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

Journal of Cardiothoracic and Vascular Anesthesia 35 (2021) 3642–3651

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Research

Predictors of Pneumothorax/Pneumomediastinum in Mechanically Ventilated COVID-19 Patients

Alessandro Belletti, MD[*,2], Diego Palumbo, MD[†,2], Alberto Zangrillo, MD[*,‡], Evgeny V. Fominskiy, MD[*], Stefano Franchini, MD[§], Antonio Dell'Acqua, MD[*], Alessandro Marinosci, MD[§], Giacomo Monti, MD[*], Giordano Vitali, MD[‖], Sergio Colombo, MD[*], Giorgia Guazzarotti, MD[†], Rosalba Lembo, MSc[*], Nicolò Maimeri, MD[*], Carolina Faustini, MD[*], Renato Pennella, MD[†], Junaid Mushtaq, MD[†], Giovanni Landoni, MD[*,‡,1], Anna Mara Scandroglio, MD[*], Lorenzo Dagna, MD[‡,¶], Francesco De Cobelli, MD[†,‡], for the COVID-BioB Study Group

[*]*Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy*
[†]*Department of Radiology, IRCCS San Raffaele Scientific Institute, Milan, Italy*
[‡]*School of Medicine, Vita-Salute San Raffaele University, Milan, Italy*
[§]*Unit of General Medicine and Advanced Care, IRCCS San Raffaele Scientific Institute, Milan, Italy*
[‖]*Department of Internal Medicine, IRCCS San Raffaele Scientific Institute, Milan, Italy*
[¶]*Unit of Immunology, Rheumatology, Allergy, and Rare Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy*

Objective: To determine the incidence, predictors, and outcome of pneumothorax (PNX)/pneumomediastinum (PMD) in coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome (ARDS).

Design: Observational study.

Setting: Tertiary-care university hospital.

Participants: One hundred sixteen consecutive critically ill, invasively ventilated patients with COVID-19 ARDS.

Interventions: The authors collected demographic, mechanical ventilation, imaging, laboratory, and outcome data. Primary outcome was the incidence of PNX/PMD. Multiple logistic regression analyses were performed to identify predictors of PNX/PMD.

Measurements and Main Results: PNX/PMD occurred in a total of 28 patients (24.1%), with 22 patients developing PNX (19.0%) and 13 developing PMD (11.2%). Mean time to development of PNX/PMD was 14 ± 11 days from intubation. The authors found no significant difference in mechanical ventilation parameters between patients who developed PNX/PMD and those who did not. Mechanical ventilation parameters were within recommended limits for protective ventilation in both groups. Ninety-five percent of patients with PNX/PMD had the Macklin effect (linear collections of air contiguous to the bronchovascular sheaths) on a baseline computed tomography scan, and tended to have a higher lung

Funding: none.

COVID-BioB Study Group collaborators: Nicola Pasculli, Giovanni Borghi, Maria Rosa Calvi, Antonella Cipriani, Francesca Guzzo, Maria Grazia Calabrò, Martina Crivellari, Annalisa Franco, Marina Pieri, Marta Mucchetti, Gabriele Todaro, Davide Losi, Silvia Strada, Gaetano Di Terlizzi, Rebecca de Lorenzo, Nicola Compagnone, and Alessandro Tomelleri.

[1]*Address correspondence to* Prof. Giovanni Landoni, MD, Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, via Olgettina 60, 20132 Milan, Italy.

E-mail address: landoni.giovanni@hsr.it (G. Landoni).

[2]Alessandro Belletti, MD, and Diego Palumbo, MD, equally contributed to the manuscript.

https://doi.org/10.1053/j.jvca.2021.02.008

involvement at intensive care unit (ICU) admission (Radiographic Assessment of Lung Edema score 32.2 ± 13.4 *v* 18.7 ± 9.8 in patients without PNX/PMD, p = 0.08). Time from symptom onset to intubation and time from total bilirubin on day two after ICU admission were the only independent predictors of PNX/PMD. Mortality was 60.7% in patients who developed PNX/PMD versus 38.6% in those who did not (p = 0.04).
Conclusion: PNX/PMD occurs frequently in COVID-19 patients with ARDS requiring mechanical ventilation, and is associated with increased mortality. Development of PNX/PMD seems to occur despite use of protective mechanical ventilation and has a radiologic predictor sign.

Key Words: SARS-CoV-2; COVID-19; acute respiratory distress syndrome; mechanical ventilation; barotrauma; pneumothorax; Macklin effect

BETWEEN THE end of 2019 and beginning of 2020, the coronavirus disease 2019 (COVID-19) pandemic spread from China to all over the world, causing more than 100 million cases and more than 2,100,000 deaths as of January 28, 2021.[1] The rapid spread of the disease, together with the high rate of severe respiratory failure, frequently caused overwhelming of healthcare systems, even in high-income countries.[2,3]

A relevant proportion of patients with COVID-19 developed acute respiratory distress syndrome (ARDS), requiring invasive ventilation for a prolonged period.[4-6]

Pneumothorax (PNX) and pneumomediastinum (PMD) occurred relatively frequently in mechanically ventilated patients with ARDS, with a reported incidence of up to 15% in recent multicenter randomized controlled trials (RCTs).[7-11] Unfortunately, management of PNX/PMD frequently is challenging.[12]

There are isolated reports of PNX/PMD as a complication of COVID-19 ARDS.[13-17] However, currently, there are few published data on the incidence and outcome of these complications in this specific patient population.[18] Furthermore, early predictors of PNX/PMD remain poorly described.

Accordingly, the authors decided to perform an observational study to investigate these issues. In particular, their primary objective was to identify the prevalence of PNX and PMD in COVID-19 patients requiring invasive mechanical ventilation, and their secondary objectives were to determine early predictors of PNX/PMD and clinical outcome of these patients.

Methods

Study Design

This study was part of the COVID-19 Biobank study, an observational study performed at a 1,350-bed university hospital in Italy. The study was registered on ClinicalTrials.gov (NCT04318366) and approved by the Hospital Ethics Committee (protocol no. 34/int/2020). A detailed description of study methodology, patient management, and clinical protocols recently has been published.[4,19-22]

Patients were managed according to recommendations from published guidelines on protective mechanical ventilation and pharmacologic treatment of ARDS.[23-27] In particular, the authors aimed for a tidal volume of 6-to-8 mL/kg of ideal body weight, a driving pressure of ≤15 cmH_2O, and a pH >7.25. Positive end-expiratory pressure (PEEP) initially was set according to the ARDSnet low PEEP/high FiO_2 table, and then individualized according to oxygenation, respiratory system mechanics, and hemodynamics. Details on the mechanical ventilation protocol previously have been published.[4]

Enrollment Criteria

Consecutively, all adult patients (age ≥18) admitted to an intensive care unit (ICU) and requiring invasive mechanical ventilation at the authors' institution between February 25, 2020, and April 27, 2020, (first Italian pandemic wave), with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were enrolled. Confirmed infection was defined as positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) from a nasal and/or throat swab together with symptoms, signs, and radiologic findings suggestive of COVID-19 pneumonia. The authors present outcomes as of June 29, 2020 (median follow-up, 34.0 [28.0-42.0] days).

