Cite this article as: Farronato A, Travaglia C, Ravasin A, Aprile V, Corzani R, Sicolo E *et al.* Patients with coronavirus disease 2019 and spontaneous pneumothorax: a propensity-matched, multicentre case-control study. Interdiscip CardioVasc Thorac Surg 2025; doi:10.1093/icvts/ivaf076.

# Patients with coronavirus disease 2019 and spontaneous pneumothorax: a propensity-matched, multicentre case-control study

Arianna Farronato (10<sup>a,\*</sup>, Chiara Travaglia<sup>b</sup>, Alice Ravasin<sup>a</sup>, Vittorio Aprile (10<sup>c</sup>, Roberto Corzani<sup>d</sup>, Elisa Sicolo<sup>c</sup>, Adriano Peris<sup>e</sup>, Stefano Romagnoli<sup>b</sup>, Marco Lucchi (10<sup>c</sup>, Piero Paladini<sup>d</sup>, Luca Voltolini<sup>a</sup> and Alessandro Gonfiotti<sup>a</sup>

Received 15 November 2024; received in revised form 15 January 2025; accepted 25 March 2025

### COVID-19 patients with spontaneous pneumothorax: a propensity-matched, multicentre case-control study.

# Summary

In an Italian retrospective cohort of 474 non-vaccinated COVID-19 patients (March 2020–May 2021), 72 developed spontaneous pneumothorax or pneumomediastinum. Propensity score and multivariable regression analyses evaluated their association with in-hospital mortality and length of hospital stay, adjusting for age, sex, and comorbidities.

Outcome	Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
In-hospital mortality	Spontaneous pneumothorax	2.44	1.70–5.55	0.03
Length of hospital stay	Spontaneous pneumothorax	1.34	1.26–1.43	<0.001
	Spontaneous pneumomediastinu m	1.21	1.13–1.30	<0.001

Legend: Coronavirus disease-19 (COVID-19), Odds Ratio (OR), Confidence Interval (CI)

### **Abstract**

**OBJECTIVES:** Pneumothorax and pneumomediastinum have been frequently reported in coronavirus disease-19 (COVID-19), thus complicating the patient's overall health-care management and survival rate. The goal of this study was to evaluate the outcomes of patients with COVID-19 who developed spontaneous pneumothorax (SPN) or spontaneous pneumomediastinum (SPM).

**METHODS:** In this Italian multicentre retrospective cohort study, medical records of non-vaccinated COVID-19 patients, from March 2020 to May 2021, were analysed. To reduce the risk of bias due to unbalanced groups, a propensity score matching approach was

<sup>&</sup>lt;sup>a</sup>Thoracic Surgery Unit, Department of Experimental and Clinical Medicine, University Hospital of Florence Careggi, Florence, Italy

<sup>&</sup>lt;sup>b</sup>Department of Health Science, Section of Anaesthesia and Intensive Care, University Hospital of Florence Careggi, Florence, Italy

<sup>&</sup>lt;sup>c</sup>Division of Thoracic Surgery, Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine, University Hospital of Pisa, Pisa, Italy

<sup>&</sup>lt;sup>d</sup>Thoracic Surgery Unit, Department of Medical, Surgical and Neuroscience Sciences, University Hospital of Siena, 53100 Siena, Italy

eIntensive Care Unit and Regional ECMO Referral Centre, Section of Anaesthesia and Intensive Care, University Hospital of Florence, Careggi, Florence, Italy

<sup>\*</sup>Corresponding author. Tel: +39-55-7946807; fax: +39-55-7949557; e-mail: arianna.farronato@gmail.com (A. Farronato).

applied using logistic regression to estimate propensity scores. Separate multivariable generalized linear models were then used to assess the risk of in-hospital death and other outcomes.

**RESULTS:** A total of 474 patients were assessed, 72 of whom developed SPN or SPM. In separate multivariable generalized linear model regression analyses of the unmatched cohort, SPN [odds ratio (OR) 2.44, 95% confidence interval (CI) 1.7–5.55; P = 0.031] was associated with an increase in the in-hospital death rate, results confirmed even after matching the 2 cohorts. SPM (OR 1.21, 95% CI 1.13–1.30, P < 0.001) and SPN (OR 1.34, 95% CI 1.26–1.43, P < 0.001) were associated with an increase in the length of hospital stay. The risk of inhospital death also increased with age, comorbidities (classified by the Charlson comorbidity index) and smoking habits.

