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Letter to the editor

Characteristic outcomes and risk assessment of pneumothorax in 21 patients with COVID-19

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The occurrence of pneumothorax (PT) in SARS-CoV-2-infected patients is an uncommon complication that is not frequently reported. When reported, it is mostly observed in ventilated patients in the intensive care unit (ICU) [1,2]. However, PT does not exclusively occur on mechanical ventilation (MV) and can arise weeks after COVID-19 onset [3]. Furthermore, although the primary mechanism behind PT is related to barotrauma, the exact risk factors are unclear [4]. Hence, we assessed the incidence of PT and compared these patients with controls without PT to identify the main risk factors for PT.

1. Methods

We performed a monocentric retrospective analysis in a French tertiary care hospital, between March 1, 2020 and March 31, 2021. We included all SARS-CoV-2-infected patients who presented with PT, which was defined by the presence of PT on chest X-rays or chest computed tomography (CT) scans. However, we excluded patients with iatrogenic PT (such as direct perforation by catheter insertion, surgery, or pleural drainage). Data on the type of ventilation at PT onset (i.e. spontaneous, oxygen supply, high-flow cannula implantation or noninvasive ventilation [NIV], or MV) and outcomes were collected for each patient. These data were then compared with those of patients without PT who were hospitalized during the same period.

1.1. Statistical analysis

Categorical data were presented as the number of missing values and absolute and relative counts. Continuous variables were compared using the Wilcoxon test, whereas categorical data were compared using the chi-square test or Fisher's exact test.

2. Results

During the study period, 1656 patients with laboratory-confirmed SARS-CoV-2 infection were hospitalized. Of these, 25 patients exhibited PT complications. Four patients were excluded because they developed PT secondary to pleural puncture ($n = 1$), surgical procedure ($n = 1$), or central catheter insertion ($n = 2$). Thus, 21 patients were included in the PT group (15, 4, and 2 right, left, and bilateral PT cases, respectively). Among these patients, three had subcutaneous emphysema and PT, whereas one had pneumomediastinum, subcutaneous emphysema, and PT (Fig. 1).

Patients with PT included three women (14.3%) and 18 men (85.7%). Their median age was 67 years (range Q1–Q3, 57–78) and the median body mass index (BMI) was 27 kg/m^2 (range Q1–Q3, 24–33). Eight patients (38.1%) were hospitalized in non-ICU wards at the time of diagnosis, including two patients who were diagnosed after being transferred from the ICU. However, MV was initiated in all 13 patients (61.9%) who were diagnosed in the ICU. Five patients (23.8%) were on ambient air, including one patient hospitalized in a medical ward and four patients diagnosed in the emergency department. Two patients (9%) received conventional oxygen therapy, and one patient (4.5%) had air leakage after high-flow cannula implantation and NIV. This patient initially developed PM and subcutaneous emphysema on day 7 and PT on day 14 while receiving conventional nasal oxygen therapy. The median time between hospital admission and PT onset was 7 days (range 1–70). Among the 13 patients who developed PT during MV, the median time between PT diagnosis and initiation of MV was 3 days (range 1–25) and four patients were diagnosed with PT on the day of orotracheal

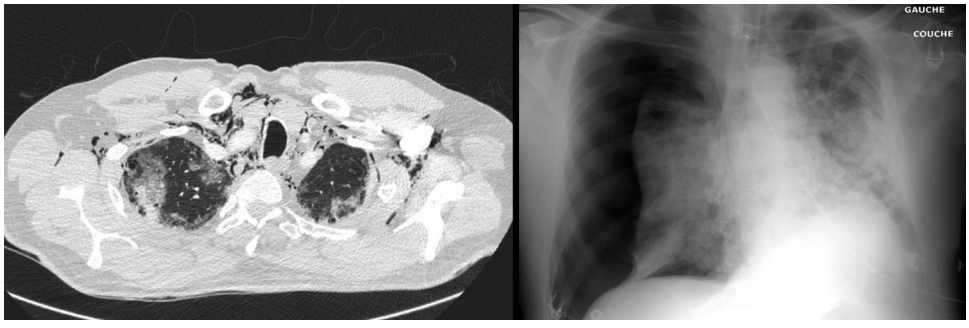

Fig. 1. Case of a 58-year-old male patient who developed pneumomediastinum or subcutaneous emphysema after high-flow cannula therapy and noninvasive ventilation (thoracic computed tomography, left panel) and who subsequently developed pneumothorax (chest X-ray, right panel).

