Respiratory physiology of COVID-19-induced respiratory failure compared to ARDS of other etiologies

Domenico Luca Grieco 1,2*, Filippo Bongiovanni 1,2, Lu Chen 3,4, Luca S. Menga 1,2, Salvatore Lucia Cutuli 1,2, Gabriele Pintaudi 1,2, Simone Carelli 1,2, Teresa Michi 1,2, Flavia Torrini 1,2, Gianmarco Lombardi 1,2, Gian Marco Anzellotti 1,2, Gennaro De Pascale 1,2, Andrea Urbani 5,6, Maria Grazia Boccia 1,2, Eloisa S. Tanzarella 1,2, Giuseppe Bello 1,2, Antonio M. Dell’Anna 1,2, Salvatore M. Maggiore 7, Laurent Brochard 3,4 and Massimo Antonelli 1,2

Abstract

Background: Whether respiratory physiology of COVID-19-induced respiratory failure is different from acute respiratory distress syndrome (ARDS) of other etiologies is unclear. We conducted a single-center study to describe respiratory mechanics and response to positive end-expiratory pressure (PEEP) in COVID-19 ARDS and to compare COVID-19 patients to matched-control subjects with ARDS from other causes.

Methods: Thirty consecutive COVID-19 patients admitted to an intensive care unit in Rome, Italy, and fulfilling moderate-to-severe ARDS criteria were enrolled within 24 h from endotracheal intubation. Gas exchange, respiratory mechanics, and ventilatory ratio were measured at PEEP of 15 and 5 cmH2O. A single-breath derecruitment maneuver was performed to assess recruitability. After 1:1 matching based on PaO2/FiO2, FiO2, PEEP, and tidal volume, COVID-19 patients were compared to subjects affected by ARDS of other etiologies who underwent the same procedures in a previous study.

Results: Thirty COVID-19 patients were successfully matched with 30 ARDS from other etiologies. At low PEEP, median [25th–75th percentiles] PaO2/FiO2 in the two groups was 119 mmHg [101–142] and 116 mmHg [87–154]. Average compliance (41 ml/cmH2O [32–52] vs. 36 ml/cmH2O [27–42], p = 0.045) and ventilatory ratio (2.1 [1.7–2.3] vs. 1.6 [1.4–2.1], p = 0.032) were slightly higher in COVID-19 patients. Inter-individual variability (ratio of standard deviation to mean) of compliance was 36% in COVID-19 patients and 31% in other ARDS. In COVID-19 patients, PaO2/FiO2 was linearly correlated with respiratory system compliance (r = 0.52 p = 0.003). High PEEP improved PaO2/FiO2 in both cohorts, but more remarkably in COVID-19 patients (p = 0.005). Recruitability was not different between cohorts (p = 0.39) and was highly inter-individually variable (72% in COVID-19 patients and 64% in ARDS from other causes). In COVID-19 patients, recruitability was independent from oxygenation and respiratory mechanics changes due to PEEP.

(Continued on next page)
Methods
This prospective study was conducted in the dedicated COVID-19 ICU of a tertiary care university hospital in Italy during March 2020. Approval was obtained by local institutional review board, and informed consent was obtained according to committee recommendations.

Patients
We screened all consecutive adult patients admitted to the ICU between March 16 and 27, 2020, who were intubated due to acute hypoxic respiratory failure and fulfilled the criteria of severe ARDS according to the Berlin definition (i.e., PaO_2/FiO_2 ≤ 200, measured at PEEP = 5 cmH_2O) [24, 25]. Patients fulfilling criteria for moderate and severe COVID-19 ARDS were included in this study. All patients were ventilated on mechanical ventilation, and the following parameters were measured: tidal volume, positive end-expiratory pressure (PEEP), respiratory rate, minute ventilation, and arterial blood gases. Patients were weaned from mechanical ventilation when they met the following criteria: (1) no reintubation within 24 h of extubation, (2) spontaneous respiratory rate > 20 breaths per minute, and (3) hemodynamic stability, defined as a > 10% increase in vasopressor requirement during the previous 6 h or norepinephrine > 0.5 μg/kg/min.