Outcomes

The primary outcome was development of PNX or PMD during ICU stay. Secondary outcomes were ICU stay, hospital length of stay, and hospital mortality.

Imaging Studies

Chest imaging studies (x-ray [CXR], computed tomography [CT] scan), as well as contrast medium administration, were performed at the discretion of the attending intensivists, according to clinical needs. Two radiologists (D.P., G.G.) independently reviewed all images to confirm diagnosis of PNX/PMD. Furthermore, to identify possible predictors of PNX/PMD, baseline chest imaging studies (performed at the hospital and/or ICU admission) also were reviewed and analyzed as follows. Baseline images were reviewed first, with radiologists blinded to subsequent development of PNX/PMD.

Chest X-ray

Radiographic Assessment of Lung Edema (RALE) semiquantitative score was used to quantify the extent and severity of lung opacities (see Supplementary materials).[28] Furthermore, all CXRs were analyzed by a deep-learning artificial intelligence (AI) system (qXR v2.1 c2, Qure.ai Technologies, India) trained to detect a number of specific abnormalities on

frontal chest x-ray, resulting in a pure quantitative severity scoring index. These scores previously have been proved to be independent and comparable predictors of adverse outcomes in patients with COVID-19 pneumonia, in an emergency department setting.[28]

Chest CT Scans

All CT images were reviewed carefully for the so-called Macklin effect, which is defined as a linear collection of air contiguous to the bronchovascular sheaths.[29] Contrast-enhanced CT, if used, the occurrence of pulmonary vascular thrombosis (defined as filling defects in the branches of the pulmonary arteries) also was considered.[30] Irrespective of the presence or absence of PNX/PMD, the diameter of the trachea and first- and second-order bronchi was systematically measured.

Data Collection

Data were collected from medical records by trained investigators independent from clinical teams. The authors obtained data on contact exposure, onset of symptoms and presenting symptoms, medical history, and current medications at time of symptom onset, daily clinical and laboratory data, treatment data, and outcome data. The authors collected daily mechanical ventilation data during the first seven days of mechanical ventilation. Laboratory data were collected at hospital admission and during the first three days of ICU stay. The authors performed an extensive round of data cleaning to check for data accuracy and outliers before analysis.

Statistical Analysis

A convenience sample was considered for this analysis, with consecutive patients included until the latest follow-up. A formal sample size calculation was, therefore, not performed; yet the authors retrospectively calculated the study power. The study power retrospectively calculated was 70%, considering a null hypothesis proportion of 0.25, and an alternative hypothesis proportion of 0.15, with an actual alpha of 0.04. Continuous variables are presented as mean and standard deviation in case of normal distribution or medians, and interquartile range in case of non-normal distribution, and categorical variables as number and percentages. Patients were divided into groups according to development of PNX and/or PMD or not until the latest follow-up.

Baseline and clinical characteristics of the patients were compared between the groups using Fisher exact tests and Wilcoxon rank-sum tests.

Logistic regression model using stepwise selection was used to identify predictors of PNX/PMD and predictors of mortality. Baseline, mechanical ventilation, and laboratory parameters were entered into the model if they had a univariate p value of less than 0.10 and a number of missing data <15%. Collinearity and overfitting were assessed using a stepwise regression model and Pearson correlation test. In the multiple logistic regression analyses, clinical factors or potential confounding variables were expressed as odds ratio (OR) with 95% confidence interval (CI).

All analyses were performed with Stata (version 15, StataCorp, College Station, Texas) by a biostatistician with extensive expertise in statistical analysis for clinical trials (R.L.).

Results

Population and Primary Outcome

From February 25, 2020, to April 27, 2020, a total of 124 patients with positive COVID-19 nasopharyngeal swab were admitted to the ICU. Of these, two patients had never been intubated and six did not have ARDS. Therefore, a total 116 patients with COVID-19 ARDS received invasive mechanical ventilation in the ICU and were included in the study (Fig 1). In total, 28 patients developed PNX or PMD (24.1%), with 22 patients developing PNX (19%) and 13 developing PMD (11.2%). Seven patients developed both PNX and PMD (6.0%).

Preadmission demographic and clinical characteristics are shown in Table 1. Most patients were men (85.2%), and the median age was 62 years. There were no significant differences at baseline between patients who developed PNX/PMD and patients who did not.

Time from symptoms to hospital admission is presented in Table 1, and was similar between the two groups (Table 1).

Time from symptom onset to intubation was 10.0 (6.0-14.0) in patients who did not develop PNX/PMD versus 13.0 (9.5-17.0) days in those who did (p = 0.004). Time from intubation to development of PNX or PMD was 14 ± 11 days.

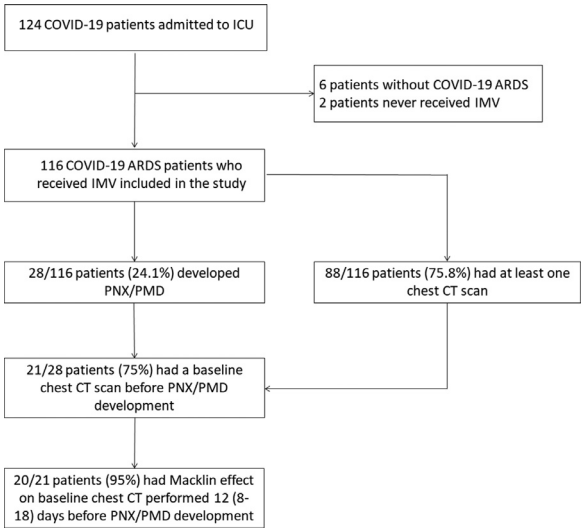

Fig 1. Study flow chart with radiologic findings. Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CT, computed tomography; ICU, intensive care unit; IMV, invasive mechanical ventilation; PNX/PMD, pneumothorax/pneumomediastinum.

