocilizumab                                 | 13/90 (14.4) | 3/30 (10.0) | 10/60 (16.7) | 0.532   |
| Clinical manifestations                     |             |      |            |         |
| Chest pain                                  | 55/123 (44.7) | 11/34 (32.4) | 44/89 (49.4) | 0.107   |
| Cough                                       | 45/134 (33.6) | 13/40 (32.5) | 32/94 (34.0) | 1       |
| Fever                                       | 50/142 (35.2) | 1740 (42.5) | 33/102 (32.4) | 0.329   |
| Dyspnea                                     | 114/136 (83.8) | 33/40 (82.5) | 81/96 (84.4) | 0.801   |
| Oxygen saturation (room air), %             | 85.0 [80.0, 91.0] | 85.5 [81.8, 88.8] | 84.5 [80.0, 91.0] | 0.752   |
| Subcutaneous emphysema                      | 40/143 (28.0) | 13/42 (31.0) | 27/101 (26.7) | 0.683   |
| Chest CT findings                           |             |      |            |         |
| Emphysema                                   | 11/137 (8.0) | 5/36 (13.9) | 6/101 (5.9) | 0.157   |
| Ground-glass opacity                        | 106/130 (81.5) | 27/31 (87.1) | 79/99 (79.8) | 0.436   |
| Pleural effusion                            | 11/136 (8.1) | 2/35 (5.7) | 9/101 (8.9) | 0.728   |
| Treatments                                  |             |      |            |         |
| Conservative care                           | 73/135 (54.1) | 33/35 (94.3) | 40/100 (40.0) | <0.001  |
| Chest tube insertion                        | 82/131 (62.6) | 0/31 (0.0) | 82/100 (82.0) | <0.001  |
| Surgery                                     | 8/139 (5.8) | 0/37 (0.0) | 8/102 (7.8) | 0.109   |
| Non-invasive ventilation                    | 9/134 (6.7) | 5/34 (14.7) | 4/100 (4.0) | 0.046   |
| Invasive mechanical ventilation             | 30/145 (20.7) | 9/40 (22.5) | 21/105 (20.0) | 0.819   |
| Outcome                                     |             |      |            |         |
| Hospital stay, days                         | 13.0 [6.0, 19.0] | 14.0 [9.5, 15.8] | 13.0 [6.0, 19.0] | 0.975   |
| ICU admission                               | 51/138 (37.0) | 14/36 (38.9) | 37/102 (36.3) | 0.842   |
| Mortality                                   | 35/151 (23.2) | 9/43 (20.9) | 26/108 (24.1) | 0.831   |

All data are presented as n (%), n/N (%), or median [interquartile range]. COVID-19, coronavirus disease 2019; CT, computed tomography; ICU, intensive care unit; PMEx, pneumomediastinum; PNx, pneumothorax. Close monitoring and/or supplemental oxygen support through a nasal cannula and reservoir mask.
Most patients who developed PNx/PMEx commonly presented with dyspnea (83.8%), chest pain (44.7%), and fever (35.2%). PNx patients were diagnosed with radiologic features such as hyperlucency, hyperinflation, cavities, or cystic lesions. For PMEx-related radiologic findings, linear or curvilinear lucencies outlining mediastinal contours were mostly observed on CXR and/or CT. Other than these common features, chest CT revealed ground-glass opacity in most (81.5%) patients and emphysema (8.0%) and pleural effusion (8.1%) in some patients. Further, 37.0% of patients required intensive care, and the in-hospital mortality rate was high (23.2%).

4.2. Comparison between Pneumomediastinum and Pneumothorax ± Pneumomediastinum

There were no differences in age, sex, comorbidity, clinical manifestations, COVID-19-associated treatments, and radiological findings between the PMEx and PNx ± PMEx groups, although obesity was more common in the PMEx group (Table 1). Due to disease-specific characteristics, most patients with PMEx were conservatively treated. However, more patients with PMEx than those with PNx received non-invasive ventilation. Overall, disease severity did not differ between the groups with respect to ICU admission, IMV requirement, and mortality.

4.3. Clinical Characteristics According to Clinical Scenarios

Supplementary Table S4 describes the patients’ clinical scenarios, classified into the following three categories: (1) group A, patients who presented to the hospital with PNx/PMEx (n = 68, 45.0%) and who had COVID-19 symptoms for a median of 7 days prior to the hospital visit; (2) group B, patients who developed PNx/PMEx during inpatient management for COVID-19 (n = 65, 43.1%) at a median of 10.0 days from admission; and (3) group C, patients who underwent re-admission within a median of 16.5 days due to development of PNx/PMEx after discharge following recent COVID-19 treatment (n = 18, 11.9%). There were no remarkable differences in the characteristics of patients who presented with the three clinical scenarios; however, the frequency of symptoms such as fever (p < 0.001), cough (p = 0.001), and mortality (p = 0.087) was higher in groups A and B than in group C.

4.4. Patient Characteristics According to Mortality

Overall, the in-hospital mortality rate was 23.2% (35/151). Table 2 demonstrates the differences between survivors and non-survivors. Compared to survivors, non-survivors were older (median 52.5 versus 67.0 years, p < 0.001) and had a frequency of comorbidities (p < 0.001), such as obesity (p = 0.007) and hypertension (p = 0.008). At presentation, the frequency of fever (p < 0.001), cough (p = 0.032), dyspnea (p = 0.026), and symptoms other than chest pain (p = 0.005) were higher in patients with adverse outcomes than in those with non-adverse outcomes. Non-survivors received more COVID-19-specific medical treatments, such as steroids (p = 0.004) and remdesivir (p = 0.037) than survivors. Although there were no differences in radiological findings, the frequency of bilateral PNx (p = 0.029) was higher among non-survivors than among survivors.
Table 2. Clinical characteristics and outcomes of patients with PNx/PMEx according to outcome.