**CONCLUSIONS:** SPN in hospitalized COVID-19 patients may be associated with an increased risk of in-hospital death and prolonged hospitalization.

Keywords: Spontaneous pneumothorax • Spontaneous pneumomediastinum • COVID-19 • ARDS • Coronavirus • SARS-CoV-2

### **ABBREVIATIONS**

CCI Charlson comorbidity index Cls Confidence intervals COVID-19 Coronavirus disease-19 **GLM** Generalized linear model ICU Intensive care unit LOS Length of stay OR Odds ratio PN Pneumothorax PM Pneumomediastinum

SARS-CoV-2 Severe acute respiratory syndrome coronavi-

rus 2

SPM Spontaneous pneumomediastinum

SPN Spontaneous pneumothorax

### **INTRODUCTION**

### **Background**

Coronavirus disease-19 (COVID-19) is a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus that has infected over 600 million people and resulted in over 6 million deaths [1]. Pneumothorax (PN) and pneumomediastinum (PM) in COVID-19 cases have been shown to complicate survival and treatment [2]. Spontaneous pneumothorax (SPN) is air in the pleural space that collapses the lungs, and spontaneous pneumomediastinum (SPM) is air that is confined in the mediastinum [3]. The impact of SPN and SPM on COVID-19 outcomes is yet to be established [2-4]. Some cases link PN to mechanical ventilation and not to a spontaneous aetiology [5, 6].

### **Objectives**

This article retrospectively examined hospitalized COVID-19 patients to determine the clinical relevance of SPN and SPM. We compared patient treatment, surgical intervention and outcomes.

### **METHODS**

# Study design

A multicentre retrospective cohort study was conducted in hospitalized patients with COVID-19 who had not been vaccinated. The

primary outcome of our study was the in-hospital deaths of patients. The secondary outcomes were the need for recovery in the intensive care unit (ICU), the need for invasive ventilation, the length of stay (LOS) in the hospital and in the ICU. We used the STROBE checklist for a case-control study (see Supplementary Material, Table S1) [7].

# Setting

The included patients were admitted to the Careggi Hospital (Florence), Cisanello Hospital (Pisa) and Le Scotte Hospital (Siena) from March 2020 to May 2021. SARS-CoV-2 infection was diagnosed in all cases with a nasopharyngeal swab for reverse transcriptase-polymerase chain reaction. Two different medical teams analysed the medical records, so the results were double-checked for compliance with the study criteria.

# **Participants**

Eligibility criteria were COVID-19 diagnosis, with or without SPN or SPM, hospital admission for clinical or radiologic diagnosis of pneumonia, age 18 or more and SARS-CoV-2 non-vaccinated patients, as shown in Table 1. Exclusion criteria were possible iatrogenic PN or PM developed during invasive or non-invasive mechanical ventilation or after invasive procedures, patients with a positive result on an reverse transcriptase-polymerase chain reaction test but without COVID-19-related pneumonia or who had already been treated with a high dose of immunosuppressive agents.

### Variables and data sources

Data obtained from the medical records included demographics (age, sex, body mass index), past medical history, symptoms, laboratory investigations, radiologic images, clinical management, surgical management, patient progress, LOS in the hospital, admission to the ICU, LOS in the ICU, kind of ventilation and in-hospital death. The independent variables were comorbidities, SPN, SPM, smoking, age and sex. The outcomes were hospital LOS, admission to the ICU, LOS in the ICU, kind of ventilation and in-hospital death. The comorbidities were classified according to the Charlson comorbidity index (CCI) [8]. A smoker was defined as a person who smoked 100 cigarettes in their lifetime and currently smokes either every day or some days, according to the definition of the United States Centers for Disease Control and Prevention [9].

### Table 1: Eligibility, inclusion and exclusion criteria

### Eligibility criteria

Nasopharyngeal swab for reverse transcriptase–polymerase chain reaction positive for SARS-CoV-2

Not vaccinated for SARS-CoV-2

Age > 18 years

Hospital admission for clinical or radiologic diagnosis of pneumonia

Inclusion criteria for group A

Spontaneous pneumo-

Spontaneous pneumothorax

mediastinum Exclusion criteria

latrogenic pneumothorax (appeared while on mechanical ventilation or after invasive procedure)

latrogenic pneumomediastinum (appeared while on mechanical ventilation or after invasive procedure)

Positive PCR test results but without need of oxygen therapy Positive PCR test results but hospitalized and treated for other pathological conditions, eg, traumatic injury, abdominal disease, neurosurgical issues

Patients with COVID-19 but already treated for other reasons with a high dose of immunosuppressive agents or chemotherapy

COVID-19: coronavirus disease-19; PCR: polymerase chain reaction; SARS-Cov-2: severe acute respiratory syndrome coronavirus 2.

