SARS-CoV-2–induced Acute Respiratory Distress Syndrome: Pulmonary Mechanics and Gas-Exchange Abnormalities

To the Editor:

In January 2020, the first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were reported in Europe. Multiple outbreaks have since then led to a global pandemic, as well as to massive medical, economic, and social repercussions (1, 2).

SARS-CoV-2 pneumonia can develop into acute respiratory distress syndrome (ARDS) when mechanical ventilation (MV) is needed (3, 4). ARDS produces abnormalities in gas exchange with a variable degree of shunt (5), high dead space ventilation (dead space volume [Vd]/tidal volume [Vt]) ratio (6), diminished pulmonary compliance (7), and alterations to the pulmonary circulation (8). The cornerstone of ARDS management is to provide adequate gas exchange without further lung injury as a result of MV. To date, information regarding the characteristics of SARS-CoV-2–induced ARDS is not completely known. However, this information is crucial to better apply MV and facilitate organ support strategies. We therefore present the characteristics of gas exchange, pulmonary mechanics, and ventilatory management of 50 patients with laboratory-confirmed SARS-CoV-2 infection, who developed ARDS and underwent invasive MV (IMV).

Methods

Descriptive analysis included 50 consecutive patients with laboratory-confirmed SARS-CoV-2 infection who developed ARDS (9) and underwent IMV. These patients were admitted to the SARS-CoV-2–dedicated intensive care units (ICUs) at Hospital Clinic of Barcelona, Spain, between March 7 and March 25, 2020.

Upon ICU admission, epidemiological characteristics, the severity of SARS-CoV-2 infection with the Acute Physiology and Chronic Health Evaluation II score, prognostic biomarkers of SARS-CoV-2 infection (described in Reference 4), time from hospital to ICU admission, time from ICU admission to intubation, oxygen therapy or noninvasive ventilation (NIV) use, and microbiology were investigated.

On the day that criteria for ARDS diagnosis were met (9) and IMV was needed, the following assessments were performed: impairment in oxygenation was analyzed with the partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) ratio, and abnormalities of CO2 metabolism were studied with the ventilatory ratio (VR), a surrogate parameter of Vd/Vt (10).

In addition, adjunctive therapies and MV parameters related with ventilation-induced lung injury (VILI) described elsewhere (11–15) were investigated.

Table 1. Characteristics of 50 patients with SARS-CoV-2–induced ARDS

| Characteristic | Median (IQR) or n (%) |
|---------------|----------------------|
| **Baseline characteristics** | |
| Age, yr | 66 (67–74) |
| Male† | 38 (72) |
| BMI, kg/m² | 27.88 (26.43–30.39) |
| Smoking status* | |
| Never | 23 (56) |
| Current | 4 (10) |
| Former | 14 (34) |
| Alcohol consumption habit | 6 (12) |
| APACHE II score at ICU admission | 13 (11–18) |
| SOFA score upon ARDS diagnosis | 7 (6–9) |
| Time from hospital admission to ICU admission, d | 2 (1–3.75) |
| Time from ICU admission to intubation, d | 1 (0–1) |
| Coinfection | 2 (4) |
| **Oxygen therapy and NIV before intubation†** | |
| Venturi and nonrebreathing oxygen mask | 43 (93) |
| High-flow oxygen therapy | 23 (50) |
| NIV | 5 (11) |
| **ARDS severity** | |
| Mild | 12 (24) |
| Moderate | 22 (44) |
| Severe | 16 (32) |
| **Management factors** | |
| Prone position | 11 (22) |
| Neuromuscular blockade use | 24 (48) |
| Recruitment maneuvers | 18 (36) |
| Vasopressor use | 16 (32) |
| Corticosteroid therapy | 18 (36) |
| **Laboratory findings‡** | |
| Hemoglobin, g/dl | 12.80 (11.83–13.40) |
| White blood cell count, ×10⁹/L | 8.11 (6.26–11.42) |
| Lymphocyte count, ×10⁹/L | 0.60 (0.40–0.90) |
| Platelet count, ×10⁹/L | 219 (174–274) |

(Continued)
Results

By March 25th, 2020, 50 patients with laboratory-confirmed SARS-CoV-2 infection and ARDS had been admitted to our hospital. Table 1 shows the demographic and clinical characteristics of these patients. The median (interquartile range [IQR]) age was 66 (57–74) years. Thirty-six patients (72%) were men. Upon ARDS diagnosis, 44% of patients were admitted as having mild ARDS and 32% were admitted as having severe ARDS. As Crs decreases alongside the collapse of alveolar units due to lung edema, several factors may provide explanations for such reported differences, including treatments, intubation strategies, and the stage of the disease. In our cohort with early SARS-CoV-2–induced ARDS, the time from ICU admission to intubation was only 24 hours, despite the use of high-flow nasal cannula or NIV in some cases.

