Table 2. Multivariable Logistic Regression of Factors Associated with 28-Day Mortality

	OR	95% CI	*P* Value
KDIGO stage 3 AKI	3.539	1.737–7.374	0.02
Congestive heart failure	2.738	0.582–16.100	0.11
Respiratory SOFA (0–4)	1.663	1.039–2.741	0.02
Age, yr	1.082	1.044–1.126	<0.001
Diabetes mellitus	0.936	0.441–1.949	0.87

Definition of abbreviations: AKI = acute kidney injury; CI = confidence interval; KDIGO = Kidney Disease Improving Global Outcomes; OR = odds ratio; SOFA = Sequential Organ Failure Assessment.

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COVID-19– versus non–COVID-19–related Acute Respiratory Distress Syndrome: Differences and Similarities

To the Editor:

The current pandemic of coronavirus disease (COVID-19) is responsible for a massive influx of patients with acute respiratory

Author Contributions: C.B., Y.Z., M.C., and M.M. collected data. Y.Z. and J.M. performed the analysis. C.B., Y.Z., J.M., and M.S. wrote the manuscript. L.K., U.F., T.S., and B.D.C. critically reviewed the manuscript. All authors approved the final version of the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.202005-2025LE on August 28, 2020

distress syndrome (ARDS). In view of some of the unusual clinical features of COVID-19, some clinicians might assume that this disease leads to atypical ARDS (1). Here, we compare the main characteristics of COVID-19 ARDS with those of non–COVID-19 ARDS.

Methods

The present study was conducted in the Department of Intensive Care Medicine at Amiens University Hospital (Amiens, France) from January 2015 to May 2016 and from June 2018 to May 2020. We retrospectively analyzed data collected in an ongoing prospective cohort study of lung recruitment maneuvers (LRMs) in consecutive patients with ARDS with a Pa_{O_2}/FI_{O_2} ratio lower than or equal to 200 mm Hg. We also included all consecutive mechanically ventilated patients admitted since February 2020 for COVID-19 ARDS and who had a Pa_{O_2}/FI_{O_2} ratio lower than or equal to 200 mm Hg. All patients with COVID-19 disease had tested positive in a real-time PCR assay for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We used lung-protective ventilation with a V_T set to 6 ml per kilogram of predicted body weight, and the positive end-expiratory pressure (PEEP) was adjusted to maintain a plateau pressure below 30 cm H_2O and a driving pressure below 15 cm H_2O. If the Pa_{O_2}/FI_{O_2} ratio fell below 150 mm Hg, the prone position was applied for at least 16 hours. We defined "oxygenation response to prone position" as patients in whom the Pa_{O_2}/FI_{O_2} ratio increased by at least 20% or at least 20 mm Hg during the first prone position session (2). In all patients, we performed a stepwise LRM with an increase in the PEEP every 2 minutes (from 25 to 40 cm H_2O) and a stable driving pressure of 15 cm H_2O. We defined "oxygenation response to LRM" as patients in whom the Pa_{O_2}/FI_{O_2} ratio increased by at least 20% 2–4 hours after the first LRM. The study was approved by the local independent ethics committee.

Results

We included a total of 63 patients with moderate to severe primary ARDS, including 24 (38%) patients with a confirmed SARS-CoV-2 infection and 39 (62%) patients with other causes of ARDS (most aspiration or community-acquired pneumonia, and influenza-related ARDS in six cases). The overall median (interquartile range

Table 1. Demographic, Radiographic, and Respiratory Characteristics of the Study Population on Admission to the ICU