Table 1
Demographic and Clinical Characteristics at Hospital Admission of Included Patients

	Without PNX/PMD (N = 88)	With PNX/PMD (N = 28)	p Value
Age, y	62 (54-69)	62 (57-70)	0.89
Female sex, no. (%)	13 (14.8)	5 (17.9)	0.77
Height, cm	173 (165-176)	176 (167-180)	0.14
Weight, kg	80 (74-90)	80 (72-95)	0.80
BMI, kg/cm^2	26.8 (24.8-30.9)	29.3 (25.3-32.0)	0.52
Ideal body weight, kg	68.8 (59.7-71.5)	71.0 (62.8-75.1)	0.14
Employed as a healthcare worker, no. (%)	3 (7.9)	1 (7.1)	0.99
Ethnic group			
Other, no. (%)	5 (5.6)	0 (0.00)	0.33
Latin American, no. (%)	12 (13.6)	5 (17.9)	0.55
Caucasian, no. (%)	71 (80.6)	23 (82.1)	0.99
Comorbidities			
Ischemic heart disease, no. (%)	6 (7.7)	2 (8.3)	0.99
Arrythmias , no. (%)	7 (9.0)	0 (0.0)	0.19
Cerebrovascular disease, no. (%)	6 (7.8)	0 (0.0)	0.33
Hypertension, no. (%)	**44 (53.0)**	**8 (32.0)**	**0.07**
Asthma, no. (%)	4 (5.2)	0 (0.0)	0.57
COPD, no. (%)	1 (1.3)	1 (4.17)	0.42
Chronic neurologic disorder, no. (%)	3 (4.0)	0 (0.0)	0.99
Moderate-to-severe renal disease, no. (%)	5 (6.7)	2 (8.3)	0.67
Diabetes type II, no. (%)	14 (17.5)	5 (20.0)	0.77
Solid tumor, no. (%)	3 (4.1)	1 (4.2)	0.99
Active smoker, no. (%)	2 (3.5)	1 (4.8)	0.99
Former smoker, no. (%)	7 (12.5)	2 (10.5)	0.99
Chronic medical therapy			
ACE inhibitors, no. (%)	9 (12.7)	3 (11.5)	0.99
Angiotensin receptor blockers, no. (%)	10 (14.1)	3 (11.5)	0.99
Calcium channel blockers, no. (%)	10 (14.1)	0 (0.0)	0.06
Beta-blockers, no. (%)	14 (19.4)	3 (11.5)	0.55
VKA, no. (%)	2 (2.7	0 (0.0)	0.99
NOACs, no. (%)	1 (1.4)	0 (0.0)	0.99
Anti-arrhythmics, no. (%)	5 (6.9)	0 (0.0)	0.32
ASA, no. (%)	13 (17.6)	5 (19.2)	0.99
Other antiplatelets, no. (%)	3 (4.2)	0 (0.0)	0.56
Statin, no. (%)	9 (12.3)	2 (7.7)	0.72
Steroids, no. (%)	4 (5.5)	0 (0.0)	0.57
Vital signs at hospital presentation			
Temperature, ˚C	38.0 ± 1.0	37.8 ± 0.9	0.40
Systolic B, mmHg	128.7 ± 22.1	120.8 ± 14.1	0.10
Diastolic B, mmHg	72.3 ± 12.8	72.6 ± 7.1	0.93
HR, beats per minute	99.5 ± 16.6	93.4 ± 17.8	0.13
RR, breaths per minute	30.9 ± 9.0	33.7 ± 8.1	0.43
Oxygen saturation, %	93 (84-96)	91 (80-96)	0.49
Neurologically oriented, no. (%)	**64 (80.0)**	**25 (96.0)**	**0.07**
Presenting symptoms			
History of fever in the previous 14 d, no. (%)	79 (98.8)	25 (92.6)	0.16
Chest pain, no. (%)	4 (7.1)	1 (4.6)	0.99
Muscle aches/myalgia, no. (%)	1 (2.0)	1 (4.6)	0.53
Joint pain arthralgia, no. (%)	1 (2.0)	0 (0.0)	0.99
Fatigue malaise, no. (%)	11 (21.6)	5 (20.8)	0.99
Shortness of breath/dyspnea, no. (%)	55 (74.0)	16 (70.0)	0.66
RALE score			
At hospital admission	15.1 ± 10.6	12.3 ± 5.1	0.39
At ICU admission	18.7 ± 10.5	32.2 ± 13.3	0.08
Qure AI score			
At hospital admission	48.2 ± 16.4	60.2 ± 29.3	0.36
At ICU admission	47.4 ± 18.1	55.8 ± 24.7	0.54
Tracheobronchial measurements, mm			
Trachea, A/P diameter	20.9 ± 2.7	21.8 ± 3.3	0.16
Trachea, L/L diameter	19.7 ± 3.4	20.3 ± 3.4	0.47
Right primary bronchus, maximum diameter	15.8 ± 2.3	16.7 ± 2.9	0.38

(*continued*)

Table 1 (*continued*)

	Without PNX/PMD (N = 88)	With PNX/PMD (N = 28)	p Value
Left primary bronchus, maximum diameter	13.9 ± 1.9	14.7 ± 1.6	0.41
Second-order bronchi, maximum diameter	8.6 ± 1.1	8.5 ± 1.3	0.52
Time from symptom onset to hospital admission, d	5.0 (3.0-9.0)	7.0 (4.5-10.0)	0.14
Time from symptom onset to intubation, d	**10.0 (6.0-14.0)**	**13.0 (9.5-17.0)**	**0.004**
Time from intubation to PNX/PMD development, d	N/A	14.0 ± 11.0	N/A

Abbreviations: ACE, angiotensin-converting enzyme; AI, artificial intelligence; A/P, antero/posterior; ASA, acetylsalicylic acid; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; HR, heart rate; ICU, intensive care unit; L/L, latero/lateral; N/A, not applicable; NOAC, novel oral anticoagulants; PMD, pneumomediastinum; PNX, pneumothorax; RALE, radiographic assessment of lung edema; RR, respiratory rate; VKA, vitamin K antagonist.
Bold values have been included in the multiple logistic regression analysis

Daily Data

Ventilatory and blood gas parameters during the first seven days of ICU admission and mechanical ventilation are presented in Table 2. There was no difference in ventilatory parameters between patients who developed PNX/PMD and patients who did not.

Daily laboratory variables in the first three days according to development of PNX or PMD are shown in Supplementary Table 1. Total bilirubin levels during the first three days of ICU admission were the only laboratory values that were significantly higher in the patients who later developed PNX or PMD.