### **Bias**

The data collection database was standardized to minimize data collection bias, approved by the statistician's team and finally sent to the affiliated centres.

# Study size

All medical records of patients who were admitted to emergency rooms or wards of hospitals affiliated with the clinical trial were analysed, the goal being to collect as many patients as possible.

# Quantitative variables

Quantitative variables were expressed in terms of mean  $\pm$  standard deviation or median with interquartile range (25–75%).

### Statistical methods

Qualitative variables were summarized using frequencies (percentages). Normally distributed quantitative variables were assessed using the Student t-test, whereas qualitative variables were contrasted using  $\chi^2$  tests. Normality was validated using Q-Q plots and density plots.

Multivariable generalized linear models (GLMs) were used to estimate the probability of ICU admission, mechanical ventilation, prolonged ICU stay and extended hospital LOS. Logistic regression (binomial GLM with binomial distribution-logit link) was applied for binary outcomes, while Poisson regression (Poisson GLM with Poisson distribution-log link) was used to analyse count-based outcomes (e.g. hospitalization days). Results were reported as P-values, pseudo R-squared, confidence intervals (CIs) and odds ratios (ORs), with statistical significance set at P < 0.05. To minimize group imbalances and reduce bias, we

applied both 1:1 nearest neighbour matching and full matching, using logistic regression adjusted for age, sex and CCI. In the end, full matching achieved a better balance of covariates. After matching, balance for age, sex and comorbidities (classified with CCI) was evaluated using standardized mean differences. Analyses were conducted for both the full cohort and the full matching propensity score matching cohort. All analyses were conducted using R (R v4.2.2, 2022).

# **Ethics**

Our study was performed according to the Declaration of Helsinki. Ethics committees of all participating hospitals approved the study protocol (Code CEAVC 24977). We obtained all signed informed consent forms to use these medical data.

### **RESULTS**

# **Participants**

A total of 6789 medical records of patients with COVID-19 admitted to our hospitals were analysed. Four hundred and seventy-four patients were selected in accordance with eligibility criteria, as assessed in Fig. 1. Patients were divided into 2 groups: group cases (or group A), patients with SPN ± SPM and group controls (or group B), patients without SPN or SPM.

# Descriptive data

The comparison of variables in an unmatched cohort is reported in Table 2 (other main characteristics in Supplementary Material, Table S2).

Group A comprised 72 patients with a median age of 67 years; the majority were male (N=52,72.2%). SPN was right-sided in 33 (55.9%) and left-sided in 17 patients (28.8%) for 59 cases of PN. Case data are reported in Table 3. Twenty-nine patients with SPN required chest tube thoracostomy for tension PN or prolonged air leak. The mean number of days of a permanent drain was 9.69 (standard deviation 7.24). Surgical management due to persistent air leak was necessary in only 2 patients: 1 surgical bullectomy and 1 pleural lavage by thoracotomy for the concomitant development of pleural empyema (stage II).

Group B included the rest of the patients (402), mostly men (N = 321, 79.7%), with a median age of 68 years.

### **Outcome data**

A total of 101 controls died in the hospital (25.1%).

The median LOS in the hospital was 29.5 days for cases and 15 days for controls. The median LOS in the ICU was 20 days for cases and 12 days for controls. In group A, 65 patients (90.3%) were admitted to the ICU after SPM or SPN versus 178 patients (43.3%) from group B. In group A, 6 patients (8.4%) also required extracorporeal membrane oxygenation support after developing SPN, with an in-hospital mortality of 60% (3 patients). The inhospital mortality rate was significantly higher among the cases than among the controls (63.8% vs 25.1%).

