Prone Position in COVID-19 and -COVID-19 Acute Respiratory Distress Syndrome: An International Multicenter Observational Comparative Study*

OBJECTIVES: Prone position is used in acute respiratory distress syndrome and in coronavirus disease 2019 acute respiratory distress syndrome. However, it is unclear how responders may be identified and whether an oxygenation response improves outcome. The objective of this study was to quantify the response to prone position, describe the differences between coronavirus disease 2019 acute respiratory distress syndrome and acute respiratory distress syndrome, and explore variables associated with survival.

DESIGN: Retrospective, observational, multicenter, international cohort study.

SETTING: Seven ICUs in Italy, United Kingdom, and France.

PATIENTS: Three hundred seventy-six adults (220 coronavirus disease 2019 acute respiratory distress syndrome and 156 acute respiratory distress syndrome).

INTERVENTION: None.

MEASUREMENTS AND MAIN RESULTS: Preproning, a greater proportion of coronavirus disease 2019 acute respiratory distress syndrome patients had severe disease (53% vs 40%), worse $\text{PaO}_2/\text{FiO}_2$ (13.0 kPa [interquartile range, 10.5–15.5 kPa] vs 14.1 kPa [interquartile range, 10.5–18.6 kPa]; $p = 0.017$) but greater compliance (38 mL/cm H$_2$O [interquartile range, 27–53 mL/cm H$_2$O] vs 31 mL/cm H$_2$O [interquartile range, 21–37 mL/cm H$_2$O]; $p < 0.001$). Patients with coronavirus disease 2019 acute respiratory distress syndrome had a longer median time from intubation to prone position (2.0 d [interquartile range, 0.7–5.0 d] vs 1.0 d [interquartile range, 0.5–2.9 d]; $p = 0.03$). The proportion of responders, defined by an increase in $\text{PaO}_2/\text{FiO}_2$ greater than or equal to 2.67 kPa (20 mm Hg), upon proning, was similar between acute respiratory distress syndrome and coronavirus disease 2019 acute respiratory distress syndrome (79% vs 76%; $p = 0.5$). Responders had earlier prone position (1.4 d [interquartile range, 0.7–4.2 d] vs 2.5 d [interquartile range, 0.8–6.2 d]; $p = 0.06$). Prone position less than 24 hours from intubation achieved greater improvement in oxygenation (11 kPa [interquartile range, 4–21 kPa] vs 7 kPa [interquartile range, 2–13 kPa]; $p = 0.002$). The variables independently associated with the “responder” category were $\text{PaO}_2/\text{FiO}_2$ preproning (odds ratio, 0.89 kPa$^{-1}$ [95% CI, 0.85–0.93 kPa$^{-1}$]; $p < 0.001$) and interval between intubation and proning (odds ratio, 0.94 d$^{-1}$ [95% CI, 0.89–0.99 d$^{-1}$]; $p = 0.019$). The overall mortality was 45%, with no significant difference observed between acute respiratory distress syndrome and coronavirus disease 2019 acute respiratory distress syndrome. Variables independently associated with mortality included age (odds ratio, 1.03 yr$^{-1}$ [95% CI, 1.01–1.05 yr$^{-1}$]; $p < 0.001$); interval between hospital admission and proning (odds ratio, 1.04 d$^{-1}$ [95% CI, 1.002–1.084 d$^{-1}$]; $p = 0.047$); and change in $\text{PaO}_2/\text{FiO}_2$ on proning (odds ratio, 0.97 kPa$^{-1}$ [95% CI, 0.95–0.99 kPa$^{-1}$]; $p = 0.002$).

*See also p. 708.

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CONCLUSIONS: Prone position, particularly when delivered early, achieved a significant oxygenation response in ~80% of coronavirus disease 2019 acute respiratory distress syndrome, similar to acute respiratory distress syndrome. This response was independently associated with improved survival.

KEY WORDS: adult; coronavirus disease 2019; intensive care units; prone position; respiratory distress syndrome

Coronavirus disease 2019 (COVID-19) pneumonia causes hypoxemic acute respiratory failure that meets the definition of acute respiratory distress syndrome (ARDS) (1–3).