Diagnosis and Treatment of PNX/PMD

Diagnosis of PNX was confirmed with CXR in 16/22 patients (72.7%) and with chest CT in the remaining 6 patients (27.3%). Pneumomediastinum was identified with CXR in 8/13 (61.5%) and with chest CT in 5/13 patients (38.5%). A subsequent confirmatory chest CT was obtained in all PMD patients.

In the majority of patients, PNX required chest tube drainage (18/22 [81.8%]), and in four patients (18.2%) management was conservative. In one patient (4.5%), chest tube drainage was not sufficient and minithoracotomy was performed.

Pneumomediastinum was managed conservatively in 12/13 (92.3%) patients. In one patient a tracheoesophageal fistula was identified, and surgical repair of the lesion was required. The patient ultimately recovered and was discharged from the hospital.

Chest Imaging

All patients had at least one baseline CXR; 88 patients (75.8%) had at least one chest CT scan, irrespective of contrast medium administration (specifically, 66 patients underwent CT pulmonary angiography). Of note, 21 of 28 patients (75%) with subsequent PNX/PMD had a baseline chest CT scan available (median time between baseline CT scan and PNX/PMD occurrence: 12 days [8-18]), and seven patients underwent CT scanning only after PNX/PMD development. Therefore, a total of 81 of 116 patients (69.8%) were included in the chest CT analysis subgroup; of these, 58 (67.9%) already were intubated at the time of the first CT scan.

Chest X-ray

Overall, median RALE and Qure AI scores for pulmonary involvement were, respectively, 12 (7-19.5) and 45.5 (38-59.5) at hospital admission, 17.5 (11.75-28) and 50.5 (32.25-65) are median RALE and Qure AI scores at ICU admission. There were no statistically significant differences between patients who then had PNX/PMD and patients who did not (Table 1). However, when considering RALE score at ICU admission, patients with PNX/PMD had a numerically higher baseline lung involvement (32.2 ± 13.4 *v* 18.7 ± 9.8 p = 0.08).

Chest CT Scans

Among patients who underwent chest CT scan, 20 of 21 patients (95.2%) with subsequent occurrence of PNX/PMD were found to have Macklin effect on baseline CT scan (Fig 2). On the contrary, five patients of the 60 without PNX/PMD who underwent chest CT scan (8.3%) demonstrated that sign ($p < 0.001$). In the subgroup of patients with PNX/PMD, the exact topographic distribution within the lung of Macklin effect was found to be peripheral (ie, adjacent to third-, fourth-, and/or fifth-order bronchi) in the vast majority of patients (18/20 [90%]).

Twenty-seven of 66 patients who underwent contrast-enhanced chest CT scan (40.9%) had pulmonary vascular thrombosis; no differences were found in terms of pulmonary vascular thrombosis incidence between patients with and without PNX/PMD (p = 0.526).

Predictors of PNX/PMD

On multiple logistic regression analysis, time from symptom onset to intubation (OR = 1.14; 95% CI, 1.02-1.27; p = 0.017) and total bilirubin level on day two of ICU stay (OR = 1.79; 95% CI, 1.12-2.87; p = 0.015) were associated with development of PNX/PMD (Table 3).

Table 2
Ventilatory and Blood Gas Parameters During the First Seven Days of Invasive Mechanical Ventilation, According to Development of Pneumothorax or Pneumomediastinum