### **COVID-19 Patients** S 6789 COVID-19 patients with Patients removed for varying C medical records who recovered in reasons: lost to follow-up, r our hospitals from March vaccinated patients, e 2020 to April 2021 incomplete medical records a n i Patients excluded for one n or more exclusion criteria: 3458 patients secondary or iatrogenic g pneumothorax, admission for other reasons, etc. 474 Patients included S t u d 72 patients with 402 patients without SPM and/or SPN y SPM or SPN

Figure 1: Flow chart. COVID-19: corona virus disease-19; PM: pneumomediastinum; PN: pneumothorax; SPM: spontaneous pneumomediastinum; SPN: spontaneous pneumothorax.

Variable Median N (%)	Group A, 72 patients	Group B, 402 patients with/ without SPN or SPM	All patients, $N = 474$	P-value
Age (years), median (Q1-Q3)	67.5 (58-73)	68.0 (56–77)	68.0 (56-77)	0.84
CCI, median (Q1-Q3)	3 (2-4)	3 (2-5)	3 (2-5)	0.16
Sex, male	52 (72.2%)	321 (79.8%)	373 (78.7%)	0.16
Smoking history				0.12
Never smoker	14 (19.4%)	89 (22.1%)	103 (21.7%)	
Current smoker	37 (51.4%)	147 (36.6%)	184 (38.8%)	
Ex smoker	14 (19.4%)	99 (24.6%)	113 (23.8%)	
Not assessed/unknown	7 (9.7%)	67 (16.6%)	74 (15.6%)	
ICU stay (days), median (Q1-Q3)	20 (6-30)	12 (0-18)	12 (0-20)	< 0.01
Hospital stay (days), median (Q1-Q3)	29.5 (19-45)	15.0 (7-28)	15.0 (8-29)	< 0.01
In-hospital deaths	46 (63.8%)	101 (25.1%)	147(36.7%)	0.01
ICU admissions	65 (90.3%)	178 (44.3%)	243 (51.3%)	< 0.01
Invasive mechanical ventilation	58 (80.6%)	152 (37.8)	210 (44.3%)	0.01

 ${\sf CCI: Charlson\ comorbidity\ index; ICU: intensive\ care\ unit;\ N:\ number;\ Q:\ quartile.}$ 

# Main results

In the multivariable GLM analysis of the unmatched cohort, SPN [odds ratio (OR) 2.44, 95% confidence interval (CI) 1.7-5.55,

P=0.031], smoking (OR 2.79, 95% CI 1.24-6.29, P=0.005), CCI (OR 1.27, 95% CI 1.08-1.49, P=0.004) and age (OR 1.03, 95% CI 1.00-1.05, P=0.043) were associated with increased in-hospital death (Table 4). SPN (OR 5.11, 95% CI 2.25-12.88, P=0.016),

smoking (OR 2.9, 95% CI 1.58-5.44, P = 0.039) and CCI (OR 1.19, 95% CI 1.03-1.37, P = 0.029) increased the risk of admission to the ICU. SPN also raised the likelihood of orotracheal intubation and invasive mechanical ventilation insertion (OR 4.94, 95% CI 2.35-11.11, P = 0.001), along with CCI (OR 1.18, 95% CI 1.02-1.36, P = 0.001) and smoking (OR 2.41, 95% CI 1.32-4.44, P = 0.001). SPN (OR 1.84, 95% CI 1.70-1.98, P = 0.001) and SPM (OR 1.27, 95% CI 1.16-1.38, P = 0.001) increased the duration of ICU stay, as did smoking (OR 1.38, 95% CI 1.27–1.49, P = 0.001) and CCI (OR 1.08, 95% CI 1.06-1.10, P < 0.0001). SPN (OR 1.34, 95% CI 1.26-1.43, P = 0.001) and SPM (OR 1.21, 95% CI 1.13-1.30, P = 0.001) were linked to longer LOSs, along with smoking (OR 1.10, 95% CI 1.04-1.17, P = 0.001) and CCI (OR 1.09, 95% CI 1.08-1.11, P = 0.001). After propensity score matching, 72 group B patients were selected. Student t-test results showed significant differences in outcomes between matched groups (in-hospital death P = 0.05, ICU admission P = 0.001, invasive ventilation P = 0.001, ICU stay P = 0.01 and hospitalization P = 0.05) (Table 5).

# **Table 3:** Characteristics of case patients

Variable	Numbers of patients	
Spontaneous pneumothorax	59	
Left side	17	
Right side	33	
Bilateral	9	
Spontaneous pneumomediastinum in total	25	
Only spontaneous pneumomediastinum	13	
Spontaneous pneumothorax requiring chest tube	29 (49.2%)	Days with drain in place Mean 9.7 (SD 7.24)
Surgical management	2 (2.8%)	
Dead	46 (63.8%)	

SD: standard deviation.