Ventilation in prone position (PP) improves oxygenation while achieving a more homogeneous distribution of the mechanical forces, therefore reducing injury (4, 5). Following the demonstration of significant decrease in mortality in moderate-to-severe ARDS in the Proning Severe ARDS Patients (PROSEVA) trial (5), PP (for at least 12 hr) has become one of the most commonly used and effective strategies in ARDS (6, 7).

During the severe acute respiratory syndrome coronavirus 2 pandemic, the Surviving Sepsis Campaign COVID-19 subcommittee recommended the use of PP (8) in moderate-to-severe COVID-19 ARDS (C-ARDS). Similar recommendations were issued by other expert panels (9–11). Accordingly, PP has been extensively applied in invasively (11) and noninvasively ventilated patients (12).

However, it is unclear: 1) how the physiologic response to PP compares between C-ARDS and ARDS; 2) how responders may be identified and whether response might translate to improved outcomes; and 3) whether the outcome benefits are conferred equally to patients with differing compliance or recruitability, which may reflect the phenotypic characteristics described in C-ARDS (13–15). Specifically, it is possible that PP is more beneficial to earlier and to patients with greater recruitability.

The aim of this study was to quantify response to PP in C-ARDS, understand the differences in response between ARDS and C-ARDS, and explore the variables associated with outcome. Our hypothesis was that the oxygenation response to PP is greater in C-ARDS and if applied early. This hypothesis was based on the fact that in early C-ARDS, hypoxemia is determined by alteration in perfusion, lung edema, or atelectasis, rather than dense consolidation of fibrosis—which may be less modifiable with PP.

MATERIALS AND METHODS

Study Population

From seven international centers (Italy—Milan; United Kingdom—London; France—three in Lyon, one in Grenoble, and one in Roanne), we included 376 consecutive adult (>18 yr) ARDS patients who, while mechanically ventilated, received at least one session of PP lasting greater than or equal to 12 hours (Fig. 1). All patients fulfilled the Berlin definition of ARDS (16) prior to proning. The decision to initiate PP and the timing were at the discretion of the treating clinician; however, PP was recommended in patients with Pao2/Fio2 ratio less than 20 kPa (150 mm Hg) and Fio2 greater than 60%, despite optimization of positive end-expiratory pressure (PEEP) (5). Among these patients, 220 were admitted to the ICU and received invasive mechanical ventilation between February 2020 and May 2020 with documented COVID-19-positive reverse transcriptase-polymerase chain reaction test results from either upper airway swab or bronchoalveolar lavage. Another 156 patients with non-COVID-19 ARDS were admitted to the ICU and ventilated between December 2017 and May 2020.

![Figure 1. Flowchart of patients inclusion in the study. ARDS = acute respiratory distress syndrome, C-ARDS = coronavirus disease 2019 acute respiratory distress syndrome.](image-url)
2020. Approval for data collection was obtained at each participating institution (Comité d’éthique du Centre Hospitalier Universitaire de Lyon Number of approval 20-42—France; Approval number 10796—London, and Comitato Etico Milano Area I—17263/2020- 2020/ST/095), consent was waived, and data were anonymized before collating into the central database.

**Measurements**

Data were collected retrospectively from clinical documentation. Raw data were collated immediately after intubation and for the first proning session, where we extracted paired measurements in supine position prior (<2 hr) to the prone positioning and immediately (<2 hr) before the patient was returned to supine position. We hypothesized that the response to the first proning session would be the most important prognostic indicator and allow comparison of the entire patient cohort.

Data included hemodynamics, gas exchange, ventilatory parameters, and respiratory mechanics, in addition to demographic and anthropometric variables. We derived values for Pao_2/Fio_2 ratio, minute volume, tidal volume per predicted body weight, ventilatory ratio (17), corrected minute volumes (18), driving pressure (19), respiratory system compliance, and mechanical power (20, 21). Predicted mortality was calculated from severity scores Acute Physiology and Chronic Health Evaluation (APACHE) II and Simplified Acute Physiology Score (SAPS) II scores.