Variable	Without PNX/PMD (N = 88)	With PNX/PMD (N = 28)	p Value
Tidal volume, day 1, mL	480 (420-500)	441 (400-480)	0.13
Tidal volume, day 2, mL	450 (420-500)	455 (420-520)	0.82
Tidal volume, day 3, mL	450 (420-500)	490 (420-550)	0.44
Tidal volume, day 4, mL	480 (440-512)	450 (450-520)	0.48
Tidal volume, day 5, mL	473 (420-500)	450 (400-500)	0.26
Tidal volume, day 6, mL	470 (420-500)	480 (400-500)	0.83
Tidal volume, day 7, mL	480 (420-580)	490 (375-590)	0.56
Tidal volume/IBW, day 1, mL/kg	6.8 (6.0-7.4)	6.8 (5.9-7.6)	0.84
Tidal volume/IBW, day 2, mL/kg	6.7 (6.1-7.4)	6.9 (6.0-7.9)	0.82
Tidal volume/IBW, day 3, mL/kg	6.7 (6.1-7.3)	6.9 (6.0-8.1)	0.85
Tidal volume/IBW, day 4, mL/kg	7.1 (6.3-7.7)	6.5 (5.7-8.1)	0.41
Tidal volume/IBW, day 5, mL/kg	7.2 (6.2-7.9)	6.1 (6.0-8.0)	0.47
Tidal volume/IBW, day 6, mL/kg	7.3 (6.3-7.8)	6.7 (5.3-8.1)	0.52
Tidal volume/IBW, day 7, mL/kg	7.2 (6.6-8.4)	7.1 (5.5-8.2)	0.68
Peak airway pressure, day 1, cmH_2O	28 (26-30)	28 (21-32)	0.74
Peak airway pressure, day 2, cmH_2O	26 (22-30)	27 (23-32)	0.62
Peak airway pressure, day 3, cmH_2O	26 (22-30)	25 (23-28)	0.99
Peak airway pressure, day 4, cmH_2O	26 (22-29)	24 (21-30)	0.61
Peak airway pressure, day 5, cmH_2O	25 (17-30)	23 (15-28)	0.50
Peak airway pressure, day 6, cmH_2O	24 (15-28)	24 (20-30)	0.64
Peak airway pressure, day 7, cmH_2O	22 (12-28)	22 (12-28)	0.25
PEEP, day 1, cmH_2O	12 (10-14)	11 (10-14)	0.19
PEEP, day 2, cmH_2O	12 (10-14)	12 (10-15)	0.68
PEEP, day 3, cmH_2O	12 (10-14)	12 (10-14)	0.63
PEEP, day 4, cmH_2O	10 (8-12)	10 (10-15)	0.56
PEEP, day 5, cmH_2O	10 (8-13)	10 (10-13)	0.69
PEEP, day 6, cmH_2O	10 (8-12)	11 (8-12)	0.83
PEEP, day 7, cmH_2O	10 (7.5-12)	10 (8-12)	0.32
Driving pressure, day 1, cmH_2O	15 (12-17)	15 (13-18)	0.56
Driving pressure, day 2, cmH_2O	14 (9-16)	15 (10-17)	0.30
Driving pressure, day 3, cmH_2O	14 (10-16)	13 (11-16)	0.72
Driving pressure, day 4, cmH_2O	14 (8-15)	12 (6-15)	0.57
Driving pressure, day 5, cmH_2O	12 (6-16)	12 (7-15)	0.81
Driving pressure, day 6, cmH_2O	12 (5-15)	14 (8-18)	0.34
Driving pressure, day 7, cmH_2O	10 (5-15)	15 (8-19)	0.19
Pa_{O_2}/F_{IO_2} ratio, day 1, mmHg/%	106.4 (80.1-148.3)	108.5 (72.5-128.3)	0.46
Pa_{O_2}/F_{IO_2} ratio, day 2, mmHg/%	129.2 (100.5-173.8)	109.0 (92.5-160.7)	0.20
Pa_{O_2}/F_{IO_2} ratio, day 3, mmHg/%	**137.2 (109.2-187.5)**	**117.1 (88.6-153.3)**	**0.09**
Pa_{O_2}/F_{IO_2} ratio, day 4, mmHg/%	125.2 (104.3-184.0)	117.6 (83.3-144.8)	0.11
Pa_{O_2}/F_{IO_2} ratio, day 5, mmHg/%	**133.3 (115.0-190.0)**	**109.8 (82.4-158.0)**	**0.03**
Pa_{O_2}/F_{IO_2} ratio, day 6, mmHg/%	**145.4 (106. 7-185.8)**	**108.3 (80.6-150.8)**	**0.02**
Pa_{O_2}/F_{IO_2} ratio, day 7, mmHg/%	125.2 (102.3-176.0)	105.9 (83.8-142.0)	0.02
Pa_{CO_2}, day 1, mmHg	47.0 (39.5-53.9)	50.1 (40.9-57.9)	0.20
Pa_{CO_2}, day 2, mmHg	48.2 (43.0-53.7)	49.5 (40.8-52.3)	0.96
Pa_{CO_2}, day 3, mmHg	48.0 (42.5-53.5)	46.9 (43.8-51.8)	0.60
Pa_{CO_2}, day 4, mmHg	48.4 (43.0-56.7)	47.0 (42.3-54.0)	0.40
Pa_{CO_2}, day 5, mmHg	51.0 (43.5-56.8)	53.0 (42.4-58.5)	0.76
Pa_{CO_2}, day 6, mmHg	49.2 (43.0-56.3)	48.5 (41.1-57.9)	0.48
Pa_{CO_2}, day 7, mmHg	49.1 (42.9-56.3)	48.5 (41.1-57.9)	0.89
pH, day 1	7.37 (7.31-7.45)	7.39 (7.32-7.45)	0.52
pH, day 2	7.41 (7.34-7.46)	7.45 (7.39-7-49)	0.19
pH, day 3	7.43 (7.37-7.48)	7.44 (7.42-7.47)	0.32
pH, day 4	7.45 (7.39-7.49)	7.44 (7.42-7.47)	0.69
pH, day 5	7.44 (7.40-7.48)	7.44 (7.39-7.48)	0.93
pH, day 6	7.46 (7.39-7.48)	7.40 (7.39 −7.46)	0.42
pH, day 7	7.45 (7.40-7.48)	7.43 (7.37-7.48)	0.38

Abbreviations: IBW, ideal body weight; Pa_{CO_2}, partial arterial carbon dioxide tension; Pa_{O_2}/F_{IO_2}, partial arterial oxygen tension to fraction of inspired oxygen ratio; PEEP, positive end-expiratory pressure; PMD, pneumomediastinum; PNX, pneumothorax.

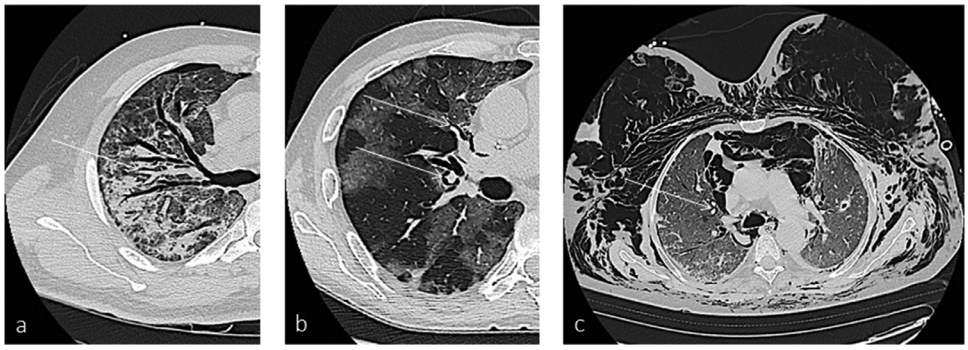

Fig 2. Lung parenchyma window axial computed tomography scans of 3 patients with severe acute respiratory syndrome coronavirus 2-associated pneumonia presenting Macklin effect (arrows) in association with pneumothorax (A), early pneumomediastinum (B), and full-blown pneumomediastinum along with subcutaneous emphysema (C).

Table 3
Predictors of Pneumothorax/Pneumomediastinum Development on Multiple Logistic Regression Analysis

Variable	OR	95% CI	p Value
Time from symptom onset to intubation, d	1.14	1.02 to 1.27	0.017
Total bilirubin, day 2, mg/dL	1.79	1.12 to 2.87	0.015
Pa_{O_2}/F_{IO_2} ratio, day 5, mmHg/%	0.99	0.98 to 1.01	0.435

Only variables with univariate p value <0.1 were included, after exclusion for collinearity/overfitting.
Abbreviations: CI, confidence interval; OR, odds ratio; P_{AO_2}/F_{IO_2}, partial arterial oxygen tension-to-fraction of inspired oxygen ratio.

Table 4
Clinical Outcomes, According to Development of Pneumothorax/Pneumomediastinum or Not

Variable	Without PNX/PMD (N = 88)	With PNX/PMD (N = 28)	p Value
Length of ICU stay, d	12.0 (7.5-21.0)	28.0 (14.5-51.0)	<0.001
Length of hospital stay, d	28.0 (15.0-44.0)	41.5 (28.0-69.5)	0.004
Longest follow-up mortality, no. (%)	34 (38.6)	17 (60.7)	0.04

Abbreviations: ICU, intensive care unit; PMD, pneumomediastinum; PNX, pneumothorax.