| Factor                        | Survivors | Non-Survivors | p-Value |
|-------------------------------|-----------|---------------|---------|
| **Age, years**                |           |               |         |
|                               | 52.5 [38.0, 65.0] | 67.0 [55.0, 75.0] | <0.001 |
| **Sex**                       |           |               |         |
| Female                        | 19/116 (16.4) | 4/35 (11.4) | 0.597  |
| Male                          | 97/116 (83.6) | 31/35 (88.6) |         |
| **Comorbidity**               |           |               |         |
| Comorbidity present           | 52/112 (46.4) | 28/35 (80.0) | <0.001 |
| Obesity                       | 8/108 (7.4) | 9/35 (25.7) | 0.007  |
| Diabetes mellitus             | 11/108 (10.2) | 6/35 (17.1) | 0.366  |
| Hypertension                  | 23/108 (21.3) | 16/35 (45.7) | 0.008  |
| Respiratory disease           | 13/108 (12.0) | 3/35 (8.6) | 0.761  |
| **COVID-19 targeted treatments** |           |               |         |
| Steroid                       | 45/88 (51.1) | 23/28 (82.1) | 0.004  |
| Convalescent plasma           | 6/63 (9.5) | 1/24 (4.2) | 0.668  |
| Intravenous immunoglobulin    | 4/66 (6.1) | 0/24 (0.0) | 0.570  |
| Lopinavir/ritonavir            | 8/66 (12.1) | 2/24 (8.3) | 1       |
| Remdesivir                    | 10/68 (14.7) | 9/24 (37.5) | 0.037  |
| Tocilizumab                   | 11/66 (16.7) | 2/24 (8.3) | 0.501  |
| Hydroxychloroquine*           | 20/67 (29.9) | 7/24 (29.2) | 1       |
| **Clinical manifestations**   |           |               |         |
| Chest pain                    | 49/95 (51.6) | 6/28 (21.4) | 0.005  |
| Cough                         | 29/102 (28.4) | 16/32 (50.0) | 0.032  |
| Fatigue                       | 3/95 (3.2) | 3/28 (10.7) | 0.131  |
| Fever                         | 21/108 (19.4) | 29/34 (85.3) | <0.001 |
| Dyspnea                       | 83/104 (79.8) | 31/32 (96.9) | 0.026  |
| Oxygen saturation (room air), % | 85.0 [80.0, 91.0] | 84.0 [75.0, 89.0] | 0.275  |
| **PNx/PMEx characteristics**  |           |               |         |
| Type of disease               |           |               | 0.038   |
| PMEx                          | 34/116 (29.3) | 9/35 (25.7) |         |
| PNx                           | 63/116 (54.3) | 13/35 (37.1) |         |
| Both                          | 19/116 (16.4) | 13/35 (37.1) |         |
| PNx location                  |           |               | 0.029   |
| Bilateral                     | 9/80 (11.2) | 8/22 (36.4) |         |
| Left                          | 32/80 (40.0) | 7/22 (31.8) |         |
| Right                         | 39/80 (48.8) | 7/22 (31.8) |         |
| Tension PNx                   | 15/104 (14.4) | 3/29 (10.3) | 0.762  |
| Subcutaneous emphysema        | 28/110 (25.5) | 12/33 (36.4) | 0.269  |
### Table 2. Cont.

| Factor                              | Survivors | Non-Survivors | p-Value |
|-------------------------------------|-----------|---------------|---------|
| **Chest CT findings**               |           |               |         |
| Emphysema                           | 7/107 (6.5) | 4/30 (13.3) | 0.256   |
| Ground-glass opacity                | 82/102 (80.4) | 24/28 (85.7) | 0.596   |
| Pleural effusion                    | 6/106 (5.7) | 5/30 (16.7)  | 0.065   |
| Visible bullae                      | 15/106 (14.2) | 1/30 (3.3)  | 0.195   |
| **Treatments**                      |           |               |         |
| Conservative care                   | 56/105 (53.3) | 17/30 (56.7) | 0.837   |
| Chest tube insertion                | 65/104 (62.5) | 17/27 (63.0) | 1       |
| Surgery                             | 8/108 (7.4) | 0/31 (0.0)   | 0.199   |
| Non-invasive ventilation            | 6/104 (5.8) | 3/30 (10.0)  | 0.418   |
| Invasive mechanical ventilation     | 11/111 (9.9) | 19/34 (55.9) | 0.001   |
| **Outcome**                         |           |               |         |
| Chest tube indwelling time, days    | 5.5 [3.0, 8.8] | 10.0 [6.0, 10.5] | 0.714   |
| Hospital stay, days                 | 12.0 [6.0, 25.0] | 14.0 [9.3, 18.0] | 0.938   |
| ICU admission                       | 23/107 (21.5) | 28/31 (90.3) | <0.001  |

All data are presented as n (%), n/N (%), or median [interquartile range]. COVID-19, coronavirus disease 2019; CT, computed tomography; ICU, intensive care unit; PMEx, pneumomediastinum; PNx, pneumothorax.

* Hydroxychloroquine was used during the early period of the pandemic when sufficient evidence was lacking. It should not be used anymore. Close monitoring and/or supplemental oxygen support through a nasal cannula and reservoir mask.

### 4.5. Risk Factor Analysis for in-Hospital Mortality

Multivariate logistic regression analysis revealed that the existence of comorbidities (OR: 3.87, 95% confidence interval [CI]: 1.27–11.9, p = 0.018), bilateral PNx (OR: 4.86; 95% CI: 1.08–21.9, p = 0.039), and fever at PNx/PMEx presentation (OR 24.1, 95% CI: 7.75–74.6, p < 0.001) were significantly associated with mortality (Table 3). The causes of death in these patients are enumerated in Supplementary Table S5. In total, 42.9% of patients died of respiratory failure due to the progression of COVID-19.

### Table 3. Risk factor analysis for in-hospital mortality among patients with COVID-19-associated PNx/PMEx.

| Factor                              | Univariate | Multivariable |
|-------------------------------------|------------|---------------|
|                                    | OR (95% CI) | p-Value       | OR (95% CI) | p-Value       |
| Male (ref. Female)                  | 1.52 (0.48–4.80) | 0.477         |             |               |
| Comorbidity present                | 4.35 (1.72–11.1) | 0.002         | 3.87 (1.27–11.9) | 0.018         |
| Diabetes mellitus                   | 1.82 (0.62–5.36) | 0.274         |             |               |
| Hypertension                        | 2.80 (1.19–6.57) | 0.018         | 1.22 (0.32–4.61) | 0.772         |
| Bilateral PNx                       | 3.67 (1.35–9.95) | 0.009         | 4.86 (1.08–21.9) | 0.039         |
| Tension PNx                         | 0.69 (0.18–2.55) | 0.572         |             |               |
| Subcutaneous emphysema              | 1.67 (0.73–3.83) | 0.222         |             |               |
| Type of diseases (ref. PMEx)        |             |               |             |               |
Table 3. Cont.

| Factor                  | Univariate          | p-Value | Multivariable       | p-Value |
|-------------------------|---------------------|---------|---------------------|---------|
| PNx                     | 0.78 (0.30–2.01)    | 0.612   | OR (95% CI)         |         |
| PNx with PMEx           | 2.58 (0.93–7.16)    | 0.068   | OR (95% CI)         |         |
| Symptoms–fever          | 24.0 (8.31–69.5)    | <0.001  | 24.1 (7.75–74.6)    | <0.001  |
| Symptoms–cough          | 2.52 (1.11–5.69)    | 0.026   | 1.13 (0.35–3.65)    | 0.838   |
| Symptoms–dyspnea        | 7.84 (1.01–60.8)    | 0.049   | 3.25 (0.33–31.9)    | 0.312   |
| CT findings–GGO         | 1.46 (0.46–4.70)    | 0.522   |                     |         |
| CT findings–emphysema   | 2.20 (0.60–8.08)    | 0.236   |                     |         |
| CT findings–pleural effusion | 3.33 (0.94–11.80) | 0.062   |                     |         |

CI, confidence interval; COVID-19, coronavirus disease 2019; CT, computed tomography; GGO, ground-glass opacity; OR, odds ratio; PMEx, pneumomediastinum; PNx, pneumothorax; ref: reference; Tx, treatments.

4.6. The CoBiF Scoring System for in-Hospital Mortality

A novel scoring system was designed to predict in-hospital mortality in patients who developed COVID-19-associated spontaneous PNx/PMEx. Multivariate logistic analyses revealed comorbidities, fever at PNx/PMEx presentation, and bilateral PNx as significant variables. Thus, the scoring system was named CoBiF (Co = comorbidities, Bi = bilateral PNx, F = fever) based on the components of this model. The predicted in-hospital mortality was proportional to the score—1.85%, 8.14%, 29.5%, 66.3%, and 90.3% with a CoBiF score of 0, 1, 2, 3, and 4, respectively (Figure 1). The AUC was 0.887 (95% CI: 0.822–0.951), and the Mantel–Haenszel chi-square test yielded a p-value of <0.0001, signifying a good fit between the model and observed data.