**Statistical Analysis**

In addition to the main etiology, we prespecified the following two groupings: 1) response to PP—we defined a positive response to PP as an absolute increase in Pao_2/Fio_2 greater than or equal to 2.67 kPa (20 mm Hg); 2) “higher or lower” compliance—based on the median value of compliance in the population. Comparisons within groupings were made with Mann-Whitney U significance tests. The difference in paired measurements between the prone and supine positions (prone minus supine or its relative change) was examined with Wilcoxon signed-rank tests. Between-group differences of categorical data were performed using Pearson χ² test.

Multivariable logistic regression models were constructed with variables that demonstrated significance in univariable logistic regression. This process was used to inform expert domain knowledge employed in variable selection for the reported multivariable logistic regression model. Data were assumed to be missing at random with no imputation or interpolation of missing values employed. Categorical data were reported as counts and percentages, and continuous data as median and interquartile ranges (IQRs) or 95% CIs, as appropriate. A value of α = 0.05 was used for all significance tests. All analysis was performed using R version 4.0.3 (Foundation for Statistical Computing, Vienna, Austria).

**RESULTS**

**Baseline Characteristics**

The flowchart of patients’ inclusion in the study is presented in Figure 1. The characteristics of patients after intubation are presented in Table E1 (http://links.lww.com/CCM/G870). In the ARDS cohort, 1.3% of patients (2/156) versus 32.1% (72/220) in the C-ARDS group had received noninvasive ventilation (NIV) preintubation. The C-ARDS cohort had a greater percentage of men, lower Sequential Organ Failure Assessment (SOFA) scores, higher Pao_2/Fio_2 ratio, greater compliance, and PEEP compared with the ARDS cohort. The majority of the C-ARDS patients had moderate ARDS (16). Baseline organ failure is reported in Table E2 (http://links.lww.com/CCM/G870).

**Preproning Characteristics**

The characteristics of patients prior to proning are reported in Table 1. The C-ARDS cohort had a significantly greater deterioration in oxygenation from intubation (–1.8 kPa [IQR, –7.0 to 0.84 kPa] for C-ARDS vs 0 [IQR, –4.2 to 3.6 kPa] for the ARDS group; p = 0.002), resulting in significantly worse Pao_2/Fio_2 ratio prior to proning (13.0 kPa [IQR, 10.5 to 15.5 kPa] for C-ARDS vs 14.1 [IQR, 10.5–18.6] in ARDS; p = 0.017). The deterioration in Pao_2/Fio_2 ratio from intubation to proning increased with time, at similar rates for both cohorts (Fig. E1, http://links.lww.com/CCM/G870). Immediately before PP, 53% of C-ARDS and 40% of ARDS patients exhibited a severe oxygenation defect. The delta changes between baseline and preproning are shown in Table 2.
TABLE 1.
Baseline Characteristics at the Time Prior to Proning, in Each Etiology Cohort

| Characteristics                                      | Overall (n = 376) | Acute Respiratory Distress Syndrome (n = 156) | Coronavirus Disease 2019 Acute Respiratory Distress Syndrome (n = 220) | p      |
|------------------------------------------------------|-------------------|-----------------------------------------------|------------------------------------------------------------------------|--------|
| **Gender, male**                                     | 276 (73%)         | 99 (63%)                                      | 177 (80%)                                                              | < 0.001|
| **Age, yr**                                          | 62 (54–71)        | 63 (52–71)                                    | 62 (56–70)                                                             | 0.5    |
| **Predicted body weight, kg**                        | 66 (57–72)        | 65 (54–72)                                    | 69 (60–73)                                                             | 0.006  |
| **Body mass index, kg/m²**                           | 28 (24–33)        | 28 (23–34)                                    | 28 (25–32)                                                             | 0.2    |
| **Admission Sequential Organ Failure Assessment**    | 7 (5–10)          | 9 (7–12)                                      | 6 (4–8)                                                                | < 0.001|