Procedures and measurements
For each patient, demographics, comorbidities, and 28-day clinical outcome were recorded. All measurements were conducted in the supine semi-recumbent position within 24 h from endotracheal intubation, before any session of prone positioning. All patients were sedated and paralyzed with cisatracurium and a tracheal tube with a size appropriate to their predicted body weight (PBW) index was used. Driving pressure and tidal PEEP were measured. Driving pressure was calculated as tidal volume × respiratory rate × PaCO_2 / (PBW × 100 × 37.5) [17].

Respiratory mechanics: Peak airway pressure, plateau pressure, respiratory system compliance, and respiratory system resistance were calculated. The compliance was calculated as tidal volume / driving pressure.

Results
We assessed respiratory mechanics potential for lung recruitment, and PEEP effects in 30 consecutive mechanically ventilated patients with COVID-19-induced ARDS. After 1:1 matching based on the degree of oxygenation impairment at same PEEP and FiO_2, we then compared these results with those obtained from a multicenter cohort of patients with ARDS of other origins who underwent the same procedures in a previous study.

Conclusions: Early after establishment of mechanical ventilation, COVID-19 patients follow ARDS physiology, with compliance reduction related to the degree of hypoxemia, and inter-individually variable respiratory mechanics and recruitable lung units, and represents the mainstay of supportive therapy [5, 7, 9]. This could have important implications regarding ventilator management. Some authors claim that ARDS may have different phenotypes (high or low elastance), independently from gas exchange outcome, are mediated by respiratory mechanics that could have important implications regarding ventilator management and is among the potentially modifiable factors capable of improving survival [11].

Acknowledgements
We acknowledge our patients and their families who agreed to participate in this study. We are grateful to the nurses, respiratory therapists, and caregivers who supported our work.

Keywords: COVID-19, ARDS, Respiratory mechanics, PEEP, Alveolar recruitment
Recruitability: A single-breath derecruitment maneuver was performed by decreasing PEEP by 10 cmH2O [28, 29]; exhaled tidal volume after PEEP lowering was recorded, and recruitment-to-inflation ratio was computed [29]—patients with recruitment-to-inflation ratio ≥ 0.5 were considered having high recruitability.

Afterwards, ventilation was resumed with previous settings and PEEP = 5 cmH2O. After 30 min, blood gasses, hemodynamics, and respiratory mechanics were re-assessed as described. Lastly, low-flow (5 l/min) inflation was performed after prolonged exhalation to assess airway closure, and airway opening pressure was recorded if present [30–33].

Comparison with non-COVID-19 ARDS
COVID-19 patients were compared to a cohort of subjects with moderate-to-severe ARDS from other etiologies who underwent exactly the same procedures in a previous study [29]. Two investigators (DLG and LC) were directly involved in patients’ enrolment in both studies. This ensures reproducibility of the measurements and consistency in ventilator settings and circuit setup. COVID-19 patients were matched in 1:1 ratio to patients from the non-COVID-19 ARDS cohort. Matching was based on PaO2/FiO2 (± 20 mmHg), FiO2 (± 0.2), PEEP (± 3 cmH2O), and tidal volume (± 1.5 ml/kg of predicted body weight). For matching, priority was given to PaO2/FiO2 (100% adherence to the criterion), followed by FiO2 (93% adherence to the criterion, for “2 matches” criterion increased to ± 0.4), tidal volume (93% adherence to the criterion, for “2 matches” criterion increased to ± 2.5 ml/kg), and PEEP (90% adherence to the criterion, for “3 matches” criterion increased to ± 5 cmH2O). Individual data of matched subjects are provided in supplementary table 1.