Correlations of SARS-CoV-2 prognostic biomarkers (4), pulmonary mechanics, and gas-exchange data were performed. Twenty-eight–day and hospital mortality, ventilator- and ICU-free days at Day 28, hospital and ICU lengths of stay, and need for tracheostomy were also evaluated (16). Finally, a subanalysis assessing differences before and after prone positioning was performed. For additional detail on the method, see the online supplement.

### Definition of abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; ARDS = acute respiratory distress syndrome; BMI = body mass index; ICU = intensive care unit; IQR = interquartile range; NIV = noninvasive ventilation; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOFA = sequential organ failure assessment.

1Missing data from nine patients.
2Missing data from four patients.
3Laboratory findings upon ARDS diagnosis.
4Six patients were still in the hospital after follow-up ending.

| Characteristic                      | Median (IQR) or n (%) |
|------------------------------------|----------------------|
| Creatinine, mg/ml                  | 0.98 (0.77–1.45)     |
| Sodium, mEq/L                      | 138 (136–140)        |
| Potassium, mEq/L                   | 3.90 (3.60–4.30)     |
| Aspartate aminotransferase, U/L    | 65 (48–82)           |
| Alanine aminotransferase, U/L      | 45 (28–76)           |
| Total bilirubin, mg/dl             | 0.50 (0.40–0.90)     |
| γ-Glutamyltransferase, U/L         | 54 (36–105)          |
| Lactate, mmol/L                    | 1.33 (1–1.59)        |
| Alkaline phosphatase, U/L          | 67 (53–86)           |
| Lactate dehydrogenase, U/L         | 442 (386–541)        |
| Albumin, g/L                       | 36 (33–38)           |
| D-dimer, ng/ml                     | 1,100 (800–3,800)    |
| Ferritin, ng/ml                    | 1,436.50 (951.25–2,149.25) |
| Procalcitonin, ng/ml               | 0.27 (0.17–0.97)     |
| C-reactive protein, mg/dl          | 15.88 (9.04–27.03)   |
| Outcomes                           |                      |
| Hospital mortality                 | 15 (34)              |
| Mortality at Day 28                | 10 (20)              |
| Ventilator-free at Day 28, d       | 9 (0–16)             |
| ICU-free at Day 28, d              | 0 (0–9)              |
| Hospital length of stay, d         | 36 (24–44)           |
| ICU length of stay, d              | 26 (17–34)           |
| Tracheostomy                       | 30 (60)              |

| Measure                             | Median (IQR)         |
|-------------------------------------|----------------------|
| Arterial blood gas                  |                      |
| pH                                  | 7.31 (7.28–7.37)     |
| PaO2, mm Hg                         | 107 (88.5–133.6)     |
| PaCO2, mm Hg                        | 47 (42.9–53.4)       |
| PaO2/FIO2                            | 174 (128–232)        |
| Ventilator ratio*                   | 1.93 (1.55–2.23)     |
| Ventilator settings, pulmonary mechanics, and other variables associated with VILI | |
| VR/PBW, ml/kg                      | 6.78 (6.30–7.32)     |
| Respiratory rate, breaths/min       | 22 (20–23)           |
| PEEP, cm H2O                        | 13 (11–14)           |
| FIO2, %                             | 62 (53–76)           |
| Peak inspiratory pressure, cm H2O   | 32 (29–34)           |
| End-inspiratory plateau pressure, cm H2O | 23 (21–25) |
| Driving pressure, cm H2O O2†         | 11 (9–13)            |
| Mechanical power, J/min†           | 22.32 (18.49–28.10)  |
| Crs, ml × cm H2O O2†                | 40.13 (32.88–51.68)  |

*Ventilatory ratio is defined as (minute ventilation [ml/min] × PaO2/FIO2)/[PBW × 100 × 37.5].
†Driving pressure is the difference between plateau pressure and PEEP.
‡Mechanical power was calculated following previously published formulas (11).
§Crs is the ratio of tidal volume to driving pressure.