Figure 1. Probability of in-hospital mortality according to the CoBiF score.
4.7. Internal and External Validation of the CoBiF Scoring System

Internal validation was conducted using the bias-corrected AUC (0.818), which demonstrated good predictability. The overall patient characteristics in the internal and external datasets are presented in Table 4. The validation cohort had a worse medical condition in terms of age and comorbidities; the original geographic areas of the two datasets were notably different. The rates of adverse outcomes, such as ICU admission and mortality, were greater in the external dataset than in the internal dataset. The AUC of the CoBiF scoring system during external validation was 0.709 (95% CI: 0.622–0.796; Figure 2).

Table 4. Clinical characteristics and outcomes of patients: comparison of the training and validation cohorts.

| Factor                                      | Training Cohort \(^\dagger\) | Validation Cohort \(^\ddagger\) | p-Value |
|---------------------------------------------|------------------------------|-------------------------------|---------|
| Age, years                                  | 56.0 [40.5, 67.5]            | 64.0 [51.0, 72.0]             | 0.004   |
| Sex                                         |                              |                               | <0.001  |
| Female                                      | 23/151 (15.2)                | 49/133 (36.8)                 |         |
| Male                                        | 128/151 (84.8)               | 84/133 (63.2)                 |         |
| Comorbidities present                       | 80/147 (54.4)                | 101/133 (75.9)                | <0.001  |
| Diabetes mellitus                           | 17/143 (11.9)                | 36/133 (27.1)                 | 0.002   |
| Obesity                                     | 17/143 (11.9)                | 32/133 (24.1)                 | 0.011   |
| Hypertension                                | 39/143 (27.3)                | 69/133 (51.9)                 | <0.001  |
| Respiratory diseases                        | 16/143 (11.2)                | 19/133 (14.3)                 | 0.473   |
| Geographical area of data sources           |                              |                               | <0.001  |
| Africa                                      | 3/151 (2.0)                  | 0/133 (0.0)                   |         |
| Asia                                        | 41/151 (27.2)                | 100/133 (75.2)                |         |
| Europe                                      | 59/151 (39.1)                | 33/133 (24.8)                 |         |
| North America                               | 42/151 (27.8)                | 0/133 (0.0)                   |         |
| South America                               | 6/151 (4.0)                  | 0/133 (0.0)                   |         |
| Clinical scenario                           |                              |                               | <0.001  |
| Initial presentation                        | 68/151 (45.0)                | 56/133 (42.1)                 |         |
| During hospitalization                      | 65/151 (43.9)                | 77/133 (57.9)                 |         |
| Recent recovery from COVID-19               | 18/151 (12.2)                | 0/133 (0.0)                   |         |
| Presenting symptom of PNx/PMEx             |                              |                               |         |
| Chest pain                                  | 55/123 (44.7)                | 48/128 (37.5)                 | 0.251   |
| Cough                                       | 45/134 (33.6)                | 86/128 (67.2)                 | <0.001  |
| Dyspnea                                     | 114/136 (83.8)               | 106/128 (82.8)                | 0.870   |
| Fever                                       | 50/142 (35.2)                | 76/133 (57.1)                 | <0.001  |
| Oxygen saturation at room air               | 85.0 [80.0, 91.0]            | 87.0 [80.0, 90.0]             | 0.784   |
| Type of PNx/PMEx                            |                              |                               | 0.004   |
| PNx alone                                   | 43/151 (28.5)                | 19/133 (14.3)                 |         |
| PMEx alone                                  | 76/151 (50.3)                | 69/133 (51.9)                 |         |
| PNx + PMEx                                  | 32/151 (21.2)                | 45/133 (33.8)                 |         |
Table 4. Cont.

| Factor                                      | Training Cohort ‡ | Validation Cohort § | p-Value |
|---------------------------------------------|-------------------|---------------------|---------|
|                                             | n = 151           | n = 133             |         |
| PNX/PMEx-related characteristics            |                   |                     |         |
| Subcutaneous emphysema                      | 40/143 (28.0)     | 62/133 (46.6)       | 0.002   |
| Tension PNx                                 | 18/133 (13.5)     | 9/103 (8.7)         | 0.305   |
| PNx location                                |                   |                     | 0.282   |
| Bilateral                                   | 17/102 (16.7)     | 26/107 (24.3)       |         |
| Left                                        | 39/102 (38.2)     | 43/107 (40.2)       |         |
| Right                                       | 46/102 (45.1)     | 38/107 (35.5)       |         |
| Radiological findings on chest CT           |                   |                     |         |
| Visible Bullae                              | 16/136 (11.8)     | 8/128 (6.2)         | 0.137   |
| Ground-glass opacity                        | 106/130 (81.5)    | 102/128 (79.7)      | 0.754   |
| Pleural effusion                            | 11/136 (8.1)      | 14/128 (10.9)       | 0.529   |
| Treatment                                   |                   |                     |         |
| Conservative care                           | 73/135 (54.1)     | 45/129 (34.9)       | 0.002   |
| Chest tube drainage                         | 82/131 (62.6)     | 97/133 (72.9)       | 0.087   |
| Surgery                                     | 8/139 (5.8)       | 2/128 (1.6)         | 0.106   |
| Outcome                                     |                   |                     |         |
| Hospital stay, days                         | 13.0 [6.0, 19.0]  | 17.0 [9.0, 26.0]    | 0.016   |
| ICU admission                               | 51/138 (37.0)     | 98/133 (73.7)       | <0.001  |
| Mortality                                   | 35/151 (23.2)     | 83/133 (62.4)       | <0.001  |

All data are presented as n (%), n/N (%), or median [interquartile range]. COVID-19, coronavirus disease 2019; CT, computed tomography; ICU, intensive care unit; PMEx, pneumomediastinum; PNx, pneumothorax. ‡ Data from case series and case reports based on the systematic review. § Patients from the International COVID-19 Pneumothorax Working Group (ICP-WG).

Figure 2. Receiver operating characteristic (ROC) curve and area under the curve (AUC) of the CoBiF score on internal and external validation.
5. Discussion

This study described the clinical manifestations, management, and prognosis of spontaneously developed PNx/PMEx among COVID-19 patients based on the current literature. This study included observations from various countries and reported real-world data by including institutions with limited resources. We have developed a novel CoBiF scoring system to predict in-hospital mortality among patients with COVID-19 who developed PNx/PMEx without prior IMV. Notably, we incorporated COVID-19 patient data from eight countries and evaluated their disease severity.