Endpoints
The aims of the study were to describe respiratory mechanics, potential for lung recruitment, and response to PEEP in COVID-19-induced ARDS patients and to compare these features to those of patients affected by ARDS of other causes.

Sample size and statistical analysis
At the time of study design, systematic data on respiratory mechanics in COVID-19 patients were lacking. Hence, a convenience sample of 30 consecutive patients was chosen to provide a timely report. Categorical data are reported as number of events (%), and continuous data are displayed as medians [interquartile range]. Comparisons of continuous variables at the two PEEP levels were performed with the T test for paired samples: mean differences [95% confidence intervals, CI95%] are displayed for most significant results. Categorical variables were compared with the McNemar test. Inter-individual variability was calculated as the ratio of standard deviation to mean of the measurements.

Comparisons of continuous variables between COVID-19 and ARDS cohort were performed with the T test for independent samples: mean differences are displayed for significant results. Categorical variables were compared with the chi-square or Fisher exact test, as appropriate.

Correlations were assessed with Pearson’s correlation: r and p are provided for each comparison. Results with two-tailed p ≤ 0.05 were considered statistically significant. Statistical analysis was performed with SPSS 20.0 (IBM Corporation, Armonk, NY, USA). Manuscript figures were prepared with GraphPad Prism (La Jolla, CA, USA).

Results
COVID-19 cohort
Thirty patients were enrolled. Demographics and relevant clinical characteristics are reported in Table 1. Twenty-three (77%) patients met the criteria for moderate ARDS, and 7 (23%) for severe ARDS.

Matched cohorts
Thirty patients from the historical ARDS cohort were successfully matched to COVID-19 patients (individual data provided in supplementary Table 1, demographics in Table 1). At low PEEP, median PaO2/FiO2 was 119 mmHg [101–142] in COVID-19 patients and 116 mmHg [87–154] in patients with ARDS from other etiologies. FiO2 was not different between cohorts (p = 0.51), while tidal volume was slightly higher, and PEEP lower, in patients with COVID-19 than controls. Although statistically significant, mean differences between cohorts were clinically negligible: 0.3 ml/kg [CI95% 0–0.6] and 0.9 cmH2O [CI95% 0.1–1.7], respectively. All COVID-19 patients were studied within 24 h from endotracheal intubation. Patients in the historical cohort underwent study procedures after a median time from ICU admission of 5 [3–10] days.

Respiratory mechanics
These results are displayed in Fig. 1 and Table 2.

Airway closure in COVID-19 cohort was less frequent than in ARDS from other etiologies: 2 (7%) vs. 10 (30%) patients (p = 0.021). At low PEEP, inter-individual variability of respiratory system compliance was 36% in COVID-19 patients and 31% in ARDS from other causes. Average respiratory system compliance and respiratory system compliance/PBW were slightly higher in patients with COVID-19 than in those affected by...
other ARDS: mean differences were 7 ml/cmH\textsubscript{2}O [CI95% 0–14] and 0.11 ml/cmH\textsubscript{2}O/kg [CI95% 0.2–0.20], respectively. This was not associated to statistically significant differences in the driving pressure \( (p = 0.098) \). In both cohorts, twenty-four (80%) patients showed driving pressure equal or lower than 14 cmH\textsubscript{2}O. In the COVID-19 cohort, respiratory system compliance \( (r = 0.52, \ p = 0.003) \) and respiratory system compliance/PBW \( (r = 0.53, \ p = 0.002) \) were linearly related to PaO\textsubscript{2}/FiO\textsubscript{2} (Fig. 2).

In COVID-19 cohort, ventilatory ratio was higher than in ARDS from other etiologies (mean difference 0.3 [CI95% 0–0.6], \( p = 0.032 \)). In COVID-19 cohort, ventilatory ratio was not related to PaO\textsubscript{2}/FiO\textsubscript{2} \( (p = 0.42) \) nor to respiratory system compliance \( (p = 0.46) \).