### **DISCUSSION**

### Key results

The mean hospital LOS for cases with SPN or SPM was 31.7 days versus 21.9 days in the controls, indicating longer hospital stays. ICU admissions were also significantly higher in the case group. Ekanem et al. [10] reported a median stay of 18.5 days, and Chopra et al. [11], a mean of 42 days. SPN is linked to longer ICU stays, greater invasive mechanical ventilation needs and worse outcomes, especially in patients with SARS-CoV-2 [2, 12]. Kawachi et al. [13] found 75% mortality in patients with SPN, and Ekanem et al. [10] found 36%. Some study results suggested worse outcomes due to severe lung damage rather than extent of SPN [14]. Chopra et al. [11] noted PN as a marker of severe COVID-19 lung disease, predicting poor prognosis in ventilated patients. Miro et al. found a fourfold increased risk of death in patients with PN [2], as did Marza et al. [4]. In contrast, Martinelli et al. [5] reported an overall survival rate of 63.1% in COVID-19 patients with SPN. Our SPN group had more in-hospital deaths (67.8% vs 36.7%), with a 2.5x increased risk according to multivariable analysis. PM was mostly self-limiting, except in rare instances, when the air leak was so massive that it could cause haemodynamic instability [19,20].

# Interpretation and generalizability

Our study found a 10% incidence of SPN and a 2.4% incidence of SPM, with a 13% incidence of having both. We included only COVID-19 patients requiring oxygen. Previous studies showed lower SPN incidence, such as 0.56% in Spain and 0.43% in the UK [2, 4]. Incidence differences may result from varied PN aetiologies (spontaneous vs iatrogenic) and small sample sizes. Tacconi *et al.* [15] reported a higher incidence of SPM in the second wave of the epidemic (1.36%), whereas our rate was 2.38%. Miro *et al.* found right-sided PN in 81% of COVID-19 patients, with our findings confirming 55% [2]. Chest tube insertion was

 Table 4:
 Multivariable generalized linear modelling regression analyses of unmatched cohort

Unmatched		In-hospital deaths	ICU admission	Invasive mechanical ventilation	ICU stay	Hospitalization
With spontaneous pneumothorax	<i>P</i> -value OR >1 (95% CI)	<b>0.031</b> <b>2.44</b> (1.7-5.55)	<b>0.016 5.11</b> (2.25–12.9)	<b>0.001 4.94</b> (2.35–11.11)	<b>0.035 1.84</b> (1.70-1.98)	<b>0.001 1.34</b> (1.26-1.43)
With spontaneous pneumomediastinum	<i>P</i> -value OR >1 (95% CI)	>0.05	>0.05	>0.05	<b>0.001</b> <b>1.27</b> (1.16-1.38)	<b>0.001 1.21</b> (1.13-1.30)
Male sex	<i>P</i> -value OR <1 (95% CI)	<0.05	>0.05	>0.05	<b>0.026</b> 0.86 (0.81-0.91)	<b>0.001</b> 0.85 (0.81-0.89)
Charlson comorbidity index	<i>P</i> -value OR >1 (95% CI)	<b>0.004</b> <b>1.27</b> (1.08–1.49)	<b>0.029</b> <b>1.19</b> (1.03-1.37)	<b>0.001</b> <b>1.18</b> (1.02-1.36)	<b>0.041</b> <b>1.08</b> (1.06-1.10)	<b>0.001</b> <b>1.09</b> (1.08-1.11)
Age	<i>P</i> -value OR >1 (95% CI)	<b>0.043 1.03</b> (1.00–1.05)	>0.05	>0.05	>0.05	>0.05
Smoker	<i>P</i> -value OR >1 (95% CI)	<b>0.005 2.79</b> (1.24–6.29)	<b>0.039</b> <b>2.9</b> (1.58-5.44)	<b>0.001 2.41</b> (1.32-4.44)	<b>0.001</b> <b>1.38(</b> 1.27-1.49)	<b>0.001</b> <b>1.10</b> (1.04-1.17 <b>)</b>

CI: confidence interval; ICU: intensive care unit; OR: odds ratio. The bold values indicate statistical significance.