Variable	Total Population (*n* = 63)	COVID-19–related ARDS (*n* = 24)	Non–COVID-19–related ARDS (*n* = 39)	*P* Value
Demographic variables				
Age, yr	61 (51–69)	67 (58–76)	59 (49–66)	**0.02**
Sex, male	42 (67)	19 (79)	23 (59)	0.10
Body mass index, kg/m^2	28.7 (24.6–35.0)	31.0 (27.7–34.8)	28.2 (23.8–35.0)	0.08
Time between symptom onset and ICU admission, d	6 (1–10)	8 (6–12)	2 (0–6)	**0.001**
Time between symptom onset and orotracheal intubation, d	7 (3–12)	10 (7–15)	5 (0–7)	**0.0001**
Comorbidities				
Chronic lung disease	23 (37)	8 (33)	15 (39)	0.68
Chronic cardiovascular disease	28 (44)	14 (58)	14 (36)	0.08
Diabetes	14 (22)	9 (38)	5 (13)	**0.03**
Obesity	26 (41)	14 (58)	12 (31)	**0.04**
Immunocompromise	19 (30)	2 (8)	17 (44)	**0.004**
Computed tomography findings	53 (84)	18 (75)	35 (90)	
Diffuse pattern	33 (62)	16 (89)	20 (57)	**0.03**
Focal pattern	14 (26)	2 (11)	12 (34)	0.10
Ground-glass opacity	31 (58)	15 (63)	16 (46)	**0.01**
Alveolar consolidation	32 (60)	11 (61)	21 (60)	>0.99
Pleural effusion	28 (53)	3 (17)	25 (78)	**0.0003**
Pulmonary embolism	2 (4)	2 (17)	0 (0)	0.22
Respiratory physiology				
FI_{O_2}, %	80 (70–100)	100 (70–100)	80 (60–100)	0.06
Pa_{O_2}/FI_{O_2} ratio, mm Hg	104 (81–126)	101 (81–126)	106 (81–124)	0.64
Severe ARDS	32 (51)	12 (50)	20 (51)	0.92
Moderate ARDS	31 (49)	12 (50)	19 (49)	0.92
pH	7.33 (7.26–7.39)	7.34 (7.31–7.39)	7.31 (7.23–7.39)	0.24
Pa_{CO_2}, mm Hg	45.0 (39.5–52.0)	43.1 (40.3–50.7)	46.0 (39.5–53.0)	0.51
Ventilatory ratio	1.91 (1.65–2.33)	1.89 (1.67–2.23)	1.99 (1.64–2.55)	0.46
V_T, ml/kg of predicted body weight	6.07 (5.71–6.45)	6.07 (5.95–6.16)	6.09 (5.36–6.80)	0.74
Plateau pressure, cm H_2O	26.0 (23.0–28.0)	26.0 (21.8–28.0)	26.0 (23.5–29.0)	0.29
PEEP applied, cm H_2O	10.0 (8.5–14.0)	12.0 (6.5–15.0)	10.0 (9.5–13.0)	0.85
Driving pressure, cm H_2O	14.0 (11.0–17.0)	13.0 (10.0–15.0)	15.0 (12.0–17.5)	0.12
Crs, ml/cm H_2O	30.0 (23.0–39.5)	32.5 (25.8–41.3)	29.0 (22.0–37.0)	0.13

Definition of abbreviations: ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease; Crs = respiratory system compliance; PEEP = positive end-expiratory pressure.

All measurements were made in the absence of inhaled nitric oxide, in the supine position, and before lung recruitment maneuvers.

Data are shown as *n* (%) or median (interquartile range). Bold values indicate a statistically significant difference with a *P* value < 0.05.