Each factor included in the CoBiF scoring system seemed to incorporate the results of previous studies on the prognosis of COVID-19 patients, representing various risk factors for mortality. These factors include age, symptoms (fever, hemoptysis, dyspnea, and loss of consciousness), comorbidities (number of diseases, cancer history, and hypertension), and laboratory findings (D-dimer level, neutrophil-to-lymphocyte ratio, lactate dehydrogenase level, and bilirubin level) [14–16]. Fever was considered a poor prognostic sign based on an Iranian national data [17], and it was observed more commonly in COVID-19-associated PNx/PMEx than in non-COVID-19-associated PNx [5]. However, the clinical interpretation of fever needs caution since the causes of it could differ according to the patients’ population; patients with fever had more underlying medical conditions in this study. As multicollinearity was not observed between comorbidity and fever in the analysis for in-hospital mortality, we could not definitively describe possible other causes for fever. In this study, the presence of fever seemed to be more related to the severity of COVID-19 infection. Even so, clinicians should consider diverse reasons for fever depending on patients’ characteristics.

The general predictive factors for COVID-19 also seem to be effective in predicting the prognosis of COVID-19-associated PNx/PMEx because they bear similarities to the risk factors used in the CoBiF score. Since most causes of death in our study were merely suggestive of the detrimental consequences of COVID-19, the specific nature of the relationship between mortality and PNx/PMEx could not be ascertained conclusively. Therefore, the treatment approach for COVID-19-associated PNx/PMEx should be in accordance with general COVID-19 management protocols based on current knowledge.

However, clinicians should focus minutely on bilateral spontaneous PNx, which is rarely reported in other respiratory diseases. Simultaneous bilateral PNx occurs in 1.0–1.6% of all patients with PNx [18–20]. These patients have adverse outcomes during hospitalization and long-term mortality [21], necessitating timely intervention [20]. Specifically, PNx is considered a poor prognostic factor, which is observed mainly in patients with underlying lung disease [19]. It is unknown whether bilateral PNx occurs more commonly in COVID-19. However, bilateral pneumonia has been observed in 75–86% of hospitalized patients with COVID-19 [22,23], with the most common CT features being peripherally distributed ground-glass opacities and bilateral lung consolidation. Moreover, the extent and intensity of opacities are suggestive of a poor prognosis [24,25]. Moreover, barotrauma in patients with IMV, i.e., PNx/PMEx, occurs more frequently in COVID-19 than in other acute respiratory distress syndromes [7]. If the vulnerability of COVID-19-infected lungs causes the development of PNx/PMEx, bilateral PNx may indicate the fatal nature of COVID-19. The causal relationship and underlying pathophysiology require further investigation.

The mechanism underlying the pathogenesis of PNx/PMEx in COVID-19 remains obscure, and several hypotheses, including air leakage through the alveolar walls [26], increased vulnerability to PNx/PMEx arising from cyst formation due to severe damage induced by inflammation [27,28], and the Macklin effect as a cause for PMEx, have been postulated [29]. However, recent studies found no difference between the histopathologic findings of COVID-19 and other causes of lung injury [28,30]. Further comparative studies are needed to elucidate the specific mechanism underlying the formation of PNx/PMEx in COVID-19.

Our study has several limitations. First, although we presented data from multiple countries, the heterogeneity in their respective clinical environments and the capacity to
deal with the pandemic could have impacted the outcomes. Second, since cases were collected based on the authors’ recall and retrospective review of medical records, publication bias could arise from the inclusion of a few patients with poor outcomes. Additionally, this study could not present the laboratory findings of the patients’ medical conditions as they were selectively reported by most studies; thus, disease severity in the patients included in this review could not be compared quantitatively. Despite our great efforts to contact the authors of these case reports, we were unable to contact all authors and validate patient data. Moreover, the medical management of COVID-19 in the included cases was highly heterogeneous; some patients were treated with medications that are no longer used for COVID-19 treatment. Therefore, the study findings should be interpreted cautiously in the evolving contemporary context of the COVID-19 pandemic, viz., the different dominant virus strains, vaccine availability, and innate immunity level.

6. Conclusions

This study is important because it comprehensively reviewed cases of spontaneous PNx/PMEx in COVID-19 and presented a numerically measured prediction model. This novel CoBiF scoring system can be applied in other clinical settings, assist clinicians in identifying patients at high risk of mortality, and facilitate more prompt management. A further improved scoring system can be devised after the accrual of more evidence and research on spontaneous PNx/PMEx in COVID-19.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11237132/s1. Supplementary Table S1. Checklist summarizing compliance with PRISMA guidelines. Supplementary Table S2. Detailed search strategy according to database. Supplementary Table S3. The Lists of included studies [6,31–132]. Supplementary Table S4. Clinical characteristic and outcome of patients according to presenting clinical scenarios. Supplementary Table S5. The Causes of death among deceased patients (n = 35). Supplementary Figure S1. PRISMA flow diagram of selection processes.

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Abbreviations

Coronavirus disease 2019 COVID-19
Pneumothorax PNx
Pneumomediastinum PMEx
invasive mechanical ventilation IMV
International COVID-19 Pneumothorax Working Group ICP-WG
Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols PRISMA-P
computed tomography CT
intensive care unit ICU
odds ratio OR
area under the curve AUC
Statistical Package for the Social Sciences SPSS
confidence interval CI

References

1. Yang, X.; Yu, Y.; Xu, J.; Shu, H.; Xia, J.; Liu, H.; Wu, Y.; Zhang, L.; Yu, Z.; Fang, M.; et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. *Lancet Respir. Med.* 2020, 8, 475–481. [CrossRef] [PubMed]

2. Sihoe, A.D.; Wong, R.H.; Lee, A.T.; Lau, L.S.; Leung, N.Y.; Law, K.I.; Yim, A.P. Severe acute respiratory syndrome complicated by spontaneous pneumothorax. *Chest* 2004, 125, 2345–2351. [CrossRef]

3. Das, K.M.; Lee, E.Y.; Al Jawder, S.E.; Enani, M.A.; Singh, R.; Skakni, L.; Al-Nakshabandi, N.; AlDossari, K.; Larsson, S.G. Acute Middle East Respiratory Syndrome Coronavirus: Temporal Lung Changes Observed on the Chest Radiographs of 55 Patients. *AJR Am. J. Roentgenol.* 2015, 205, W267–W274. [CrossRef] [PubMed]

4. Marciniak, S.J.; Farrell, J.; Rostron, A.; Smith, I.; Openshaw, P.J.M.; Baillie, J.K.; Docherty, A.; Semple, M.G. COVID-19 pneumothorax in the UK: A prospective observational study using the ISARIC WHO clinical characterisation protocol. *Eur. Respir. J.* 2021, 58, 2100929. [CrossRef] [PubMed]

5. Miró, Ò.; Llorens, P.; Jiménez, S.; Piñera, P.; Burillo-Putze, G.; Martin, A.; Martin-Sánchez, F.J.; Garcia-Lambechets, E.J.; Jacob, J.; Alquézar-Arbé, A.; et al. Frequency, Risk Factors, Clinical Characteristics, and Outcomes of Spontaneous Pneumothorax in Patients with Coronavirus Disease 2019: A Case-Control, Emergency Medicine-Based Multicenter Study. *Chest* 2021, 159, 1241–1255. [CrossRef]

6. López Vega, J.M.; Parra Gordo, M.L.; Diez Tascón, A.; Ossaba Vélez, S. Pneumomediastinum and spontaneous pneumothorax as an extrapulmonary complication of COVID-19 disease. *Emerg. Radiol.* 2020, 27, 727–730. [CrossRef]

7. McGuinness, G.; Zhan, C.; Rosenberg, N.; Azour, L.; Wickstrom, M.; Mason, D.M.; Thomas, K.M.; Moore, W.H. High Incidence of Barotrauma in Patients with COVID-19 Infection on Invasive Mechanical Ventilation. *Radiology* 2020, 202352. [CrossRef]