Table 5:         comparison of variables and outcomes in matched cohort	Table 5:	comparison	of variables and	outcomes in	matched cohort
---	----------	------------	------------------	-------------	----------------

Variable Median N (%)	Case, matched 72 patients	Control, matched 72 patients	144 all patients matched	P-value	SMDFull matching
Age (years), median (Q1-Q3)	67.5 (58-73)	69.0 (55-72)	68.0 (56-73)	0.13	0.06
CCI, median (Q1-Q3)	3 (2-4)	3 (1-4)	3 (2-4)	0.24	-0.021
Sex, male	52 (72.2%)	50 (69.5%)	102 (70.8%)	1.00	0.06
Smoking history				0.56	
Never smoker	14 (19.4%)	12 (16.7%)	26 (18.0%)		
Current smoker	37 (51.4%)	26 (36.0%)	63 (43.8%)		
Ex smoker	14 (19.4%)	21 (29.2)	35 (24.3%)		
Not assessed/unknown	7 (9.7%)	13 (18.0%)	20 (14.0%)		
ICU stay (days)	20 (6-30)	0 (15)	11 (0-28)	0.01	
Hospitalization (days)	29.5 (19-45)	16.5 (18)	21.5 (14-40)	0.05	
In-hospital deaths	46 (63.8%)	14 (19.4%)	60 (41.7%)	0.001	
ICU admission	65 (90.3%)	34 (47.2%)	90 (62.5%)	0.001	
Invasive mechanical ventilation	58 (80.6%)	14(19.5%)	72 (50.0%)	0.001	

CCI: Charlson comorbidity index; ICU: intensive care unit; N: number; Q: quartile; SMD: standardized mean difference.

needed in 64% of patients in Chong's review, whereas a chest tube was required in only half of our patients [12]. Several studies reported similar rates of chest tube use (56-78%), and surgical interventions were rare [4-17]. Geraci et al. [10-17] treated 78% of PN cases with chest tubes, with 40% complications, whereas Ekanem et al. reported 73% of SPN cases treated similarly. Marza et al. [4] found that 56% of COVID-19 SPN cases were treated with chest tubes, and only 6.7% required operations. In Geraci's study, 5% of patients underwent operations for persistent air leaks, compared to 3.4% in our study [17]. Martinelli et al. [5] reported 1 case of bullectomy. Raveglia et al. [18] studied 83 patients with thoracic complications due to COVID-19; 33 of these had complicated PN, with a 72% survival rate. No age correlation was found in our study, aligning with Chong's review, though age remains an important factor related to death [2-12, 21]. Studies showed gender differences, with more males affected by SPN [4-10]; similar findings were seen in our data (69.5% male). Nonetheless, in the literature the correlation between smoking habits and poor prognosis in patients with COVID-19 is still controversial, as reported in the World Health Organization's Scientific Brief [22, 23, 24]. Comorbidities like hypertension and lung disease were common in our patients. We found a link between comorbidity, classified thanks to CCI, and more deaths and longer stays in the hospital and in the ICU. Chong et al. [12] found no link between pre-existing lung disease and PN risk, though the pathophysiology of PN in patients with COVID-19 remains unclear. Cates et al. [25] noted a higher risk of PN in COVID-19 patients compared to those with influenza. McGuinness et al. [16] attributed PN to barotrauma from mechanical ventilation, though this situation does not explain spontaneous PN. The mechanism of SPN may involve structural lung changes and inflammation. Kawachi et al. [13, 28] identified cyst formation in 2 cases of PN, and radiologic progression from consolidation to bullae was observed in some studies. Some authors blame pulmonary infarction for their aetiology [5-27]. Cysts were found in 4 patients in our study. Moreover, in SARS patients with acute respiratory distress syndrome, cyst development has been described and the process that seems to underline this disease was presumed to be ischaemic parenchymal damage and inflammation [26-29].

## Limitations

This study has several limitations:

- 1. Its retrospective design limits control over confounding variables.
- The small sample size reflects the low incidence of SPN/SPM, making cases and controls non-representative of all patients with COVID-19.
- 3. The multicentre setting may have introduced variations in patient management, despite adherence to international guidelines.
- 4. Missing data on body mass index and other variables prevented the inclusion of other patients in the analysis.
- Patient transfers from first-level hospitals may have led to data loss.
- 6. No standardized criteria were used for intubation in mechanically ventilated patients.
- 7. Surgical decisions were clinician-dependent, limiting assessment of the impact of the operations on outcomes.

