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 [V_D]/tidal volume [V_T] 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 (Pa_{O_2})/fraction of inspired oxygen (FI_{O_2}) ratio, and abnormalities of CO_2 metabolism were studied with the ventilatory ratio (VR), a surrogate parameter of V_D/V_T (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 (57–74)
Male	36 (72)
BMI, kg/m^2	27.68 (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, $\times 10^9$/L	8.11 (6.26–11.42)
Lymphocyte count, $\times 10^9$/L	0.60 (0.40–0.90)
Platelet count, $\times 10^9$/L	219 (174–274)

(Continued)

A complete list of Covid Clinic Critical Care Group members may be found before the beginning of the References.

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Data Sharing Statement: Deidentified data including data dictionaries will be available when requested. Requests for data sharing to be made to the corresponding author atorres@clinic.cat.

Author Contributions: A.T. had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. E.B., A.M., and A.T. provided the concept and design. All authors contributed to acquisition. E.B., A.M., A.T., A.C., M.F., C.C., L.B., R.M., R.L.-A., H.Y., M.Y., L.F.-B., A.C.P., and I.V. provided analysis and interpretation of data. E.B., A.M., and A.T. drafted the manuscript. E.B. and A.M. provided statistical analysis. All authors contributed to the critical revision of the manuscript for important intellectual content.

This letter has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Table 1. (*Continued*)

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	15.68 (9.64–27.03)
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)

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.
*Missing data from nine patients.
†Missing data from four patients.
‡Laboratory findings upon ARDS diagnosis.
§Six patients were still in the hospital after follow-up ending.

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

Measure	Median (IQR)
Arterial blood gas	
pH	7.31 (7.28–7.37)
Pa_{CO_2}, mm Hg	47 (42.9–53.4)
Pa_{O_2}, mm Hg	107 (88.5–133.6)
Pa_{O_2}/FI_{O_2}	174 (128–232)
Ventilatory ratio*	1.93 (1.55–2.23)
Ventilator settings, pulmonary mechanics, and other variables associated with VILI	
V_T/PBW, ml/kg	6.78 (6.30–7.32)
Respiratory rate, breaths/min	22 (20–23)
PEEP, cm H_2O	13 (11–14)
FI_{O_2}, %	62 (53–76)
Peak inspiratory pressure, cm H_2O	32 (29–34)
End-inspiratory plateau pressure, cm H_2O	23 (21–25)
Driving pressure, cm H_2O†	11 (9–13)
Mechanical power, J/min‡	22.32 (18.49–28.10)
Crs, ml × cm H_2O^{-1}§	40.13 (32.88–51.68)

Definition of abbreviations: ARDS=acute respiratory distress syndrome; Crs = static compliance of the respiratory system; FI_{O_2} = fraction of inspired oxygen; IQR = interquartile range; Pa_{CO_2} = partial pressure of carbon dioxide; Pa_{O_2} = partial pressure of oxygen; PBW = predicted body weight; PEEP = positive end-expiratory pressure; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VILI = ventilation-induced lung injury; V_T = tidal volume.
*Ventilatory ratio is defined as (minute ventilation [ml/min] × Pa_{CO_2} [mm Hg])/(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.

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.

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 initially classified as having moderate ARDS, whereas 24% were classified as having mild ARDS and 32% were classified as having severe ARDS. The outcomes of these patients are shown in Table 1. ICU and hospital lengths of stay were prolonged, and tracheostomy was performed in 30 (60%) patients. Hospital mortality was 34%.

Table 2 shows the results for gas exchange, pulmonary mechanics, and variables associated with VILI upon ARDS diagnosis. Excluding baseline mechanical power, other MV parameters associated with VILI were within normal range.

There was no correlation between Pa_{O_2}/FI_{O_2} and the static compliance of the respiratory system (Crs) (Figure 1A). Notwithstanding, a weak yet significant correlation was found between VR and both positive end-expiratory pressure and end-inspiratory plateau pressure (Figures 1C and 1D).However, D-dimer was not significantly correlated with VR (Figure 1B).