8. Palumbo, D.; Campochiaro, C.; Belletti, A.; Marinoci, A.; Dagna, L.; Zangrillo, A.; De Cobelli, F. Pneumothorax/pneumomediastinum in non-intubated COVID-19 patients: Differences between first and second Italian pandemic wave. *Eur. J. Intern. Med.* 2021, 88, 144–146. [CrossRef]

9. Lee, S.W. Methods for testing statistical differences between groups in medical research: Statistical standard and guideline of Life Cycle Committee. *Life Cycle 2022*, 2, e1. [CrossRef]

10. Udwadia, Z.E.; Toraskar, K.K.; Pinto, L.; Mullerpatan, J.; Wagh, H.D.; Mascarenhas, J.M.; Gandhi, B.M.; Tripathi, A.; Sunaval, A.; Agrawal, U.; et al. Increased frequency of pneumothorax and pneumomediastinum in COVID-19 patients admitted in the ICU: A multicentre study from Mumbai, India. *Clin. Med.* 2021, 21, e615–e619. [CrossRef]
11. Marza, A.M.; Petrica, A.; Lunegau, D.; Sutoi, D.; Mocanu, A.; Pettache, I.; Mederle, O.A. Risk Factors, Characteristics, and Outcome in Non-Ventilated Patients with Spontaneous Pneumothorax or Pneumomediastinum Associated with SARS-CoV-2 Infection. Int. J. Gen. Med. 2022, 15, 489–500. [CrossRef] [PubMed]

12. Hamouri, S.; AlQudah, M.; Albawaih, O.; Al-zoubi, N.; Syaj, S. Spontaneous pneumothorax, pneumomediastinum and subcutaneous emphysema in non-ventilated COVID-19 patients. Future Sci OA 2022, 8, FS0771. [CrossRef] [PubMed]

13. Akram, J.; Yousaf, Z.; Alabbas, Y.; Almoyaaf, M.I.A.; Ibrahim, A.S.S.; Khurma, N. Epidemiological and outcome analysis of COVID-19-associated pneumothorax: Multicentre retrospective critical care experience from Qatar. BMJ Open 2022, 12, e053398. [CrossRef] [PubMed]

14. Liang, W.; Liang, H.; Ou, L.; Chen, B.; Chen, A.; Li, C.; Li, Y.; Guan, W.; Sang, L.; Lu, J.; et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Intern. Med. 2020, 180, 1081–1089. [CrossRef]

15. Estenssoro, E.; Loudet, C.I.; Rios, F.G.; Kanore Edul, V.S.; Plotnikow, G.; Andriam, M.; Romero, I.; Piezny, D.; Bezzi, M.; Mandich, V.; et al. Clinical characteristics and outcomes of invasively ventilated patients with COVID-19 in Argentina (SATI-COVID): A prospective, multicentre cohort study. Lancet Respir. Med. 2021, 9, 989–998. [CrossRef]

16. Han, Y.J.; Lee, K.H.; Lee, J.-Y.; Kim, O.Y.; Moon, S.; Kim, S.; Ryu, S.; Lee, D.; Kim, J.Y.; Kim, T.; et al. Extrapulmonary clinical manifestations of COVID-19: An umbrella review of meta-analysis. Life Cycle 2022, 2, e6. [CrossRef]

17. Sohrabi, M.-R.; Amin, R.; Maher, A.; Bahadorimonfare, A.; Janbaz, S.; Hannani, K.; Kolahi, A.-A.; Zali, A.-R. Sociodemographic determinants and clinical risk factors associated with COVID-19 severity: A cross-sectional analysis of over 200,000 patients in Tehran, Iran. BMC Infect. Dis. 2021, 21, 474. [CrossRef]

18. Graf-Deuel, E.; Knoblauch, A. Bilateral simultaneous spontaneous pneumothorax. Chest 1994, 105, 1142–1146. [CrossRef]

19. Sayar, A.; Turna, A.; Metin, M.; Kıcıkuykâyçi, N.; Solak, O.; Gürses, A. Simultaneous bilateral spontaneous pneumothorax report of 12 cases and review of the literature. Acta Chir. Belg. 2004, 104, 572–576. [CrossRef]

20. Lee, S.-C.; Cheng, Y.-L.; Huang, C.-W.; Tzao, C.; Hsu, H.-H.; Chang, H. Simultaneous bilateral primary spontaneous pneumothorax. Respirology 2008, 13, 145–148. [CrossRef]

21. Huang, T.-W.; Cheng, Y.-L.; Tzao, C.; Hung, C.; Hsu, H.-H.; Chen, J.-C.; Lee, S.-C. Factors related to primary bilateral spontaneous pneumothorax. Thorac. Cardiovasc. Surg. 2007, 55, 310–312. [CrossRef] [PubMed]

22. Bao, C.; Liu, X.; Zhang, H.; Li, Y.; Liu, J. Coronavirus Disease 2019 (COVID-19) CT Findings: A Systematic Review and Meta-analysis. J. Am. Coll. Radial. 2020, 17, 701–709. [CrossRef] [PubMed]

23. Schalekamp, S.; Huisman, M.; Dijk RA van Boomsma, M.F.; Freire Jorge, P.J.; de Boer, W.S.; Herder, G.J.M.; Bonarius, M.; Groot, O.A.; Jong, E. Model-based Prediction of Critical Illness in Hospitalized Patients with COVID-19. Radiol. Radiol. Soc. North Am. 2021, 298, E46–E54. [CrossRef] [PubMed]

24. Kanne, J.P.; Bai, H.; Bernheim, A.; Chung, M.; Kallmes, D.F.; Little, B.P.; Rubin, G.D.; Sverzuttelli, N. COVID-19 Imaging: What We Know Now and What Remains Unknown. Radiology 2021, 299, 204522. [CrossRef] [PubMed]

25. Toussie, D.; Voutsinas, N.; Finkelstein, M.; Cedillo, M.A.; Manna, S.; Maron, S.Z.; Jacobi, A.; Chung, M.; Bernheim, A.; Eber, C.; et al. Clinical and Chest Radiography Features Determine Patient Outcomes in Young and Middle-aged Adults with COVID-19. Radiology 2020, 297, E197–E206. [CrossRef] [PubMed]

26. Hamad, A.-M.M.; Elmahrhouk, A.F.; Abdullatayy, O.A. Alveolar air leakage in COVID-19 patients: Pneumomediastinum and/or pneumopericardium. Heart Lung 2020, 49, 881–882. [CrossRef] [PubMed]

27. Everden, S.; Zaki, I.; Trevelyan, G.; Briggs, J. COVID-19 pneumonitis and cystic lung disease, pneumothorax and pneumomediastinum. Thorax 2022, 77, 210–211. [CrossRef] [PubMed]

28. Konopka, K.E.; Nguyen, T.; Jentzen, J.M.; Rays, O.; Schmidt, C.J.; Wilson, A.M.; Farver, C.F.; Myers, J.L. Diffuse alveolar damage (DAD) resulting from coronavirus disease 2019 Infection is Morphologically Indistinguishable from Other Causes of DAD. Histopathology 2020, 77, 570–589. [CrossRef]