### **CONCLUSION**

SPN in hospitalized COVID-19 patients may be linked to a higher risk of in-hospital death. Additionally, both SPM and SPN could lead to longer hospital stays. More research is needed to better understand the mechanisms behind these conditions in patients with COVID-19. Many aspects, including their causes, risk factors and the best ways to manage them, are still uncertain and need further exploration to improve patient care in the future.

# **SUPPLEMENTARY MATERIAL**

Supplementary material is available at ICVTS online.

### **FUNDING**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflict of interest: none declared.

# **DATA AVAILABILITY**

The data underlying this article will be shared on reasonable request to the corresponding author.

### **ETHICS STATEMENT**

Our study was conducted in accordance with the ethical principles outlined in the WMA Declaration of Taipei and received approval from the institutional research ethics committee (CEAVC 24977, approval date: 22 March 2024). Because it was a retrospective observational study, no interventions or modifications were made to standard clinical practice during the data collection process. All procedures adhered to ethical guidelines for the collection, storage and use of research data for scientific purposes. The retrospective nature of the study and the challenges posed by the COVID-19 pandemic during the first wave in Italy significantly influenced the consent process. During this period, many patients admitted to hospitals were critically ill, making it impossible to obtain written informed consent. Additionally, due to the ongoing pandemic and the need to limit unnecessary hospital visits to reduce the risk of viral transmission, patients were not asked to visit the hospital solely to provide written consent.

Given these circumstances, verbal consent was obtained from patients upon admission. This approach was approved by the ethics committee and aligned with the urgent need to minimize physical contact and prioritize patient safety. Furthermore, the study was multicentric, with participants residing in diverse and often distant geographical locations, which further complicated the logistics of obtaining written consent.

For patients who died during the study period, it was not feasible to secure specific consent posthumously. However, for surviving patients, comprehensive information about the study was provided through follow-up phone calls. This procedure ensured that all participants were fully informed about the purpose and scope of the research. Additionally, efforts were made to address any questions or concerns raised during these communications, especially for those who were unable to return to the hospital for follow-up visits.

By adhering to these measures, we ensured the ethical conduct of our study while prioritizing patient safety and compliance with pandemic-related restrictions. If further details are required, we remain available to provide additional clarification.

### **Author contributions**

Arianna Farronato: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing—original draft; Writing—review & editing. Chiara Travaglia: Data curation; Writing—review & editing. Alice Ravasin: Data curation. Vittorio Aprile: Data curation. Roberto Corzani: Data curation. Elisa Sicolo: Data curation. Adriano Peris: Validation. Stefano Romagnoli: Validation. Marco Lucchi: Supervision; Validation. Piero Paladini: Validation. Luca Voltolini: Supervision; Validation. Alessandro Gonfiotti: Conceptualization; Formal analysis; Project administration; Supervision; Validation; Writing—review & editing.

### **Reviewer information**

Interdisciplinary CardioVascular and Thoracic Surgery thanks Gonzalo Varela, Stefan B. Watzka and the other, anonymous reviewer(s) for their contributions to the peer review process of this article.