### Comparison of SARS-CoV-2–induced ARDS and VILI of 50 patients with SARS-CoV-2–induced ARDS upon ARDS diagnosis

| Measure                             | Median (IQR)         |
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**Table 1.** Gas exchange, pulmonary mechanics, and VILI of 50 patients with SARS-CoV-2–induced ARDS upon ARDS diagnosis

| Characteristic                      | Median (IQR) or n (%) |
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| Hospital length of stay, d         | 36 (24–44)           |
| ICU length of stay, d              | 26 (17–34)           |
| Tracheostomy                       | 30 (60)              |

**Table 2.** Gas exchange, pulmonary mechanics, and VILI of 50 patients with SARS-CoV-2–induced ARDS upon ARDS diagnosis

**Table 1.** (Continued)
We found no correlation between Crs and $\text{PaO}_2/\text{FiO}_2$. Crs estimates the amount of aerated lung volume in ARDS (7). These results might therefore suggest that the proportion of nonaerated or poorly aerated to well-aerated lung volume is not the only determinant for such a degree of hypoxemia. This may not be specific to SARS-CoV-2–induced ARDS, as other factors apart from the amount of aerated lung tissue (i.e., lung perfusion) are largely known to influence pulmonary shunt (24). However, some authors have reported that lung perfusion in SARS-CoV-2–induced ARDS is more impaired than ARDS by other causes (21). We identified remarkable abnormal lung perfusion in computed tomographic scans performed in these patients (Figure E1).

We found no correlation between D-dimer and VR, suggesting that high $V_D/V_T$ might not be related to a coagulation disorder (i.e., pulmonary microthrombosis). Nonetheless, as suggested by its association with VR, high end-inspiratory and end-expiratory pressures (i.e., mean airway pressures) could increase $V_D/V_T$ if the lung is overdistended and perfusion is decreased.

Although driving pressure and end-inspiratory plateau pressure were within the protective range, mechanical power was found to be slightly high and might have promoted lung injury (25). In patients undergoing prone positioning, $\text{PaO}_2/\text{FiO}_2$ improvement was followed by an increase in Crs, suggesting recruitment and aeration of previously collapsed alveoli. In our study, mortality was similar to that reported in other studies of critically ill patients with SARS-CoV-2 pneumonia (3, 19).

This study presents some limitations. Four manual end-inspiratory and end-expiratory pauses could not be performed in all patients because of protective equipment shortages. However, all patients included had at least one end-inspiratory and end-expiratory pause done on the first day. These results cannot be extrapolated to late SARS-CoV-2–induced ARDS.

In summary, SARS-CoV-2–induced ARDS presents with an impairment in gas exchange and pulmonary mechanics comparable with those of prior ARDS cohorts. However, lung perfusion in SARS-CoV-2–induced ARDS warrants further investigation.

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**Figure 1.** Correlation between pulmonary mechanics and gas-exchange abnormalities. (A) Correlation between Crs and $\text{PaO}_2/\text{FiO}_2$. (B) Correlation between ventilatory ratio and D-dimer concentration. (C) Correlation between plateau pressure and ventilatory ratio. (D) Correlation between PEEP and ventilatory ratio. Solid lines are the regression lines, whereas shaded bands display 95% confidence intervals. Crs = static compliance of the respiratory system; $\text{PaO}_2/\text{FiO}_2$ = ratio between partial pressure of oxygen and fraction of inspired oxygen, PEEP = positive end-expiratory pressure.
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Urban–Rural Disparities in Pulmonary Hypertension Mortality

Urban–rural disparities in life expectancy in the United States have been widely documented, and this gap appears to be widening (1, 2). Published studies have shown that rural Americans are more likely to die of a range of cardiopulmonary diseases because of poor access to specialty care (2, 3). To date, there remains a paucity of similar data in the populations of patients with pulmonary hypertension (PH)—an often overlooked cause of morbidity and mortality in many cardiopulmonary disorders. Here, we examined urban–rural disparities in all-cause mortality in a nationally representative cohort of patients with PH in the United States.

Methods

We performed a retrospective cohort study of nonelderly adults with PH (18–64 yr old) drawn from a commercial health insurance/Medicare Advantage database (years 2000–2011), including enrollees across all 50 states of the United States. The database comprises

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