29. Belletti, A.; Palumbo, D.; Zangrillo, A.; Fominskii, E.V.; Franchini, S.; Dell’Acqua, A.; Marinisco, A.; Monti, G.; Vitali, G.; Colombo, S.; et al. Predictors of Pneumothorax/Pneumomediastinum in Mechanically Ventilated COVID-19 Patients. J. Cardiothorac. Vasc. Anesth. 2021, 35, 3642–3651. [CrossRef]

30. Ferrando, C.; Suarez-Sipmann, F.; Mellado-Artigas, R.; Hernández, M.; Gea, A.; Arruti, E.; Aldecoa, C.; Martinez-Pallí, G.; Martinez-González, M.A.; Slutsky, A.S.; et al. Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS. Intensive Care Med. 2020, 46, 2200–2211. [CrossRef]

31. Amoah, K.; Gunasekaran, K.; Rahi, M.S.; Buscher, M.G. A case of secondary tension pneumothorax in COVID-19 pneumonia in a patient with no prior history of lung disease. SAGE Open Med. Case Rep. 2020, 8, 2050313X20967504. [CrossRef] [PubMed]

32. Caviezel, C.; Weiss, L.; Haessig, G.; Alfaré, C.; Haberecker, M.; Varga, Z.; Frauenfelder, T.; Opitz, I. Case report of sequential bilateral spontaneous pneumothorax in a never-ventilated, lung-healthy COVID-19-patient. Int. J. Surg. Case Rep. 2020, 75, 441–445. [CrossRef] [PubMed]

33. Ferreira, J.G.; Rapparini, C.; Gomes, B.M.; Pinto, L.A.C.; Freire, M.S.D.S.E. Pneumothorax as a late complication of COVID-19. Rev. Inst. Med. Trop Sao Paulo 2020, 62, e61. [CrossRef] [PubMed]

34. Gillespie, M.; Dincher, N.; Fazio, P.; Okorji, O.; Finkle, J.; Can, A. Coronavirus disease 2019 (COVID-19) complicated by Spontaneous Pneumomediastinum and Pneumothorax. Respir. Med. Case Rep. 2020, 31, 101232. [CrossRef] [PubMed]
35. Kolani, S.; Houari, N.; Haloua, M.; Lamrani, Y.A.; Boubou, M.; Serraj, M.; Aamara, B.; Maaroufi, M.; Alami, B. Spontaneous pneumomediastinum occurring in the SARS-CoV-2 infection. *IDCases* 2020, 21, e00806. [CrossRef] [PubMed]

36. Mimouni, H.; Diyas, S.; Ouachou, J.; Laaribi, I.; Oujidi, Y.; Merbouh, M.; Bkiyer, H.; Housni, B. Spontaneous Pneumomediastinum Associated with COVID-19 Pneumonia. *Case Rep. Med.* 2020, 2020, 4969486. [CrossRef]

37. Muhammad, A.I.; Boynton, E.J.; Naureen, S. COVID-19 with bilateral pneumothoraces- case report. *Respir. Med. Case Rep.* 2020, 31, 101254. [CrossRef]

38. Rehman, T.; Josephson, G.; Sunbuli, M.; Chadaga, A.R. Spontaneous Pneumothorax in an Elderly Patient with Coronavirus Disease (COVID-19) Pneumonia. *Ochsner. J.* 2020, 20, 343–345. [CrossRef]

39. Shan, S.; Guangming, L.; Wei, L.; Xuedong, Y. Spontaneous pneumomediastinum, pneumothorax and subcutaneous emphysema in COVID-19: Case report and literature review. *Rev. Inst. Med. Trop Sao Paulo* 2020, 62, e76. [CrossRef]

40. Abluwalia, A.S.; Qarni, T.; Narula, N.; Sadiq, W.; Chalhoub, M.N. Bilateral pneumothorax as possible atypical presentation of coronavirus disease 2019 (COVID-19). *Respir. Med. Case Rep.* 2020, 31, 101217. [CrossRef]

41. Wang, W.; Gao, R.; Zheng, Y.; Jiang, L. COVID-19 with spontaneous pneumomediastinum and subcutaneous emphysema. *J. Travel. Med.* 2020, 27, taaa062. [CrossRef] [PubMed]

42. Liu, K.; Zeng, Y.; Xie, P.; Ye, X.; Xu, G.; Liu, J.; Wang, H.; Qian, J. COVID-19 with cystic features on computed tomography: A case report. *Medicine* 2020, 99, e20175. [CrossRef] [PubMed]

43. Rohailla, S.; Ahmed, N.; Gough, K. SARS-CoV-2 infection associated with spontaneous pneumothorax. *CMAJ* 2020, 192, E510. [CrossRef] [PubMed]

44. Bellini, D.; Lichtner, M.; Vicini, S.; Rengo, M.; Ambrogi, C.; Carbone, I. Spontaneous pneumomediastinum as the only CT finding in an asymptomatic adolescent positive for COVID-19. *BJR Case Rep.* 2020, 6, 20200051. [CrossRef] [PubMed]

45. Flower, L.; Carter, J.-P.L.; Rosales Lopez, J.; Henry, A.M. Tension pneumothorax in a patient with COVID-19. *BMJ Case Rep.* 2020, 13, e235861. [CrossRef] [PubMed]

46. Ucpinar, B.A.; Sahin, C.; Yanc, U. Spontaneous pneumomediastinum and subcutaneous emphysema in COVID-19 patient: Case report. *J. Infect. Public Health* 2020, 13, 887–889. [CrossRef]

47. Goldman, N.; Ketheevaran, B.; Wilson, H. COVID-19-associated pneumomediastinum. *Clin. Med. (Lond)* 2020, 20, e91–e92. [CrossRef]

48. Wegner, U.; Jeffery, G.; Abrajan, O.; Sampablo, I.; Singh, C. Spontaneous Pneumomediastinum Associated With SARS-CoV-2: Infrequent Complication of the Novel Disease. *Cureus* 2020, 12, e1989. [CrossRef]

49. Giné, C.; Lain, A.; García, L.; López, M. Thoracoscopic Bullectomy for Persistent Air Leak in a 14-Year-Old Child with COVID-19 Bilateral Pulmonary Disease. *J. Laparoscop. Adv. Surg. Tech. A* 2020, 30, 935–938. [CrossRef]

50. Khurram, R.; Johnson, F.T.F.; Naran, R.; Hare, S. Spontaneous tension pneumothorax and acute pulmonary emboli in a patient with COVID-19 infection. *BMJ Case Rep.* 2020, 13, e237475. [CrossRef]

51. Kong, N.; Gao, C.; Xu, M.-S.; Xie, Y.-L.; Zhou, C.-Y. Spontaneous pneumomediastinum in an elderly COVID-19 patient: A case report. *World J. Clin. Cases* 2020, 8, 3573–3577. [CrossRef] [PubMed]

52. Sonia, F.; Kumar, M. A Complication of Pneumothorax and Pneumomediastinum in a Non-Intubated Patient With COVID-19: A Case Report. *Cureus* 2020, 12, e10044. [CrossRef] [PubMed]

53. Alhakeem, A.; Khan, M.M.; Al Soub, H.; Yousaf, Z. Case Report: COVID-19-Associated Bilateral Spontaneous Pneumomediastinum-A Literature Review. *Am. J. Trop. Med. Hyg.* 2020, 103, 1162–1165. [CrossRef] [PubMed]