Secondary Outcomes

At latest follow-up on June 29, 2020, patients had been followed for a median period of 34.0 (28.0-42.0) days. Overall, 51 (43.9%) died during the study period, with a mortality rate of 17/28 (60.7%) among patients who developed PNX/PMD *v*ersus 34/88 patients (34.6%) among patients who did not (Table 4).

Development of PNX or PMD was associated with an increased risk of death, by univariate analysis (Supplementary Tables 2-4). On multiple logistic regression analysis, development of PNX/PMD (OR = 3.64; 95% CI, 1.24-10.70; p = 0.019) and platelet levels on day two after ICU admission (OR = 0.996; 95% CI, 0.993-0.999; p = 0.04) were the only independent predictors of mortality.

Discussion

Key Findings

In this single-center study, the authors found that almost one of four patients with COVID-19 ARDS requiring mechanical ventilation developed PNX or PMD, and that development of this complication was associated with increased risk of mortality. Furthermore, they identified time from symptom onset to intubation and total bilirubin as the only independent predictors of PNX/PMD development, and mechanical ventilation parameters did not differ between patients with and without PNX/PMD. Finally, almost all of the patients who developed PNX/PMD had the Macklin effect on baseline chest CT.

Relationship to Previous Studies

Wali et al. presented data from a small case series of five patients who developed PMD. Similar to the authors' study, patients in their case series were ventilated with protective ventilation strategies, and developed PMD after four-to-14 days of mechanical ventilation.[16]

In a recently published observational study, Lemmers et al. investigated the incidence of PMD and subcutaneous emphysema in patients with COVID-19 and non−COVID-19 ARDS, and found a 13% incidence of PMD in COVID-19 ARDS versus 1.9% in non-COVID-19 ARDS.[17] Furthermore, mortality was 56.5% in COVID-19 ARDS patients who developed PMD/subcutaneous emphysema versus 50% of patients who did not. Of note, Lemmers et al. found that patients developed PMD/subcutaneous emphysema despite applying protective mechanical ventilation. In the authors' study, they observed a similar incidence of PMD. Compared with the study by Lemmers et al., the authors investigated daily ventilatory parameters during the first seven days of ICU stay and found no difference between PNX/PMD patients and those who did not develop these complications. In addition, the authors investigated early predictors of PNX/PMD. They found that time from symptom onset to intubation and total bilirubin were the only predictors of these complications. Interestingly, and in contrast to the authors' cohort, Lemmers et al. found

that PMD/subcutaneous emphysema was not associated with higher risk of mortality.

In another study, Fiacchini et al. investigated the incidence of tracheal complications in 30 patients with COVID-19 ARDS requiring prolonged mechanical ventilation versus a control group of ICU patients without ARDS.[31] In their study, the incidence of PNX was 20%, while the incidence of PMD was 33%. The authors can hypothesize that Fiacchini et al. reported a higher incidence than the authors' group because they investigated the selected group of patients requiring more than 14 days of mechanical ventilation, while the authors included all patients requiring invasive ventilation. Unfortunately, they did not report data on mechanical ventilation parameters other than positive end-expiratory pressure (PEEP); therefore, the authors cannot comment on possible differences in ventilation strategies.

Additional studies reported incidence of barotrauma in mechanically ventilated COVID-19 ARDS patients ranging from 10%-to-14%.[32-35] Contrary to the authors' study, none of these present data on early predictors of PNX/PMD and data on mechanical ventilation settings were limited to the time of PNX/PMD development,[33,35] at the initial setting,[32] or absent.[34] Similarly to the authors' study, PNX was managed with chest tube drainage in at least 50% of patients presented in available case series.[33,35] Notably, in the study by Capaccione et al., the time from intubation to PNX onset was 14.9 days, similar to the authors' study;[32] and in the study by Edwards et al., PNX or PMD occurred fewer than four days from start of mechanical ventilation.[33]

Previous studies on non−COVID-19 ARDS reported variable incidence of PNX/PMD, ranging from less than 3% of patients to almost 15%.[7-9,36] These rates were lower than what the authors found in their study and those reported in other COVID-19 case series, despite use of similar mechanical ventilation strategies, as recommended by current guidelines.

Significance of Study Findings

Results of the authors' study highlighted, and published data collectively suggested, that patients with COVID-19 ARDS were at higher risk of developing PNX/PMD as compared with patients with ARDS due to non−COVID-19 causes. Interestingly, this seemed to occur regardless of mechanical ventilation setting, as already suggested in previous studies performed in a mixed ICU population.[36] These findings suggested that SARS-CoV-2 may induce a specific type of lung damage that increases frailty of airways tissue, given also the high risk of serious tracheal complications found in these patients.[31] The pathogenesis of SARS-CoV-2 lung damage remains poorly understood, but it seems to involve microvascular thrombosis, interstitial inflammatory infiltrates, bradykinin-dependent lung angioedema formation, and endothelial barrier disruption.[37,38] Actually, the pathophysiology of airway and lung damage in both "typical" and COVID-19−related ARDS remain poorly understood.[39] There is general agreement that diffuse alveolar damage is the main histopathologic feature, including capillary congestion, necrosis of pneumocytes, formation of hyaline membranes, interstitial and alveolar edema, hyperplasia of type 2 pneumocyte, platelet−fibrin microthrombi, and diffuse macrophage and lymphocyte inflammatory infiltrate.[40] Airway inflammation also has been reported,[41] and the authors recently proposed that even COVID-19−related pulmonary vascular thrombotic complications were due to local inflammatory endothelial damage, with a superimposed thrombotic late complication, rather than recurrent thromboembolism from peripheral deep vein thrombosis.[30] It is possible that the inflammatory and ischemic damage to small airways, together with the prolonged mechanical ventilation that COVID-19 frequently requires, led to the increased risk of developing PNX/PMD. However, recent studies suggested that lung damage induced from SARS-CoV-2 is indistinguishable from damage induced by other causes,[42] and whether COVID-19 ARDS represent a typical or atypical form of ARDS remains a matter of debate.[43-45] With regard to this point, the authors' findings could provide an in vivo anatomic depiction of a possible pathogenetic mechanism underlying PNX/PMD development in ARDS COVID-19 patients. The presence of the so-called Macklin effect implies a rupture along the alveolar tree (primum movens) with centripetal dissection along the bronchovascular sheaths toward the pulmonary hila.[29] This radiologic appearance could, therefore, represent macroscopic evidence of the proposed virus-induced frailty of airways tissue. In further support of this hypothesis, patients with a major baseline lung involvement at ICU admission were found to be more likely to develop PNX/PMD. Finally, a documented tracheal lesion was identified in one patient only in the authors' cohort, and tracheal/main bronchi diameters were not significantly different between patients with and without PNX/PMD. Taken together, these observations worked against the idea of a "central" barotrauma as the primum movens of PNX/PMD.