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Table 1
Baseline characteristics, laboratory findings, and outcomes of patients.

		Pneumothorax patients (n = 21)	Controls (n = 1,631)	All patients (n = 1,652)	p
Gender	Male	18 (85.7%)	897 (55.0%)	915 (55.4%)	0.003
	Female	3 (14.3%)	734 (45.0%)	737 (44.6%)	
Age (years)	Median (Q1–Q3)	66.54 (57.4–78.1)	72.97 (60.5–83.5)	72.92 (60.4–83.5)	0.109
BMI (kg/m^2)	Missing (%)	8 (38.10%)	467 (28.63%)	475 (28.75%)	
	Median (Q1–Q3)	27.1 (24.3–32.9)	26.2 (22.8–30.2)	26.2 (22.8–30.2)	0.392
Risk factor(s)		19 (90.5%)	1443 (88.8%)	1462 (88.8%)	0.804
Chronic pulmonary disease		4 (19.0%)	402 (24.7%)	406 (24.7%)	0.536
Diabetes		5 (23.8%)	449 (27.6%)	454 (27.6%)	0.693
Cancer		4 (19.0%)	387 (23.8%)	391 (23.8%)	0.601
Neurological disorders		7 (33.3%)	337 (20.7%)	344 (20.9%)	0.183
HIV		–	3 (0.2%)	3 (0.2%)	0.781
Pregnancy		–	2 (0.1%)	2 (0.1%)	0.821
Tobacco smoking	Missing	12	972	984	
	No	4 (44.4%)	355 (53.9%)	359 (53.7%)	0.497
	Yes and Active	2 (22.2%)	192 (29.1%)	194 (29.0%)	
Day(s) since first symptoms	Missing (%)	0	221 (13.55%)	221 (13.38%)	
	Median (Q1–Q3)	−4.0 (−9–0)	−5.0 (−8– − 1)	−5.0 (−8– − 1)	0.581
Ventilation at admission	Missing	2	112	114	
	Spontaneous ambient air	15 (78.9%)	1018 (67.0%)	1033 (67.2%)	0.253
Body temperature (°C)	Missing (%)	9 (42.86%)	215 (13.18%)	224 (13.56%)	
	Median (Q1–Q3)	38.40 (37.1–38.6)	37.40 (36.6– − 38.3)	37.40 (36.6–38.3)	0.155
Leucocytes (g/L)	Missing (%)	1 (5.00%)	14 (0.88%)	15 (0.93%)	
	Median (Q1–Q3)	7.420 (4.92–10.73)	6.500 (4.75–9.04)	6.530 (4.75–9.06)	0.570
Neutrophils (g/L)	Missing (%)	1 (5.00%)	28 (1.76%)	29 (1.80%)	
	Median (Q1–Q3)	6.370 (3.20–9.17)	4.870 (3.31–7.21)	4.885 (3.31–7.24)	0.249
Lymphocytes (g/L)	Missing (%)	1 (5.00%)	38 (2.39%)	39 (2.42%)	
	Median (Q1–Q3)	0.580 (0.49–0.95)	0.820 (0.56–1.20)	0.820 (0.55–1.20)	0.066
Calcium (mmol/L)	Missing (%)	15 (75.00%)	1145 (72.06%)	1160 (72.09%)	
	Median (Q1–Q3)	1.960 (1.92–2.06)	2.160 (2.08–2.26)	2.160 (2.08–2.26)	0.006
Albumin (g/L)	Missing (%)	14 (70.00%)	1,132 (71.24%)	1,146 (71.22%)	
	Median (Q1–Q3)	32.0 (30–34)	37.0 (33–40)	37.0 (33–40)	0.050
Phosphate (mmol/L)	Missing (%)	16 (80.00%)	1,467 (92.32%)	1,483 (92.17%)	
	Median (Q1–Q3)	0.9 (1–1)	1.0 (1–1)	1.0 (1–1)	0.051
GFR (mL/min/1.73 m^2)	Missing (%)	0	36 (2.27%)	36 (2.24%)	
	Median (Q1–Q3)	66.0 (47–93)	71.0 (49–89)	71.0 (49–89)	0.577
CRP (mg/L)	Missing (%)	1 (5.00%)	32 (2.01%)	33 (2.05%)	
	Median (Q1–Q3)	112.0 (29–241)	56.0 (18–106)	56.0 (18–107)	0.012
ASAT (IU/L)	Missing (%)	8 (40.00%)	564 (35.49%)	572 (35.55%)	
	Median (Q1–Q3)	47.5 (36–69)	37.0 (25–56)	37.0 (25–56)	0.131
ALA (IU/L)	Missing (%)	5 (25.00%)	369 (23.22%)	374 (23.24%)	
	Median (Q1–Q3)	29.0 (18–50)	26.5 (17–44)	27.0 (17–44)	0.689
LDH (IU/L)	Missing (%)	12 (60.00%)	805 (50.66%)	817 (50.78%)	
	Median (Q1–Q3)	386.5 (295–482)	272.0 (212–362)	272.0 (212–362)	0.034
Steroids use		11 (52.4%)	475 (29.1%)	486 (29.4%)	0.027
Type of care	ICU	13 (61.9%)	279 (17.1%)	294 (17.8%)	<0.001
Death	Yes	11(52.4%)	269 (16.5%)	280 (16.9%)	<0.001