54. Quincho-Lopez, A.; Quincho-Lopez, D.L.; Hurtado-Medina, F.D. Case Report: Pneumothorax and Pneumomediastinum as Uncommon Complications of COVID-19 Pneumonia-Literature Review. *Am. J. Trop. Med. Hyg.* 2020, 103, 1170–1176. [CrossRef]

55. Yasukawa, K.; Vanamadevan, A.; Rollins, R. Bulla Formation and Tension Pneumothorax in a Patient with COVID-19. *Am. J. Trop. Med. Hyg.* 2020, 103, 943–944. [CrossRef]

56. Salah, O.; Faisal, M.; Alshahwani, I.; Elliday, A. Bilateral Hemopneumothorax in COVID-19. *Cureus* 2020, 12, e10314. [CrossRef]

57. Chen, X.; Zhang, G.; Tang, Y.; Peng, Z.; Pan, H. The coronavirus diseases 2019 (COVID-19) pneumonia with spontaneous pneumothorax: A case report. *BMJ Infect. Dis.* 2020, 20, 662. [CrossRef]

58. Fahad, A.M.; Mohammad, A.A.; Al-Khalidi, H.A.; Alshewere, A.S. Spontaneous pneumothorax as a complication in COVID-19 male patient: A case report. *Clin. Case Rep.* 2020, 8, 3116–3119. [CrossRef]

59. Fan, Q.; Pan, F.; Yang, L. Spontaneous pneumothorax and subpleural bullae in a patient with COVID-19: A 92-day observation. *Eur. J. Cardiothorac. Surg.* 2020, 58, 858–860. [CrossRef] [PubMed]

60. Bellini, R.; Saldanini, M.C.; Cuttin, S.; Mauro, S.; Scarppazza, P.; Cotsoglu, C. Spontaneous pneumothorax as unusual presenting symptom of COVID-19 pneumonia: Surgical management and pathological findings. *J. Cardiothorac. Surg.* 2020, 15, 310. [CrossRef]

61. Hameed, M.; Jamal, W.; Yousaf, M.; Thomas, M.; Haq, I.U.; Ahmed, S.; Ahmad, M.; Khatib, M. Pneumothorax in COVID-19 Pneumonia: A case series. *Respir. Med. Case Rep.* 2020, 31, 101265. [CrossRef] [PubMed]

62. Berhane, S.; Tabor, A.; Sahu, A.; Singh, A. Development of bullous lung disease in a patient with severe COVID-19 pneumonia. *BMJ Case Rep.* 2020, 13, e237455. [CrossRef] [PubMed]

63. Manna, S.; Maron, S.; Cedillo, M.A.; Voutsinas, N.; Toussie, D.; Finkelstein, M.; Steinberger, S.; Chung, M.; Bernheim, A.; Eber, C.; et al. Spontaneous subcutaneous emphysema and pneumomediastinum in non-intubated patients with COVID-19. *Clin. Imaging* 2020, 67, 207–213. [CrossRef] [PubMed]
91. Cancelliere, A.; Procopio, G.; Mazzitelli, M.; Lio, E.; Petullà, M.; Serapide, F.; Pelle, M.C.; Davoli, C.; Trecarichi, E.M.; Torti, C.; et al. A case report of pneumomediastinum in a COVID-19 patient treated with high-flow nasal cannula and review of the literature: Is this a “spontaneous” complication? Clin. Case Rep. 2021, 9, e04007. [CrossRef] [PubMed]

92. Bosher, O.; Syed, M.A.; Bikmalia, S. Favourable outcome after a delayed complication secondary to COVID-19. BMJ Case Rep. 2021, 14, e241049. [CrossRef] [PubMed]

93. Hua, D.T.; Shah, F.; Perez-Corrall, C. A case of spontaneous pneumomediastinum in a patient with severe SARS-CoV-2 and a review of the literature. SAGE Open Med. Case Rep. 2021, 9, 2050313X211010021. [CrossRef] [PubMed]

94. Belarbi, Z.; Brem, F.L.; Nasri, S.; Imane, S.; Noha, E.O. An uncommon presentation of COVID-19: Concomitant acute pulmonary embolism, spontaneous tension pneumothorax, pneumomediastinum and subcutaneous emphysema (a case report). Pan. Afr. Med. J. 2021, 39, 26. [CrossRef]

95. Heijboer, F.; Oswald, L.; Cretier, S.; Braunstahl, G.-J. Pneumomediastinum in a patient with COVID-19 due to diffuse alveolar damage. BMJ Case Rep. 2021, 14, e242527. [CrossRef]

96. Pimenta, I.; Varudo, R.; Lança, S.; Gonzalez, F.A. Exuberant spontaneous pneumothorax, pneumomediastinum, pneumopericardium and subcutaneous emphysema in COVID-19 pneumonia. BMJ Case Rep. 2021, 14, e243861. [CrossRef]

97. Marzocchi, G.; Vassallo, A.; Monteduro, F. Spontaneous pneumothorax as a delayed complication after recovery from COVID-19. BMJ Case Rep. 2021, 14, e243578. [CrossRef]

98. Buonsenso, D.; Gatto, A.; Graglia, B.; Rivetti, S.; Ferretti, S.; Paradiso, F.V.; Chiaretti, A. Early spontaneous pneumothorax, pneumomediastinum and pneumorrhachis in an adolescent with SARS-CoV-2 infection. Eur. Rev. Med. Pharmacol. Sci. 2021, 25, 4413–4417.

99. Cherian, A.; Jha, A.K.; Padala, S.R.A.N.; Senthilnathan, M. Unusual complications of spontaneous pneumomediastinum and subcutaneous emphysema in patients with SARS-CoV-2 infection: A case report. Indian J. Anesth 2021, 65, 483–486.

100. Montgomery, A.B.; Finck, C. Spontaneous hemopneumothorax in an adolescent with COVID-19. J. Pediatr. Surg. Case Rep. 2021, 69, 101852. [CrossRef]

101. Essa, R.A.; Ahmed, S.K.; Bapir, D.H.; Abubakr, C.P. Subcutaneous emphysema and spontaneous pneumomediastinum in non-intubated COVID-19 patient: Presenting unusual case report. Int. J. Surg. Case Rep. 2021, 84, 106071. [CrossRef] [PubMed]

102. Jafari, R.; Cegolon, L.; Masghsoudi, H.; Zhao, S.; Fathi, S.; Khedmat, L.; Javanbakht, M. Simultaneous Giant cavity pulmonary embolism, spontaneous pneumomediastinum and pneumorrhachis in an adolescent with SARS-CoV-2 infection. Respirol. Case Rep. 2021, 9, e243951. [CrossRef] [PubMed]

103. Hogan, G. COVID-19-Associated Pneumomediastinum: An Emerging Clinical Presentation. Cureus 2021, 13, e18796. [CrossRef] [PubMed]

104. Mohamed, A. Tension pneumothorax complicating COVID-19 pneumonia. Clin. Case Rep. 2021, 9, e04342. [CrossRef]

105. Jafari, R.; Cegolon, L.; Dehghanpoor, F.; Javanbakht, M.; Tabatabaei, S.M.H. Typical COVID-19 case with primary pneumomediastinum in a 37 year old male. Radiol. Case Rep. 2021, 16, 2286–2288. [CrossRef]