Indeed, the authors found that time from symptom onset to intubation was a significant, independent predictor of PNX/PMD development. A possible explanation for this finding was that delayed intubation increased the risk of self-induced lung injury and, therefore, lung and airway inflammatory damage and fibrosis.[46,47] Interestingly, total bilirubin levels also were associated with risk of developing PNX/PMD. A possible explanation was that these patients developed right heart dysfunction secondary to hypoxia-induced pulmonary vasoconstriction and pulmonary hypertension or prolonged period of high PEEP during noninvasive ventilation before intubation, with subsequent increased central venous pressure and venous congestion-induced liver damage.[48,49] Alternatively, increased bilirubin level might simply be a marker of a more severe condition with initial multiple organ dysfunction.

The authors' study suggested that clinicians caring for patients with COVID-19 ARDS should be aware of the high risk of developing PNX/PMD despite protective mechanical ventilation strategies, especially if the Macklin effect is identified on chest CT scan or if intubation occurred after more than ten days after symptom onset.[50] Therefore, a high index of suspicion always should be present when dealing with unclear respiratory or hemodynamic deterioration in patients with

COVID-19 ARDS. Extra care should be given to patients with the Macklin effect by CT scan to avoid further damage (eg, by avoiding high airway pressure and favoring use of extracorporeal technologies instead). It remains to be determined whether avoiding intubation may be a strategy to reduce risk of barotrauma and PNX/PMD development.

Strengths and Limitations of the Study

Compared with other studies investigating PNX/PMD, the authors' study included a larger number of mechanical ventilation and laboratory parameters, which allowed for a better understanding of potential clinical risk factors of developing these complications. Furthermore, the authors also included a detailed review of chest imaging studies.

The authors' findings were limited by the single-center design, which may limit generalizability of the findings. However, these findings seemed consistent with data already present in medical literature.

The authors did not apply a specific protocol for imaging and laboratory studies; therefore, they acknowledge that they might have missed a few cases of PNX/PMD. However, they believe that such cases (if any) would not be clinically relevant. Furthermore, all patients requiring prolonged mechanical ventilation and ICU stay underwent repetitive chest imaging to monitor disease progression.

The authors' data collection was limited to the first Italian pandemic wave (March-April 2020). They cannot exclude different incidence and outcome of PNX/PMD as their expertise on COVID-19 ARDS management increases. Unfortunately, data from the second Italian pandemic wave are not yet available. Furthermore, only data for the first seven days of mechanical ventilation were available in the authors' dataset. They cannot exclude that a difference in ventilatory parameters emerged at a later stage.

These results were limited by the relatively small sample size of the study. However, it remains one of the largest studies on the topic and with the greatest amount of data, including mechanical ventilation and radiologic data.

The authors reported an apparently high rate of death in their study (43.9%). However, this mortality rate was in line with previous multicenter studies on ARDS patients,[51] and lower than that observed in the Lombardy region during the same period.[6]

Future Studies and Prospects

Because the COVID-19 pandemic still is ongoing, future studies should better define the pathophysiology of lung injury and respiratory failure induced by SARS-CoV-2 to develop specific treatment strategies. Furthermore, given the specific characteristics that COVID-19 ARDS seems to have, which may differ from non–COVID-19 ARDS, specific intensive care management strategies should be investigated in an adequately designed randomized trial, including optimal timing of intubation, ARDS-management strategies, fluid management, and antithrombotic and anti-inflammatory therapy. Finally, future studies should address prevention and management of COVID-19–associated PNX/PMD.

Conclusions

Patients with COVID-19 ARDS requiring invasive mechanical ventilation are at high risk of developing PNX or PMD. Development of these complications is associated with increased risk of adverse outcome. Time from symptom onset to intubation and organ failure seem to be early predictors of these complications. Macklin effect on CT scan seems to be a predictor of subsequent PNX/PMD development.

Acknowledgments

The authors thank all the personnel of San Raffaele Hospital for the dedication to these patients and for the support in data collection.

Conflict of Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.jvca.2021.02.008.

References

1 World Health Organization. WHO coronavirus disease (COVID-19) dashboard. Available at: https://covid19.who.int/. Accessed January 28, 2021.
2 Monti G, Cremona G, Zangrillo A, et al. Home ventilators for invasive ventilation of patients with COVID-19. Crit Care Resusc 2020;22:266–70.
3 Zangrillo A, Beretta L, Silvani P, et al. Fast reshaping of intensive care unit facilities in a large metropolitan hospital in Milan, Italy: Facing the COVID-19 pandemic emergency. Crit Care Resusc 2020;22:91–4.
4 Zangrillo A, Beretta L, Scandroglio AM, et al. Characteristics, treatment, outcomes and cause of death of invasively ventilated patients with COVID-19 ARDS in Milan, Italy. Crit Care Resusc 2020;22:200–11.
5 Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA 2020;323:1574–81.
6 Grasselli G, Greco M, Zanella A, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Intern Med 2020;180:1345–55.
7 Guérin C, Reignier J, Richard J-C, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159–68.
8 Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: A multicentre, randomised controlled trial. Lancet Respir Med 2020;8:267–76.
9 National Heart, Lung, and Blood Institute PETAL Clinical Trials Network, Moss N, Huang DT, Brower RG, et al. Early neuromuscular blockade in the acute respiratory distress syndrome. N Engl J Med 2019;380:1997–2008.
10 Cavalcanti AB, Suzumura ÉA, Laranjeira LN, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome—A randomized clinical trial. JAMA 2017;318:1335–45.
11 Simonis FD, Serpa Neto A, Binnekade JM, et al. Effect of a low vs intermediate tidal volume strategy on ventilator-free days in intensive care unit