**Response to PEEP—gas exchange and respiratory mechanics**
These results are displayed in Table 2 and Figs. 3 and 4.
High PEEP yielded improvement in PaO$_2$/FiO$_2$ in both cohorts. The PEEP-induced improvement in PaO$_2$/FiO$_2$ was greater in COVID-19 patients than among subjects with non-COVID-19 ARDS: median PEEP-induced changes in PaO$_2$/FiO$_2$ were 42 mmHg [24–62] vs. 27 mmHg [5–42], respectively ($p = 0.005$). In 27 (97%) patients of COVID-19 cohort, high PEEP yielded improvement in PaO$_2$/FiO$_2$.

In both cohorts, PEEP did not affect PaCO$_2$ nor ventilatory ratio. In COVID-19 patients, respiratory system compliance and driving pressure did not change with high PEEP: in ARDS from non-COVID-19 etiology, high PEEP reduced compliance by 5 ml/cmH$_2$O [CI95%: 2–8] and increased driving pressure by 2 cmH$_2$O [CI95%: 1–3].

In both cohorts, high PEEP caused reduction in systolic arterial pressure, without affecting heart rate and diastolic pressure.

**Response to PEEP—recruitability**

Median recruitment-to-inflation ratio (i.e., recruitability) was 0.73 [0.43–1.04] in COVID-19 patients and 0.55 [0.35–1.08] in ARDS from other causes ($p = 0.39$). Inter-individual variability of the recruitment-to-inflation ratio was 72% and 64%, respectively. Recruitment-to-inflation ratio was greater than 0.5 in 22 COVID-19 patients (73%) vs. 17 patients (57%) from the non-COVID-19 ARDS cohort ($p = 0.28$).

In COVID-19 patients, recruitment-to-inflation ratio had a weak but significant inverse correlation with respiratory system compliance recorded at low PEEP ($r = −0.37$, $p = 0.04$). Recruitment-to-inflation ratio had no relationship with the change in PaO$_2$/FiO$_2$ caused by high PEEP ($p = 0.45$) but had a reverse linear relationship with the change in PaCO$_2$ due to PEEP ($r = −0.46$, $p = 0.010$) (Fig. 4).

Recruitment-to-inflation was not different between patients who showed increased, decreased, or unchanged respiratory system compliance (and driving pressure) with high PEEP ($p = 0.14$).

**Clinical outcome**

At 28 days, 19 (63%) patients in the COVID-19 cohort had died and 3 (10%) were still on mechanical ventilation.

**Discussion**

The result of this matched-cohort study can be summarized as follows:
In COVID-19 patients, the severity of hypoxemia was related to respiratory system compliance reduction. This suggests that aeration loss is a relevant mechanism of hypoxemia.

Similarly to ARDS from other causes, respiratory mechanics of COVID-19 patients was highly heterogeneous.

Average respiratory system compliance and ventilatory ratio of COVID-19 patients were slightly higher than those of ARDS from other etiologies. Although statistically significant, differences appear clinically small.

The potential for PEEP-induced lung recruitment was variable. Average recruitability was similar to ARDS from non-COVID etiology. COVID-19 patients showed frank oxygenation response to PEEP independently from recruitability.

**Respiratory mechanics**

Few data are available about respiratory mechanics and response to PEEP COVID-19 patients with acute respiratory failure [18–20, 34]. Our study compared respiratory mechanics and response to PEEP of patients with COVID-19 with those of matched ARDS from other etiologies, who have undergone the same procedures.

In our study, respiratory mechanics was highly heterogeneous both in COVID-19 patients and in ARDS of other etiologies. Average values of respiratory system compliance were slightly higher in COVID-19 patients. Albeit statistically significant, mean difference (7 ml/cmH\textsubscript{2}O) may not be clinically relevant. This may depend on the small differences in body mass index between the two cohorts, and heterogeneous ARDS causes in the control group. In COVID-19 patients, compliance reduction was linearly related to oxygenation impairment: this indicates that aeration loss is a causative mechanism of hypoxemia, which is the hallmark of ARDS pathophysiology (i.e., the baby lung) [35–38].