Eleven patients underwent prone positioning on the day of ARDS diagnosis (*see* Table E1 in the online supplement). On average, Pa_{O_2}/FI_{O_2} increased from the supine to the prone position by +59 (IQR, 32–143; $P = 0.002$). Significant differences were also found in Crs between supine to prone position with an increase of +5.45 (IQR, 4.32–18.25; $P = 0.015$).

Discussion

SARS-CoV-2–induced ARDS produced an impairment in gas exchange and pulmonary mechanics comparable with those of prior cohorts with non–SARS-CoV-2 ARDS (10, 13, 17, 18). As in other studies, VR was high, and the most frequent presentation was moderate ARDS (10, 17, 19). On average, Crs in the cohort with SARS-CoV-2–induced ARDS was also found to be comparable, but with remarkable heterogeneity (13, 18). Other studies have reported similar (20), higher (21), or lower Crs (19, 22, 23) in SARS-CoV-2–induced 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.

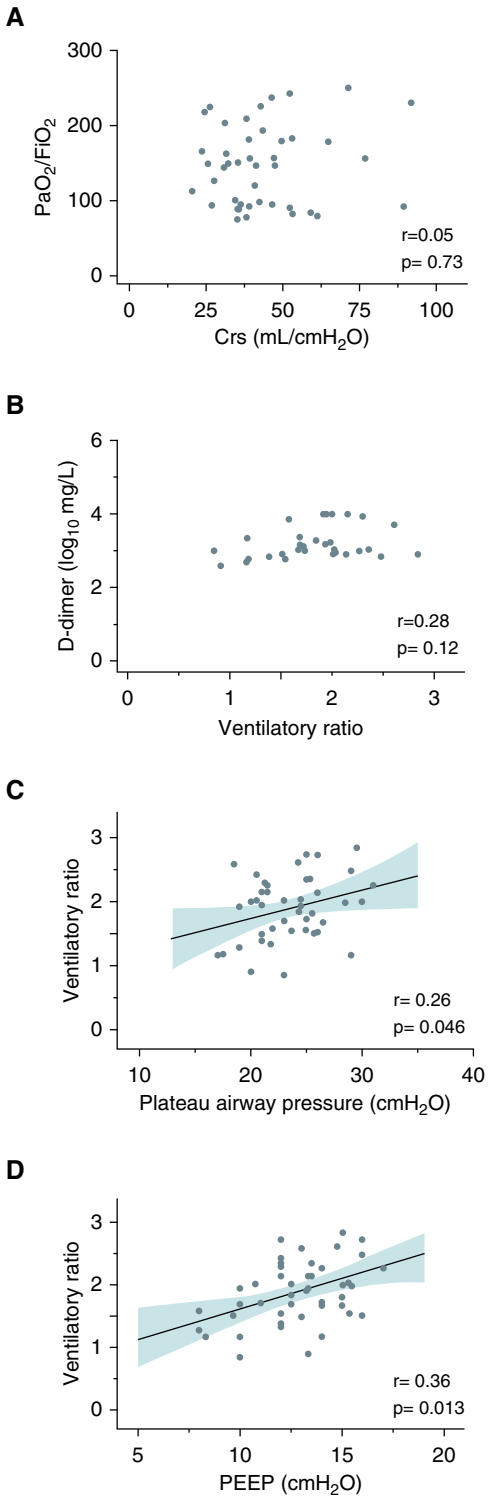

Figure 1. Correlation between pulmonary mechanics and gas-exchange abnormalities. (*A*) Correlation between Crs and $Pa_{O_2}/F_{I_{O_2}}$. (*B*) Correlation between ventilatory ratio and D-dimer concentration. (*C*) Correlation between plateau pressure and ventilatory ratio. (*D*) Correlation between PEEP and ventilatory ratio. Solid lines are the regression lines, whereas shaded bands display 95% confidence intervals. Crs = static compliance of the respiratory system; $Pa_{O_2}/F_{I_{O_2}}$ = ratio between partial pressure of oxygen and fraction of inspired oxygen, PEEP = positive end-expiratory pressure.

We found no correlation between Crs and $Pa_{O_2}/F_{I_{O_2}}$. 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, $Pa_{O_2}/F_{I_{O_2}}$ 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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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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