patients without ARDS: A randomized clinical trial. JAMA 2018;320:1872–80.
12 Slade M. Management of pneumothorax and prolonged air leak. Semin Respir Crit Care Med 2014;35:706–14.
13 Zhou C, Gao C, Xie Y, et al. COVID-19 with spontaneous pneumomediastinum. Lancet Infect Dis 2020;20:510.
14 Loffi M, Regazzoni V, Sergio P, et al. Spontaneous pneumomediastinum in COVID-19 pneumonia. Monaldi Arch Chest Dis 2020;90:604–7.
15 Lei P, Mao J, Wang P. Spontaneous pneumomediastinum in a patient with coronavirus disease 2019 pneumonia and the possible underlying mechanism. Korean J Radiol 2020;21:929–30.
16 Wali A, Rizzo V, Bille A, et al. Pneumomediastinum following intubation in COVID-19 patients: A case series. Anaesthesia 2020;75:1076–81.
17 Lemmers DHL, Abu Hilal M, Bnà C, et al. Pneumomediastinum and subcutaneous emphysema in COVID-19: Barotrauma or lung frailty? ERJ Open Res 2020;6;00385-2020.
18 Gordo MLP, Weiland GB, García MG, et al. Radiologic aspects of COVID-19 pneumonia: Outcomes and thoracic complications. Radiologia 2021;63:74–88.
19 Fominskiy EV, Scandroglio AM, Monti G, et al. Prevalence, characteristics, risk factors, and outcomes of invasively ventilated COVID-19 patients with acute kidney injury and renal replacement therapy. Blood Purif 2021;50:102–9.
20 Sartini C, Tresoldi M, Scarpellini P, et al. Respiratory parameters in patients with COVID-19 after using noninvasive ventilation in the prone position outside the intensive care unit. JAMA 2020;323:2338–40.
21 Morselli F, Vitali G, Brioschi E, et al. Feasibility and safety of angiotensin II administration in general ward patients during COVID-19 pandemic: A case series. Crit Care Resusc 2020;22:388–90.
22 Zangrillo A, Landoni G, Beretta L, et al. Angiotensin II infusion in COVID-19-associated vasodilatory shock: A case series. Crit Care 2020;24:227.
23 Fan E, Del Sorbo L, Goligher EC, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: Mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2017;195:1253–63.
24 Claesson J, Freundlich M, Gunnarsson I, et al. Scandinavian clinical practice guideline on fluid and drug therapy in adults with acute respiratory distress syndrome. Acta Anaesthesiol Scand 2016;60:697–709.
25 Vignon P, Evrard B, Asfar P, et al. Fluid administration and monitoring in ARDS: Which management? Intensive Care Med 2020;46:2252–64.
26 Alhazzani W, Belley-Cote E, Møller MH, et al. Neuromuscular blockade in patients with ARDS: A rapid practice guideline. Intensive Care Med 2020;46:1977–86.
27 Foti G, Giannini A, Bottino N, et al. Management of critically ill patients with COVID-19: Suggestions and instructions from the coordination of intensive care units of Lombardy. Minerva Anestesiol 2020;86:1234–45.
28 Mushtaq J, Pennella R, Lavalle S, et al. Initial chest radiographs and artificial intelligence (AI) predict clinical outcomes in COVID-19 patients: Analysis of 697 Italian patients. Eur Radiol 2021;31:1770–9.
29 Murayama S, Gibo S. Spontaneous pneumomediastinum and Macklin effect: Overview and appearance on computed tomography. World J Radiol 2014;6:850.
30 De Cobelli F, Palumbo D, Ciceri F, et al. Pulmonary vascular thrombosis in COVID-19 pneumonia [e-pub ahead of print]. J Cardiothorac Vasc Anesth 2021. https://doi.org/10.1053/j.jvca.2021.01.011; In press.
31 Fiacchini G, Tricò D, Ribechini A, et al. Evaluation of the incidence and potential mechanisms of tracheal complications in patients with COVID-19. JAMA Otolaryngol Neck Surg 2021;147:70–6.
32 Capaccione KM, D'souza B, Leb J, et al. Pneumothorax rate in intubated patients with COVID-19 [e-pub ahead of print]. Acute Crit Care 2021. https://doi.org/10.4266/acc.2020.00689; In press.
33 Edwards JA, Breitman I, Bienstock J, et al. Pulmonary barotrauma in mechanically ventilated coronavirus disease 2019 patients: A case series. Ann Med Surg 2021;61:24–9.
34 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.
35 Wong K, Kim DH, Iakovou A, et al. Pneumothorax in COVID-19 acute respiratory distress syndrome: Case series. Cureus 2020;12:e11749.
36 Anzueto A, Frutos-Vivar F, Esteban A, et al. Incidence, risk factors and outcome of barotrauma in mechanically ventilated patients. Intensive Care Med 2004;30:612–9.
37 Ciceri F, Beretta L, Scandroglio AM, et al. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): An atypical acute respiratory distress syndrome working hypothesis. Crit Care Resusc 2020;22:95–7.
38 Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A review. JAMA 2020;324:782–93.
39 Ortiz G, Garay M, Capelozzi V, et al. Airway pathological alterations selectively associated with acute respiratory distress syndrome and diffuse alveolar damage—Narrative review. Arch Bronconeumol 2019;55:31–7.
40 Carsana L, Sonzogni A, Nasr A, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: A two-centre descriptive study. Lancet Infect Dis 2020;20:1135–40.
41 Borczuk AC, Salvatore SP, Seshan SV, et al. COVID-19 pulmonary pathology: A multi-institutional autopsy cohort from Italy and New York City. Mod Pathol 2020;33:2156–68.
42 Konopka KE, Nguyen T, Jentzen JM, et al. Diffuse alveolar damage (DAD) resulting from coronavirus disease 2019 infection is morphologically indistinguishable from other causes of DAD. Histopathology 2020;77:570–8.
43 Ferrando C, Suarez-Sipmann F, Mellado-Artigas R, 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;46:2200–11.
44 Chiumello D, Busana M, Coppola S, et al. Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: A matched cohort study. Intensive Care Med 2020;46:2187–96.
45 Goligher EC, Ranieri VM, Slutsky AS. Is severe COVID-19 pneumonia a typical or atypical form of ARDS? And does it matter? Intensive Care Med 2021;47:83–5.
46 Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? Crit Care 2020;24:154.
47 Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. Am J Respir Crit Care Med 2017;195:438–42.
48 Kim JH, Lerose CC, Landoni G, et al. Differences in biomarkers pattern between severe isolated right and left ventricular dysfunction after cardiac surgery. J Cardiothorac Vasc Anesth 2020;34:650–8.
49 Vieillard-Baron A, Matthay M, Teboul JL, et al. Experts' opinion on management of hemodynamics in ARDS patients: Focus on the effects of mechanical ventilation. Intensive Care Med 2016;42:739–49.
50 Cabrini L, Ghislanzoni L, Severgnini P, et al. Early versus late tracheal intubation in COVID-19 patients: A pro-con debate also considering heart-lung interactions [e-pub ahead of print]. Minerva Cardioangiol 2021. https://doi.org/10.23736/S0026-4725.20.05356-6; In press.
51 Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016;315:788–800.