Gattinoni et al. have hypothesized that the acute respiratory failure caused by COVID-19 is a time-related disease spectrum within different phenotypes [18]. Our results indicate that, soon after intubation, heterogeneity and average values of respiratory mechanics are similar to ARDS of other etiologies. Our data come from a limited sample. However, results appear consistent with

---

**Table 2** Respiratory mechanics

|                         | Low PEEP COVID-19 | Low PEEP Non-COVID-19 | p     | High PEEP COVID-19 | High PEEP Non-COVID-19 | p  |
|-------------------------|-------------------|-----------------------|-------|--------------------|------------------------|----|
| Set PEEP, cmH\textsubscript{2}O | 5 [5–5]*          | 5 [5–8]*              | 0.031 | 15 [15–15]*        | 15 [15–18]*            | 0.011 |
| Total PEEP, cmH\textsubscript{2}O | 5 [5–6]*          | 8 [6–9]*              | <0.001| 15 [15–16]*        | 16 [15–18]*            | 0.001 |
| Tidal volume, ml        | 431 [395–473]     | 414 [370–443]         | 0.15  | 431 [395–473]      | 417 [357–445]          | 0.20 |
| Tidal volume/PBW, ml/kg | 6.4 [6–6.8]       | 6.5 [6.7–6.3]         | 0.037 | 6.4 [6–6.8]        | 6 [5.8–6.3]            | 0.036 |
| Respiratory rate, breaths/minute | 28 [26–30]       | 26 [24–30]            | 0.16  | 28 [26–30]        | 26 [24–30]             | 0.11 |
| PaO\textsubscript{2}/FiO\textsubscript{2}, mmHg | 119 [101–142]*   | 116 [87–154]*         | 0.92  | 165 [132–196]*     | 150 [121–192]*         | 0.049 |
| pH                      | 7.35 [7.29–7.42]  | 7.37 [7.33–7.40]      | 0.63  | 7.35 [7.32–7.42]   | 7.36 [7.32–7.40]       | 0.45 |
| PaCO\textsubscript{2}, mmHg | 43 [37–49]       | 43 [37–49]            | 0.76  | 43 [36–49]        | 45 [35–49]             | 0.91 |
| Ventilatory ratio       | 2.1 [1.7–2.3]     | 1.6 [1.4–2.1]         | 0.032 | 2.1 [1.7–2.4]      | 1.7 [1.4–2.2]          | 0.08 |
| Standardized minute ventilation, liters/minute | 12.4 [10.7–15.6] | 11.1 [9.5–13.3]       | 0.12  | 12.4 [10.7–15.9]   | 11.5 [9.7–14.2]        | 0.29 |
| Peak pressure, cmH\textsubscript{2}O | 29 [23–32]*     | 33 [29–39]*           | 0.003 | 39 [36–41]*        | 41 [39–46]*            | 0.043 |
| Plateau pressure, cmH\textsubscript{2}O | 15 [14–17]*     | 19 [16–22]*           | <0.001| 26 [25–29]*       | 30 [28–33]*            | <0.001 |
| Inspiratory resistance, cmH\textsubscript{2}O/liters/second | 12 [10–14]      | 14 [11–16]*           | 0.09  | 12 [10–14]        | 12 [10–14]*            | 0.55 |
| Driving pressure, cmH\textsubscript{2}O | 10 [8–12]       | 11 [9–13]*            | 0.09  | 10 [9–14]         | 13 [11–17]*            | 0.007 |
| Patients with driving pressure ≤14 cmH\textsubscript{2}O, no. (%) | 24 (80)         | 25 (83)               | 1     | 24 (80)           | 21 (70)                | 0.55 |
| Respiratory system compliance, ml/cmH\textsubscript{2}O | 41 [32–52]      | 36 [27–42]*           | 0.045 | 39 [27–53]        | 32 [23–40]*            | 0.003 |
| Respiratory system compliance/PBW, ml/cmH\textsubscript{2}O/kg | 0.62 [0.48–0.78] | 0.54 [0.46–0.63]*     | 0.018 | 0.57 [0.45–0.75]  | 0.47 [0.37–0.56]*       | <0.001 |
| Arterial pressure, mmHg | Systolic          | 130 [112–140]*        | 0.27  | 118 [110–126]*     | 116 [104–126]*         | 0.71 |
|                         | Diastolic         | 70 [57–80]            | 0.017 | 65 [54–70]        | 57 [54–62]             | 0.08 |
|                         | Heart rate, beats per minute | 78 [70–93] | 82 [74–101] | 0.15 | 80 [70–92] | 85 [75–103] | 0.15 |