### **REFERENCES**

- World Health Organization. COVID-19 Weekly Epidemiological Update. 2022. https://www.who.int/docs/default-source/coronaviruse/situation-reports/2022 (30 December 2022, date last accessed).
- [2] Miro O, Llorens P, Jimenez S et al.; Spanish Investigators on Emergency Situations Team (SIESTA) Network. Frequency, risk factors, clinical characteristics, and outcomes of spontaneous pneumothorax in patients with coronavirus disease 2019: a case-control, emergency medicinebased multicenter study. Chest 2021;159:1241–55.
- [3] Jantz MA, Antony VB. Pathophysiology of the pleura. Respiration 2008; 75:121–33.
- [4] Marza AM, Petrica A, Lungeanu D et al. 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.
- [5] Martinelli AW, Ingle T, Newman J et al. COVID-19 and pneumothorax: a multicentre retrospective case series. Eur Respir J 2020;56:2002697.
- [6] Zantah M, Dominguez Castillo E, Townsend R et al. Pneumothorax in COVID-19 disease- incidence and clinical characteristics. Respir Res 2020:21:236.
- [7] Vandenbroucke JP, von Elm E, Altman DG et al.; STROBE initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med 2007; 147:W163-94.
- [8] Charlson ME, Pompei P, Ales KL et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. I Chronic Dis 1987;40:373–83.
- [9] Glossary of Adult Tobacco Use by the Centers for Disease Control and Prevention. https://www.cdc.gov/nchs/nhis/tobacco/tobacco\_glossary.htm.
- [10] Ekanem E, Podder S, Donthi N et al. Spontaneous pneumothorax: an emerging complication of COVID-19 pneumonia. Heart Lung 2021; 50:437-40.
- [11] Chopra A, Al-Tarbsheh AH, Shah NJ et al. Pneumothorax in critically ill patients with COVID-19 infection: incidence, clinical characteristics and outcomes in a case-control multicenter study. Respir Med 2021; 184:106464.
- [12] Chong WH, Saha BK, Hu K et al. The incidence, clinical characteristics, and outcomes of pneumothorax in hospitalized COVID-19 patients: a systematic review. Heart Lung 2021;50:599-608.
- [13] Kawachi J, Koyama H, Aida Y. Pneumothorax with coronavirus disease 2019 in non-ventilated patients: a single-center retrospective case series. Authorea Preprints 2021; PPR:PPR368231.
- [14] Shan S, Guangming L, Wei L et al. Spontaneous pneumomediastinum, pneumothorax and subcutaneous emphysema in COVID-19: case report and literature review. Rev Inst Med Trop Sao Paulo 2020:62:e76.
- [15] Tacconi F, Rogliani P, Leonardis F et al. Incidence of pneumomediastinum in COVID-19: a single-center comparison between 1st and 2nd wave. Respir Investig 2021;59:661–5.
- [16] McGuinness G, Zhan C, Rosenberg N et al. Increased incidence of barotrauma in patients with COVID-19 on invasive mechanical ventilation. Radiology 2020;297:E252-62.
- [17] Geraci TC, Williams D, Chen S et al. Incidence, management, and outcomes of patients with COVID-19 and pneumothorax. Ann Thorac Surg 2022;114:401-7.
- [18] Raveglia F, Scarci M, Rimessi A et al. The role of surgery in patients with COVID-19-related thoracic complications. Front Surg 2022; 9:867252.
- [19] Hamad AMM, Elmahrouk AF, Abdulatty OA. Alveolar air leakage in COVID-19 patients: pneumomediastinum and/or pneumopericardium. Heart Lung 2020;49:881-2.

- [20] Campisi A, Poletti V, Ciarrocchi AP et al. Tension pneumomediastinum in patients with COVID-19. Thorax 2020;75:1130-1.
- [21] Guo T, Shen Q, Guo W et al. Clinical characteristics of elderly patients with COVID19 in Hunan Province, China: a multicenter, retrospective study. Gerontology 2020;66:467–75.
- [22] World Health Organization. Smoking and COVID-19: Scientific Brief. 2020. https://www.who.int/news-room/commentaries/detail/smoking-and-covid-19 (23 January 2025, date last accessed).
- [23] Bense L, Eklund G, Wiman LG. Smoking and the increased risk of contracting spontaneous pneumothorax. Chest 1987;92:1009-12.
- [24] Shastri MD, Shukla SD, Chong WC *et al.* Smoking and COVID-19: what we know so far. Respir Med 2021;176:106237.
- [25] Cates J, Lucero-Obusan C, Dahl RM et al. Risk for in-hospital complications associated with COVID-19 and influenza–Veterans Health

- Administration, United States, October 1, 2018-May 31, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1528-34.
- [26] Wang J, Su X, Zhang T et al. Spontaneous pneumomediastinum: a probable unusual complication of coronavirus disease 2019 (COVID-19) pneumonia. Korean J Radiol 2020;21:627–8.
- [27] Sun R, Liu H, Wang X. Mediastinal emphysema, giant bulla, and pneumothorax developed during the course of COVID-19 pneumonia. Korean J Radiol 2020;21:541-4.
- [28] Liu K, Zeng Y, Xie P et al. COVID-19 with cystic features on computed tomography: a case report. Medicine (Baltimore) 2020; 99:e20175.
- [29] Joynt GM, Antonio GE, Lam P et al. Late-stage adult respiratory distress syndrome caused by severe acute respiratory syndrome: abnormal findings at thin-section CT. Radiology 2004;230:339–46.