| **Etiology**                                         |                   |                                               |                                                                        |        |
|------------------------------------------------------|-------------------|-----------------------------------------------|------------------------------------------------------------------------|--------|
| Coronavirus disease 2019                             | 58.5% (220/376)   | -                                             | 100%                                                                  | -      |
| Pneumonia                                            | 26.6% (100/376)   | 64.1% (100/156)                               | 0                                                                     | -      |
| Aspiration                                           | 2.9% (11/376)     | 7.1% (11/156)                                 | 0                                                                     | -      |
| Nonpulmonary sepsis                                  | 12% (45/376)      | 28.8% (45/156)                                | 0                                                                     | -      |

| **Respiratory variables**                            |                   |                                               |                                                                        |        |
|------------------------------------------------------|-------------------|-----------------------------------------------|------------------------------------------------------------------------|--------|
| Respiratory rate, /min                               | 24 (20–28)        | 26 (24–30)                                    | 22 (18–28)                                                             | < 0.001|
| Peak airway pressure, cm H₂O                         | 35 (29–39)        | 37 (32–44)                                    | 32 (28–37)                                                             | < 0.001|
| Plateau airway pressure, cm H₂O                      | 25 (22–29)        | 25 (22–29)                                    | 26 (22–29)                                                             | 0.5    |
| Positive end-expiratory pressure, cm H₂O             | 11 (9–14)         | 10.0 (8–12)                                   | 12 (10–14)                                                             | < 0.001|
| Mechanical power, J/min                              | 25 (19–30)        | 26 (19–30)                                    | 25 (19–30)                                                             | 0.7    |
| Tidal volume, mL                                     | 425 (370–480)     | 400 (350–447)                                 | 440 (382–509)                                                          | < 0.001|
| Tidal volume per PBW, mL/kg                          | 6.31 (5.9–7.1)    | 6.1 (5.9–6.6)                                 | 6.51 (6.0–7.6)                                                         | < 0.001|
| Driving pressure, cm H₂O                             | 12.0 (10.0–16.0)  | 13.0 (10.0–19.5)                              | 12.0 (8.8–15.0)                                                        | < 0.001|
| Compliance, mL/cm H₂O                                | 35 (25–46)        | 31 (21–37)                                    | 38 (27–53)                                                             | < 0.001|
| FIO₂, %                                              | 70 (60–92)        | 70 (55–100)                                   | 75 (60–90)                                                             | 0.13   |
| Pac₂, kPa                                            | 9.4 (8.4–10.9)    | 9.60 (8.62–11.43)                             | 9.20 (8.29–10.70)                                                      | 0.05   |
| PacO₂, kPa                                           | 6.3 (5.5–7.4)     | 6.2 (5.5–7.3)                                 | 6.4 (5.5–7.4)                                                          | 0.4    |
| Pac₂/PacO₂, ratio, kPa                               | 13.3 (10.4–17.1)  | 14.1 (10.5–18.6)                              | 13.0 (10.5–15.5)                                                       | 0.02   |
| Minute volume, L/min                                 | 10.2 (8.3–11.7)   | 10.5 (8.6–11.9)                               | 9.9 (8.2–11.6)                                                         | 0.07   |
| Corrected minute volume, L/min                       | 11.8 (9.2–14.9)   | 12.0 (9.7–14.9)                               | 11.4 (8.9–14.9)                                                        | 0.4    |
| Ventilatory ratio                                    | 1.99 (1.52–2.54)  | 2.06 (1.65–2.57)                              | 1.92 (1.44–2.42)                                                       | 0.01   |
| Mechanical power per PBW, J/min/kg                   | 0.38 (0.31–0.47)  | 0.39 (0.33–0.48)                              | 0.37 (0.30–0.46)                                                       | 0.1    |

| **Disease severity, n**                              | 362               | 148                                           | 214                                                                    | 0.02   |
|------------------------------------------------------|-------------------|-----------------------------------------------|------------------------------------------------------------------------|--------|
| Severe                                               | 179 (49.4%)       | 62 (41.9%)                                    | 117 (54.8%)                                                            |        |
| Moderate                                             | 168 (46.4%)       | 76 (51.4%)                                    | 92 (43.0%)                                                             |        |
| Mild                                                 | 15 (4.1%)         | 10 (6.8%)                                     | 5 (2.3%)                                                               |        |