Data are expressed as medians [interquartile range], if not otherwise specified.
*p < 0.05 for the comparison between low and high PEEP within the COVID-19 cohort.

*p < 0.05 for the comparison between low and high PEEP within the non-COVID-19 cohort.
those of a recent large study on 742 patients [39] and with the recently published physiologic data by Haudebourg and coworkers [19]. They found no major differences in respiratory mechanics between patients with ARDS from COVID-19 and other etiologies. They did not exactly match their patients as done in our study, but could not detect relevant differences between ARDS from COVID-19 and other etiologies. Also, other authors have reported high heterogeneity in the respiratory mechanics and response to PEEP of COVID-19 patients [22, 40, 41]. These considerations strengthen the hypothesis that, from a ventilatory standpoint, clinicians should approach COVID-19 patients who fulfill ARDS criteria with our current evidence-based practices, informed by bedside physiology [15, 42–44].

Whether the microvascular involvement represents a disease-specific feature of COVID-19 disease is debated [27, 45]. In our study, ventilatory ratio was slightly higher in COVID-19 patients than in ARDS of other causes. The ventilatory ratio is correlated with dead space and can reflect microvascular thrombosis, which yields ventilation-perfusion mismatch [22]. However, microcirculatory involvement and increased dead space are hallmarks of ARDS as well [46, 47]. Larger cohorts will be needed to subtle differences on this specific aspect.

**Response to PEEP—gas exchange**

More than 95% of patients improved oxygenation with high PEEP, independently from recruitability. The oxygenation improvement achieved with high PEEP was greater in COVID-19 patients than in patients affected by ARDS of other causes, although the potential for lung recruitment was not different. PEEP-induced improvement in oxygenation without alveolar recruitment could be caused by decreased cardiac output, with redistribution of lung perfusion towards the normally aerated compartment [22, 34]. This indicates that, similarly to ARDS from other causes, the oxygenation response to PEEP is not informative about alveolar recruitment in COVID-19 as well.
Interestingly, PEEP-induced alveolar recruitment was correlated with PaCO₂ changes, and all patients with low potential for lung recruitment developed increases in PaCO₂ with high PEEP. Changes in PaCO₂ due to PEEP reflect dead space modifications. In case of poorly recruitable lungs, alveolar dead space increases due to compression of pulmonary vessels [48], and airway dead space augments due to gas compression in the respiratory circuit and airways [32]. With alveolar recruitment, overdistension by tidal volume is mitigated, and this reduces ventilation-perfusion mismatch [49, 50].