106. Ramezani, R.; Jafari, F.; Fahami, Y.; Pakniyat, A.; Rad, M.G. A case report of pneumomediastinum and subcutaneous emphysema associated with pandemic COVID-19 in a 43-year-old man. Clin. Imaging 2021, 76, 74–76. [CrossRef]

107. Protrka, M.R.; Ivanac, G.; Dudarić, L.; Vujević, F.; Brklijačić, B. Spontaneous pneumomediastinum, pneumothorax and subcutaneous emphysema: Radiological aspects of rare COVID-19 complications in 3 patients. Radiol. Case Rep. 2021, 16, 3237–3243. [CrossRef]

108. Alaviani, N.; Stephens, J.R.; DeWalt, D.A. Spontaneous Pneumomediastinum in a Patient with COVID-19 Pneumonia. J. Gen. Intern. Med. 2021, 36, 2845–2846. [CrossRef]

109. Bozan, Ö.; Atiş, Ş.E.; Çekmen, B. A rare complication of Covid-19: Spontaneous pneumothorax following pneumomediastinum; case report. Am. J. Emerg. Med. 2021, 47, 342.e1–342.e2. [CrossRef]

110. Hogan, G. COVID-19-Associated Pneumomediastinum: An Emerging Clinical Presentation. Cureus 2021, 13, e18287. [CrossRef]

111. Kasturi, S.; Muthirevula, S.; Chinthareddy, R.R.; Lingaraju, V.C. Delayed recurrent spontaneous pneumothorax post-recovery from COVID-19 infection. Indian J. Thorac. Cardiovasc. Surg. Surg. 2021, 37, 551–553. [CrossRef] [PubMed]

112. Luorio, A.; Nagar, F.; Attianese, L.; Grasso, A.; Torretta, G.; Fusco, P.; Ferrara, M.; Ferraro, F. Spontaneous Pneumomediastinum and Pneumothorax in Nonintubated COVID-19 Patients: A Multicenter Case Series. Am. J. Case Rep. 2021, 22, e931800-1–e931800-5. [CrossRef] [PubMed]

113. S. Rashid Ali, M.R. The first reported use of autologous blood pleurodesis for treatment of prolonged air leak in COVID-19-related spontaneous pneumomediastinum and pneumothorax: A case report. Respirol. Case Rep. 2021, 9, e0840. [CrossRef] [PubMed]

114. Komiya, K.; Hamanaka, R.; Shuto, H.; Yoshikawa, H.; Yokoyama, A.; Hiramatsu, K.; Kadota, J.-I. Re-expansion pulmonary edema following a pneumothorax drainage in a patient with COVID-19. BMC Pulm. Med. 2021, 21, 293. [CrossRef]

115. Fantin, A.; Castaldo, N.; Vailati, P.; Morana, G.; Patruno, V. Full medical treatment of COVID-19 associated large pneumothorax—A case report. Monaldi Arch. Chest. Dis. 2021, 92. [CrossRef]

116. Gutierrez-Arizá, J.C.; Rodríguez Yanez, T.; Martinez-Ávila, M.C.; Almanza Hurtado, A.; Dueñas-Castell, C. Pneumomediastinum and Pneumothorax Following Non-invasive Respiratory Support in Patients with Severe COVID-19 Disease. Cureus 2021, 13, e18796. [CrossRef]
117. Shah, S.; Pokhrel, A.; Chamlagain, R.; Adhikari, Y.R.; Kandel, B.; Dhital, R.; Paudel, B.S.; Yadav, S. Case report of a spontaneous pneumothorax after the recovery from COVID-19 pneumonia: A delayed complication. Clin. Case Rep. 2021, 9, e04971. [CrossRef] [PubMed]

118. Mitsuyama, Y.; Tanaka, S.; Ike, A.; Tanaka, J.; Fujiyama, G. Refractory pneumothorax secondary to COVID-19 treated by autologous blood patch pleurodesis. QJM 2021, hcab254. [CrossRef]

119. Polistina, G.E.; Lanza, M.; Di Somma, C.; Annunziata, A.; Fiorentino, G. A Rare Evolution to Pneumopericardium in Patient with COVID-19 Pneumonia Treated with High Flow Nasal Cannula. Medicina (Kaunas) 2021, 57, 1122. [CrossRef]

120. Ulutas, H.; Celik, M.R.; Gulcek, I.; Kalkan, M.; Agar, M.; Kilic, T.; Gulcek, E. Management of spontaneous pneumothorax in patients with COVID-19. Interact. CardioVascular Thorac. Surg. 2021, 34, ivab280. [CrossRef]

121. Habib, M.B.; Mohammad Obeidat, I.; Ali, K.; Abdelrazek, M.; Mohamed, M.F.H. Bronchopleural fistula causing persistent pneumothorax in COVID-19 pneumonia patient with no risk factors. Clin. Case Rep. 2021, 9, e05128. [CrossRef] [PubMed]

122. Panico, R.; Cai, J.; Butts, C.A.; To, J.Q. Understanding the course of COVID-19-induced pneumomediastinum. JAAPA 2021, 34, 31–33. [CrossRef] [PubMed]

123. Ufuk, F.; Yavas, H.G.; Kis, A. An unusual cause of spontaneous pneumothorax: Post-COVID-19 pulmonary fibrosis. Am. J. Emerg. Med. 2021, 49, 440.e5–440.e6. [CrossRef] [PubMed]

124. Abbas, M.; Bonnier, A.; Chong, W.H.; Chenna, P. Successful use of endobronchial valve for persistent air leak in a patient with COVID-19 and bullous emphysema. BMJ Case Rep. 2021, 14, e246671. [CrossRef]

125. Endres, F.; Spiro, J.E.; Bolt, T.A.; Tufman, A.; Ockert, B.; Swed, S. Subcutaneous emphysema and spontaneous pneumomediastinum in non-intubated COVID-19 patient: The first case report in Syria. Ann. Med. Surg. 2021, 72, 103074. [CrossRef]

126. Al Armashi, A.R.; Somoza-Cano, F.J.; Patell, K.; Homeida, M.; Desai, O.; Al Zubaidi, A.; Altaqi, B.; Ravakhab, K. Spontaneous pneumomediastinum: A collaborative sequelae between COVID-19 and self-inflicted lung injury—A case report and literature review. Radiol. Case Rep. 2021, 16, 3655–3658. [CrossRef]

127. Natarajan, P.; Skidmore, J.; Aduroja, O.; Kunam, V.; Schiller, D. Bilateral pneumatoceles resulting in spontaneous bilateral pneumothoraces and secondary infection in a previously healthy man with COVID-19. Bayl. Univ. Med. Cent. Proc. 2021, 34, 590–592. [CrossRef]

128. Sahagun, J.; Chopra, A.; David, A.G.; Dao, D.; Chittivelu, S. Secondary Spontaneous Pneumothorax in a COVID-19 Recovered Patient. Curesus 2021, 13, e16415. [CrossRef] [PubMed]

129. Younes, I.; Mohammadian, M.; Elkattawy, S.; Singh, Z.; Brescia, M.L. SARS-CoV-2 Associated with Pneumothorax: A Case Report and Literature Review. Cureus 2020, 12, e12191. [CrossRef] [PubMed]