| **Organ support**                                    |                   |                                               |                                                                        |        |
|------------------------------------------------------|-------------------|-----------------------------------------------|------------------------------------------------------------------------|--------|
| Vasopressors                                         | 299 (80%)         | 144 (92%)                                     | 155 (70%)                                                              | < 0.001|
| Renal replacement therapy                            | 40 (12%)          | 25 (16%)                                     | 15 (8.1%)                                                              | 0.023  |
| Neuromuscular blockade                               | 308 (82%)         | 147 (94%)                                    | 161 (73%)                                                              | < 0.001|
| Inhaled nitric oxide                                 | 15 (4.0%)         | 6 (3.8%)                                     | 9 (4.1%)                                                               | > 0.9  |

PBW = predicted body weight.
TABLE 2. Change in Parameter Values on Prone Positioning and Outcome in Each Etiology Cohort

| Variables                              | Overall (n = 376) | Acute Respiratory Distress Syndrome (n = 156) | Coronavirus Disease 2019 Acute Respiratory Distress Syndrome (n = 220) | p     |
|----------------------------------------|-------------------|-----------------------------------------------|---------------------------------------------------------------------|-------|
| Respiratory rate, /min                 | Δ                 |                                               |                                                                     |       |
| Δ                                       | 0 (–1 to 2)       | 0 (–2 to 2)                                   | 0 (–1 to 2)                                                       | 0.3   |
| Δ%                                     | 0 (–6 to 8)       | 0 (–6 to 7)                                   | 0 (–5 to 11)                                                      |       |
| Peak airway pressure, cm H₂O           | Δ                 |                                               |                                                                     |       |
| Δ                                       | –1 (–4 to 2)      | –1 (–5 to 2)                                  | 0 (–3.0 to 2.2)                                                   | 0.02  |
| Δ%                                     | –3 (–10 to 7)     | –3 (–11 to 5)                                 | 0 (–9 to 8)                                                      |       |
| Plateau airway pressure, cm H₂O        | Δ                 |                                               |                                                                     |       |
| Δ                                       | –1 (–3 to 1)      | –1 (–4.5 to 1.0)                              | 0 (–2 to 1)                                                      | 0.01  |
| Δ%                                     | –4 (–12 to 5)     | –5 (–16 to 4)                                 | 0 (–8 to 5)                                                      |       |
| Positive end-expiratory pressure, cm H₂O | Δ               |                                               |                                                                     |       |
| Δ                                       | 0 (–1.0 to 0.3)   | 0 (–1 to 2)                                   | 0 (–1 to 0)                                                      | 0.2   |
| Δ%                                     | 0 (–11 to 2)      | 0 (–11 to 20)                                 | 0 (–9 to 0)                                                      |       |
| Mechanical power, J/min                | Δ                 |                                               |                                                                     |       |
| Δ                                       | –0.75 (–4.1 to 2.7) | –1.1 (–4.2 to 2.0)                           | –0.49 (–3.9 to 3.4)                                              | 0.2   |
| Δ%                                     | –3 (–16 to 12)    | –5 (–16 to 8)                                 | –2 (–17 to 17)                                                   |       |
| Tidal volume, mL                       | Δ                 |                                               |                                                                     |       |
| Δ                                       | 0 (–24 to 13)     | 0 (–14.5 to 8.5)                              | 0 (–33 to 20)                                                    | 0.8   |
| Δ%                                     | 0 (–6 to 3)       | 0 (–5 to 2)                                   | 0 (–7 to 4)                                                      |       |
| Driving pressure, cm H₂O               | Δ                 |                                               |                                                                     |       |
| Δ                                       | –1 (–3 to 1)      | –1 (–4 to 0)                                  | 0 (–2 to 1)                                                      | 0.001 |
| Δ%                                     | –7 (–22 to 8)     | –12 (–25 to 0)                                | 0 (–18 to 10)                                                   |       |
| Compliance, mL/cm H₂O                  | Δ                 |                                               |                                                                     |       |
| Δ                                       | 2.5 (–2.7 to 8.6) | 4.1 (–0.98 to 8.36)                           | 1 (–3.9 to 8.7)                                                  | 0.06  |
| Δ%                                     | 8 (–8 to 27)      | 16 (–5 to 31)                                 | 3 (–10 to 24)                                                   |       |
| Fio₂, %                                | Δ                 |                                               |                                                                     |       |
| Δ                                       | –20 (–35 to –10)  | –20 (–36.0 to –9.8)                           | –20 (–35 to –10)                                                 | > 0.9 |
| Δ%                                     | –30 (–44 to –14)  | –30 (–45 to –14)                              | –30 (–44 to –14)                                                |       |
| Pao₂, kPa                               | Δ                 |                                               |                                                                     |       |
| Δ                                       | 1.0 (–0.6 to 2.8) | 0.8 (–0.8 to 3.6)                             | 1.1 (–0.5 to 2.5)                                                | > 0.9 |
| Δ%                                     | 11 (–6 to 32)     | 9 (–8 to 39)                                  | 12 (–5 to 30)                                                   |       |
| Paco₂, kPa                              | Δ                 |                                               |                                                                     |       |
| Δ                                       | –0.25 (–0.91 to 0.53) | –0.37 (–1.20 to 0.27)                     | –0.13 (–0.71 to 0.67)                                           | < 0.01|
| Δ%                                     | –4 (–14 to 9)     | –7 (–17 to 5)                                 | –2 (–11 to 12)                                                  |       |
| Pao₂/Fio₂ ratio, kPa                    | Δ                 |                                               |                                                                     |       |
| Δ                                       | 8.2 (3.2–16.3)    | 9.3 (4.4–18.6)                                | 7.7 (3.0–14.0)                                                   | 0.1   |
| Δ%                                     | 60 (29–121)       | 60 (29–134)                                   | 60 (22–109)                                                     |       |
| Minute volume, L/min                   | Δ                 |                                               |                                                                     |       |
| Δ                                       | 0 (–0.74 to 0.92) | 0 (–0.80 to 0.54)                             | 0 (–0.72 to 1.17)                                               | 0.2   |
| Δ%                                     | 0 (–8 to 10)      | 0 (–9 to 5)                                   | 0 (–7 to 13)                                                    |       |
| Corrected minute volume, L/min         | Δ                 |                                               |                                                                     |       |
| Δ                                       | –0.3 (–1.9 to 1.2) | –0.69 (–2.4 to 0.6)                           | 0.21 (–1.3 to 1.9)                                              | < 0.001|
| Δ%                                     | –2 (–17 to 11)    | –7 (–20 to 5)                                 | 2 (–11 to 17)                                                   |       |
| Ventilatory ratio                      | Δ                 |                                               |                                                                     |       |
| Δ                                       | –0.05 (–0.33 to 0.21) | –0.14 (–0.39 to 0.09)                  | 0.03 (–0.21 to 0.29)                                            | < 0.001|
| Δ%                                     | –2 (–17 to 11)    | –7 (–20 to 5)                                 | 2 (–11 to 17)                                                  |       |