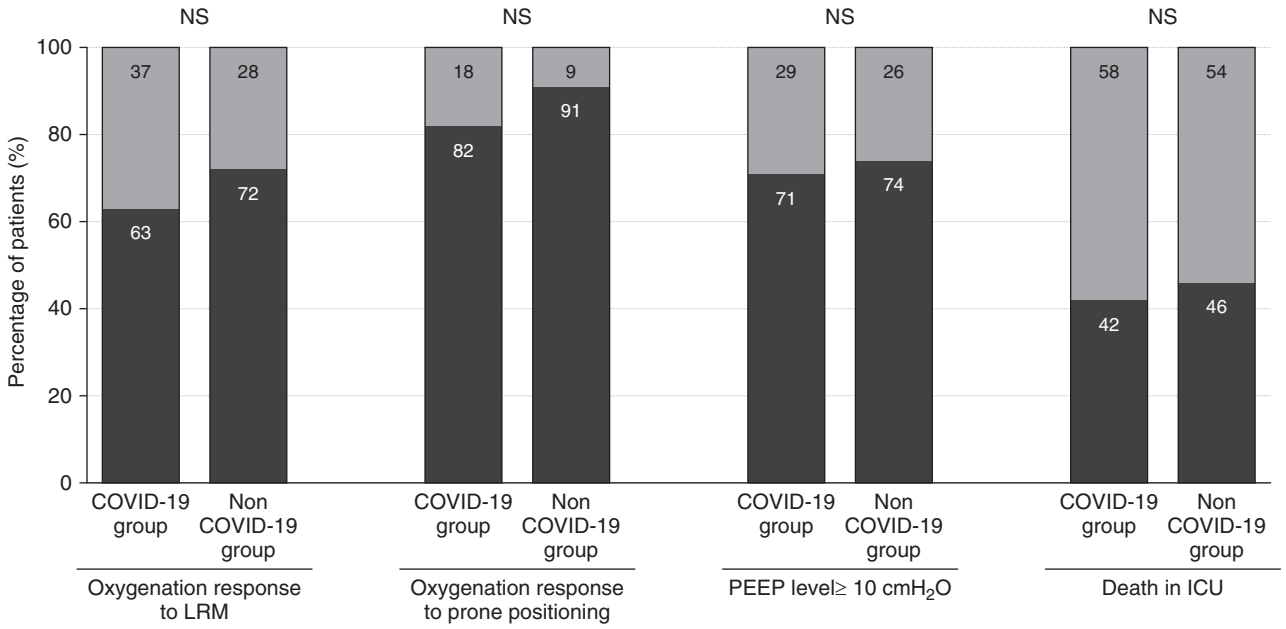

Figure 1. Assessment of interventions and clinical outcomes in mechanically ventilated patients with acute respiratory distress syndrome. We defined an oxygenation response to LRMs as an increase in the Pa_{O_2}/FI_{O_2} ratio by at least 20% in the 2–4 hours after the maneuver. Likewise, we defined an oxygenation response to prone positioning as an increase in the Pa_{O_2}/FI_{O_2} ratio by at least 20% or at least 20 mm Hg during the first prone position session. Here, we report on the first LRM or the first prone position session for each included patient only. COVID-19 = coronavirus disease; LRMs = lung recruitment maneuvers; NS = not significant; PEEP = positive end-expiratory pressure.

[IQR]) age was 61 (51–69). Patients in the COVID-19 group were older ($P = 0.02$) and more likely to suffer from obesity ($P = 0.04$) and diabetes ($P = 0.03$). The prevalence of immunodeficiency was significantly higher in the non–COVID-19 group ($P = 0.004$). The median (IQR) time between symptom onset and orotracheal intubation was longer in the COVID-19 group (10 vs. 5 d; $P = 0.0001$) (Table 1).

With regard to the computed tomography (CT) scan, a diffuse pattern with ground-glass opacity predominated in the COVID-19 group ($P = 0.03$ and $P = 0.01$, respectively). Alveolar consolidation was relatively common in both the COVID-19 and non–COVID-19 groups (61% vs. 60%; $P > 0.99$), whereas pleural effusion was more common in the non–COVID-19 group ($P = 0.0003$) (Table 1).

There were no significant intergroup differences with regard to the ventilator settings, such as the predicted V_T, the respiratory rate, and the PEEP. The driving pressure and the respiratory system compliance were 13 (10–15) cm H_2O and 33 (26–41) ml/cm H_2O in the COVID-19 group and 15 (12–18) cm H_2O and 29 (22–37) ml/cm H_2O in the non–COVID-19 group ($P = 0.12$ and $P = 0.13$, respectively) (Table 1). Arterial blood variables (including pH, Pa_{O_2}, and Pa_{CO_2}) were also similar in the two groups, as was the ventilatory ratio—a surrogate for dead space ventilation ($P = 0.46$). Lastly, about half of the patients in each group had severe ARDS (Table 1).

Concerning the treatment of ARDS, an oxygenation response to LRMs was observed in 15 (63%) of the patients in the COVID-19 group and in 28 (72%) in the non–COVID-19 group ($P = 0.44$). Overall, 43 (68%) patients underwent a prone position session. The oxygenation response to prone positioning did not differ significantly when comparing the two groups (82 vs. 91%; $P = 0.10$). With regard to other supportive therapies, the frequency and duration of neuromuscular blockade and inhaled nitric oxide administration were similar in the two groups. On discharge from the ICU, the survival rate was 42% in the COVID-19 group and 46% in the non–COVID-19 group ($P = 0.80$). The median length of stay in the ICU and duration of mechanical ventilation were similar in the two groups (Table 1 and Figure 1).