Results are presented as n (%) or median (Q1–Q3), percentages were calculated for non missing values only.
BMI: body mass index; HIV: human immunodeficiency virus; GFR: glomerular filtration rate; CRP: C-reactive protein; ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase; LDH: lactate dehydrogenase; ICU: intensive care unit.

intubation. The median maximum positive end-expiratory pressure (PEEP) was 15.5 cmH2O (range 12–24). Characteristics of the 21 patients with PT and 1631 controls are summarized in Table 1.

Therapeutic management for 18 patients (85.7%) consisted of intercostal drain insertion, including secondary thoracotomy in one patient. Three patients (27.3%) were managed conservatively either because of the minimum extent of PT (n = 2) or a poor condition (n = 1). Eleven patients died (52.4%), with nine deaths occurring in patients with MV-related PT. Significant differences were identified between patients with PT and controls in the sex ratio, lactate dehydrogenase (LDH) level, calcium level, and C-reactive protein (CRP) level at the time of PT, ICU hospitalization, and death (all P <0.05).

3. Discussion

Barotrauma, primarily during MV, undetected bullous lung disease, and/or diffuse alveolar damage followed by alveolar rupture are all causes of primary PT [5]. Spontaneous PT is caused by repetitive intense episodes of dry cough with a sudden increase in distal airway pressure, causing alveolar rupture and secondary gas leakage in the peribronchovascular pulmonary interstitium. Air can dissect proximally from this area, eventually reaching the mediastinum [6]. For MV-related PT, barotrauma is usually attributable to the rupture of hyperinflated alveoli which is facilitated in patients with SARS-CoV-2-associated acute respiratory distress syndrome (ARDS) by the need for high PEEP to prevent alveolar collapse [7]. PT is thought to be more common in patients with SARS-CoV-2 than in ARDS patients without SARS-CoV-2, suggesting a link with the lung frailty observed during COVID-19 [8]. The frequency of PT in our study was similar to previous findings [1,5,6]. The study by Geraci et al. reported a rate of 7.5%, but their study included iatrogenic cases [9]. PT induced by MV during COVID-19 is more frequently described in the literature, with reported rates of 13%–26% [2,7].

When comparing 21 patients with air leakage with 1631 controls, we found that patients with PT included a significantly higher proportion of men, a finding already reported in most studies analyzed in a meta-analysis by Chong et al. [1]. Moreover, patients with PT had higher CRP and LDH levels at baseline, which could account for the more severe status at baseline and thus a higher level of lung

injury, thereby favoring air leakage as previously described [10]. Patients had a high death rate, especially those on MV, in line with numerous reports highlighting the severity of this complication in these fragile patients [1,2,5,9,10].

4. Conclusion

Although PT can occur in the context of SARS-CoV-2 infections in various ventilation modes, it is most common in serious COVID-19 patients on MV. Male sex, higher baseline CRP, and LDH levels were identified as risk factors in our study. Additionally, mortality was frequent, particularly in patients on MV. Physicians should be aware of the risk of PT when the state of COVID-19 patients deteriorates.

Authors' contributions

All authors approved the submitted final version and participated in data collection and analysis. MM conceived the study. MM and LP wrote the manuscript. MM, LP, and VG revised the manuscript for content. CK performed the statistical analysis.

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans as well as in accordance with the EU Directive 2010/63/EU for animal experiments.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s) and/or volunteers.

Disclosure of interest

The authors declare that they have no competing interest.

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Ethics approval and consent to participate

The study was approved under a consent waiver by the Ethics Committee of Medicine Odontology and Pharmacy Faculties and Hospitals (University Hospital of Strasbourg; N°CE-2020-32).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used in this study are available from the first author upon reasonable request.

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