Outcome

|                        | overall | Acute Respiratory Distress Syndrome | Coronavirus Disease 2019 Acute Respiratory Distress Syndrome | p     |
|------------------------|---------|------------------------------------|----------------------------------------------------------------|-------|
| Hospital to ICU admission, d | 0.7 (0.0–3.0) | 0.0 (0.0–1.0) | 1.0 (0.0–3.0) | < 0.001|
| ICU length of stay, d   | 20 (12–33) | 18 (11–26) | 22 (14–39) | < 0.001|
| Hospital admit to proning, d | 4.6 (2.0–7.9) | 2.8 (1.4–7.7) | 5.4 (2.8–8.0) | < 0.001|
| Intubation to proning, d | 1.3 (0.6–4.2) | 1.0 (0.5–2.9) | 2.0 (0.7–5.0) | 0.03 |
| Duration of initial proning session, hr | 16.0 (15.0–18.0) | 16.0 (14.0–18.0) | 16.0 (15.5–18.0) | 0.2 |
| Number of proning sessions | 2 (1–5) | 2 (1–3) | 4 (2–6) | < 0.001|

(Continued)
Patients underwent their first PP session after a median of 1.3 days [IQR, 0.6–4.2 d]. Patients with C-ARDS had a longer median time from intubation to PP (2.0 d [IQR, 0.7–5.0 d] vs 1.0 [IQR, 0.5–2.9]; \( p = 0.03 \)).