Discussion

Our results showed that the main characteristics of pressure measurements and respiratory mechanics (such as the plateau pressure, driving pressure, and respiratory system compliance) did not differ significantly when comparing COVID-19 and non–COVID-19 ARDS. Overall, the median (IQR) respiratory system compliance was 30 (23–40) ml/cm H_2O; the two groups did not differ significantly in this respect. This value is close to those reported in the literature for COVID-19 and non–COVID-19 ARDS (3–6). Our results go against the assumptions initially made by many clinicians (ourselves included) whereby lung mechanics in COVID-19 ARDS are relatively unaffected but gas exchanges are more severely impaired than in non–COVID-19 ARDS (1). In fact, our results suggest that the dissociation between lung mechanics and gas exchange is no greater in COVID-19 ARDS than in non–COVID-19 ARDS. In contrast, we observed significant differences in the pattern of chest CT scan involvement: diffuse ground-glass opacity was more frequent in COVID-19 ARDS, whereas pleural effusion was less frequent.

Our second key finding was that the potential for lung recruitment appears to be maintained in COVID-19 ARDS, because the effects of LRMs or prone positioning are similar to those observed in non–COVID-19 ARDS. Our results are in line with

recent publications (6–8). Pan and colleagues evaluated the potential for lung recruitment (as the recruitment-to-inflation ratio) in COVID-19 ARDS. The researchers found that lung recruitability was generally poor on the first day of observation but increased by alternating the prone and supine positions (8). This can be easily explained by the appearance of basilar consolidation over the course of COVID-19 ARDS. This consolidation accounts for 13–53% of the CT patterns, depending on when the scan is performed; the later the CT scan, the more frequent the consolidation (9, 10). In the present study, the predominant pattern in COVID-19 ARDS was diffuse ground-glass opacity, together with alveolar consolidation in about 60% of cases. This consolidation might be explained by the long median (IQR) time interval between the onset of symptoms and orotracheal intubation (10 [7–15] d) in our study population. Other studies have reported similar findings, but we cannot rule out the possible occurrence of "patient self-inflicted lung injury" due to excessive breathing efforts and delayed intubation (4, 7).

Our study had some important limitations. First, the study population was small and we did not prespecify the target sample size. Second, we only assess basic respiratory mechanical variables; the comparison of advanced parameters (such as transpulmonary pressures or ventilation–perfusion mismatches) might have revealed additional intergroup differences.

Conclusions

The main features of respiratory mechanics, the response to treatment (such as the oxygenation response to LRMs or prone position), and prognosis are similar in COVID-19 and non–COVID-19 ARDS. The oxygenation response to LRM and a high PEEP appear to be very heterogeneous in COVID-19 ARDS; this would argue in favor of a personalized ventilation strategy. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Complement Inhibition with the C5 Blocker LFG316 in Severe COVID-19

To the Editor:

In critically ill patients with coronavirus disease (COVID-19), a hyperinflammatory host response contributes to organ dysfunction and death. The role of complement in these events is unclear. Complement activation yields powerful proinflammatory effectors, notably C5a and membrane attack complex, and triggers coagulation (1); it has been implicated in bacterial sepsis and septic shock, sepsis-like syndromes associated with coronavirus infections, and COVID-19–associated microvascular injury and thrombosis (2–4). Recently, the C5a/C5aR1 axis was implicated in

W.M.Z. was funded by a Wellcome Trust Institutional Strategic Support Fund Fellowship. M.J.P. was funded by the Welsh Clinical Academic Training program and is a participant in the NIH Graduate Partnership Program. B.P.M. was supported by the UK Dementia Research Institute, Cardiff.

Author Contributions: J.C., M.J.P., B.E.S., C.F., M.M., and M.P.W. identified patients, organized treatment, and collected and analyzed all patient data. W.M.Z., M.J.P., S.J., and B.P.M. conducted and/or reviewed all laboratory data. R.A.H. and N.W. proposed the study and facilitated drug supply for compassionate use. M.P.W. and B.P.M. supervised and coordinated the research and wrote initial manuscript drafts. All authors contributed to revisions, approved the final manuscript, and accept accountability for all aspects of the work.

Originally Published in Press as DOI: 10.1164/rccm.202007-2778LE on September 8, 2020