Response to PEEP—recruitability

In our study, recruitability of COVID-19 patients was variable, with an average value similar to ARDS from other etiologies. Our results are consistent with most recent data indicating great heterogeneity in the response to PEEP in COVID-19 patients [19, 22, 23]. This has relevant clinical implications, as PEEP setting should balance between its capability to recruit new alveoli and the unavoidable overdistension in already open tissue [51, 52]. As such, a high PEEP should be beneficial only in patients having greater potential for lung recruitment, in whom PEEP increases the size of the aerated lung available for tidal ventilation. Conversely, in non-recruitable patients, PEEP only enhances lung injury by increased static stress and strain [50]. Recruitability could not be predicted by changes in oxygenation, compliance, or driving pressure in response to PEEP, which represent popular proposed PEEP-setting strategies [53]. This suggests that bedside assessment of the potential for lung recruitment appears warranted in COVID-19 patients. The recently developed recruitment-to-inflation ratio (which represents recruited volume normalized to
aerated lung size) offers a simple, timely, and reproducible assessment of gas recruitment [29]. This may help distinguish patients showing high vs. low recruitability at the bedside, possibly supporting PEEP setting.

Clinical outcome
In our study, 28-day mortality of COVID-19 patients was higher than that reported for ARDS of other causes in a large multicenter observational study (35% for moderate and 43% for severe ARDS) [14]. We report high mortality rate despite tidal volume, plateau, and driving pressure were within a relatively safe range and prone position was applied in most of the patients. The majority of our patients were intubated after receiving noninvasive respiratory support, which could have selected the most severe population at higher risk for mortality [14, 54–56]. However, the small size of our cohort precludes from further speculation on the reasons for this high mortality.

Limitations
This study has limitations.
First, our COVID-19 patients were studied within 24 h after endotracheal intubation: it is possible that respiratory physiology varies over time, as suggested by other investigator showing low respiratory system compliance and minimal recruitability at a later stage of COVID-19 ARDS [57]. This reinforces the clinical message of our
study, which addresses individualized interventions based on bedside assessment of physiology.

Second, while the matched comparison with non-COVID-19 historical cohort has several strengths, we cannot exclude that uncontrolled individual characteristics of studied patients affected some of study results. In particular, duration of intubation prior to measurements could not be matched, and patients in the control group showed heterogeneous causes of ARDS: both these features may have affected study results.

**Conclusion**

Early after establishment of mechanical ventilation, patients with COVID-19 show a conventional ARDS phenotype, with heterogeneity in respiratory mechanics, aeration loss related to the degree of hypoxemia, and inter-individually variable recruitability. Physiological differences between COVID-19 patients and ARDS from other etiologies appear clinically negligible. Until other data emerge, clinicians treating COVID-19 patients should adhere to most recent guidelines regarding ARDS management.

**Supplementary information**

Supplementary information accompanies this paper at https://doi.org/10.1186/s13054-020-03253-2.

**Additional file 1 : Supplementary Table 1. Individual data of studied patients.**

**Abbreviations**

ARDS: Acute respiratory distress syndrome; PEEP: Positive end-expiratory pressure; BMI: Body mass index; ICU: Intensive care unit

**Acknowledgements**

The authors are grateful to all ICU doctors, residents, and nurses whose efforts, devotion to patients, and passion have made possible this timely report.

**Authors’ contributions**

DLG, FB, LC, LB, and MA conceived the study. DLG, SLC, GP, EST, SC, TM, FT, and MA organized the study as an interdepartmental, retrospective, observational study. Lancet Respir Med. 2020;2600:1–7.

Richardson S, Hirsch J, Narasimhan M, Crawford J, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;100222:1–8.

Arentz M, Yim E, Kralff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA. 2020.

Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med. 2013; 369:2126–36.

Laffey JG, Bellani G, Pham T, Fan E, Madotto F, Bajwa EK, et al. Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study. Intensive Care Med. 2016;42:1865–76.

Henderson WR, Chen L, Amato M, Brochard L. Fifty years of research in ARDS. Respiratory mechanics in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2017;196:822–33.

Amato MBP, Meade MO, Slutsky AS, Brochard L, Costa ELV, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015;372:747–55.

Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute distress syndrome in intensive care units in 50 countries. JAMA. 2016;315:788–800.

Goligher EC, Dres M, Patel BK, Sahetaya SK, Belitler JR, Telias I, et al. Lung and diaphragm-protective ventilation. Am J Respir Crit Care Med. 2020.