The length of the first PP session was similar between C-ARDS (16 hr [IQR, 14–18 hr]) and ARDS (16 hr [IQR, 16–18 hr]; \( p = 0.2 \)).

### Response to Proning

The median and proportional change in the physiologic parameters between supine and prone are shown in Table 2. Both C-ARDS and ARDS cohorts had a similar improvement in oxygenation, with a median reduction in \( \text{FiO}_2 \) of 0.20 [IQR, 0.35–0.10] and increase in \( \text{PaO}_2 \) (1 kPa [IQR, –0.6 to 2.8 kPa]) and \( \text{Pao}_2/\text{FiO}_2 \) (8.2 kPa [IQR, 3.2–16.3 kPa]), which equated to a 60% (IQR, 23–121%) increase from supine position (Fig. 2).

Following PP, the ventilatory ratio decreased by 7% (IQR, –20 to 5) in ARDS, whereas increased by 2% (IQR, –11 to 17) in C-ARDS with wide variation in individual response. There was an improvement in the compliance of the respiratory system (16% [IQR, –5 to 31] vs 2% [IQR, –10 to 24]; \( p = 0.013 \), and driving pressure in the ARDS population -12% (IQR, –25 to 0).

Overall, 77% of patients could be classified as responders, with an increase in \( \text{Pao}_2/\text{FiO}_2 \) of greater than or equal to 2.7 kPa (20 mm Hg) upon proning, with similar prevalence or responders in the both cohorts (ARDS 78% vs C-ARDS 76%; \( p = 0.7 \)).

### Prediction of \( \text{Pao}_2/\text{FiO}_2 \) Response to Proning

Lower supine \( \text{Pao}_2/\text{FiO}_2 \), shorter duration of intubation pre-pronning (i.e., earlier proning), and non-COVID-19 ARDS were associated with a greater increase in \( \text{Pao}_2/\text{FiO}_2 \) following PP. Although later PP was negatively associated with oxygenation response, we found this effect was near constant after the first 24 hours, and therefore, the timing of PP was analyzed as a dichotomous variable.
(≤ 24 or > 24 hr) (Fig. E2, http://links.lww.com/CCM/G870). The resulting model explained a significant and moderate amount of the variance ($R^2 = 0.15; p < 0.001$) in the increase in oxygenation, with an intercept corresponding to an increase in the $Pao_2/Fio_2$ of 23.9 kPa (95% CI, 20.2–27.7), for an ARDS patient proned within 24 hours of intubation (intercept at a theoretical supine $Pao_2/Fio_2$ of 0 kPa). Further details on the regression model can be found in Supplement Sections 4.2 and 4.3 (http://links.lww.com/CCM/G870).

The variables independently associated with “responder” category in a multivariable logistical model were $Pao_2/Fio_2$ preproning (odds ratio, [OR], 0.89 kPa$^{-1}$ [95% CI, 0.85–0.93 kPa$^{-1}$]; $p < 0.001$) and the interval between intubation and proning (OR, 0.94 d$^{-1}$ [0.89–0.99 d$^{-1}$]; $p = 0.019$).

The point estimate for OR related to COVID-19 status was 0.67 but with wide 95% CI [0.38–1.17], therefore not significantly associated with response when timing of proning was also included in the model.

Response to Prone Position in the Low and High Compliance Groups

We further analyzed the two cohorts based on the supine respiratory system compliance dichotomized based on the median supine preproning value of 34.6 mL/cm H$_2$O.

There was no difference in the proportion of responders based on the compliance category (77% in ARDS and 69% in C-ARDS, for the low compliance category; $p = 0.3$, and 72% in ARDS and 78% in C-ARDS, for the high compliance category; $p = 0.5$). Equally, the proportion of responders was similar in high and low compliance for the C-ARDS (78% vs 69%; $p = 0.2$) and ARDS (72% vs 78%; $p = 0.6$).

Outcome

Mortality for the overall population including both cohorts was 45%. Predicted hospital mortality, calculated from SAPS II and APACHE II scores, for the C-ARDS cohort was significantly lower than the ARDS cohort and also significantly underestimated mortality in the C-ARDS cohort. Indeed, the hospital mortality for C-ARDS was estimated at 20% (12–31), whereas the actual mortality was 43%. Mortality predictions were accurate for ARDS population 55% (30–83%) predicted mortality and 47% actual mortality in the population.

In the C-ARDS cohort, there was a trend for lower mortality in responders (39% vs 54%; $p = 0.07$), whereas there was no difference in outcome between the responders and nonresponders in ARDS (48% vs 55%; $p = 0.5$) (Table E4, http://links.lww.com/CCM/G870).

The survival was similar for the two cohorts regardless of compliance category (66% in ARDS and 56% in C-ARDS, for the low compliance category; $p = 0.3$, and 49% in ARDS and 49% in C-ARDS, for the low compliance category; $p = 0.2$). However, there was a trend for greater survival in the C-ARDS cohort with higher compliance (61% vs 46%; $p = 0.07$).

Variables independently associated with mortality included age (OR, 1.03 yr$^{-1}$ [95% CI, 1.01–1.05 yr$^{-1}$]; $p < 0.001$), predicted hospital mortality (OR, 1.013

Figure 2. $Pao_2/Fio_2$ ratio in supine and prone position. The conversion factor between kPa and mm Hg is 1 kPa = 7.500617 mm Hg. ARDS = acute respiratory distress syndrome, C-ARDS = coronavirus disease 2019 acute respiratory distress syndrome.
[95% CI, 1.005–1.023]; \( p = 0.002 \), interval from hospital admission to proning (OR, 1.040 d\(^{-1}\) [95% CI, 1.002–1.084 d\(^{-1}\); \( p = 0.047 \)), and \( \text{PaO}_2/\text{FiO}_2 \) response to proning (OR, 0.97 kPa\(^{-1}\) [95% CI, 0.95–0.99 kPa\(^{-1}\); \( p = 0.002 \)) (Fig. 3).

COVID-19 infection status (OR, 0.68 [95% CI, 0.43–1.08]; \( p = 0.1 \)) and change in \( \text{Paco}_2 \) (OR, 0.93 kPa\(^{-1}\) [95% CI, 0.81–1.07 kPa\(^{-1}\); \( p = 0.3 \)) were not significantly associated with outcome, and there was no significant interaction between COVID-19 status and \( \text{Paco}_2 \) response (OR, 1.22 [95% CI, 0.9–1.68]; \( p = 0.3 \)).

**DISCUSSION**

This study shows that PP, particularly when delivered early, resulted in a significant oxygenation response in almost 80% of patients with C-ARDS and non-COVID-19 ARDS, and this response was independently associated with improved survival. The C-ARDS cohort had greater respiratory compliance despite a worse oxygenation compared with the ARDS cohort. These characteristics are consistent with the greater lung gas volumes observed in C-ARDS (1, 2) and the fact that the relatively higher compliance coexists with severe oxygenation defect (3).

The majority of patients showed an improvement in the \( \text{PaO}_2/\text{FiO}_2 \) ratio following the first episode of PP (22, 23) with similar proportions in both cohorts, and their oxygenation response was not affected by the respiratory compliance.

This study also shows that greater oxygenation response to PP was observed in patients proned within 24 hours of intubation. Longer time from intubation to PP decreased the chance of oxygenation response by 6%/d and increased the risk of death by 6%/d. The relationship between timing of proning and outcome is consistent with the results of large observational study that showed a 16% relative risk reduction of death in patients who were proned within 2 days of ventilation (24) and a more recent U.K. study (25).

The other factor associated with greater oxygenation response to PP was a lower \( \text{PaO}_2/\text{FiO}_2 \) ratio preproning (i.e., more severe disease had greater response), consistent with ARDS (4–6, 26) and C-ARDS (27) data that demonstrate higher likelihood of response to PP in the moderate-to-severe category.

When time-to-proning and change in \( \text{PaO}_2/\text{FiO}_2 \) were included in the same model, the oxygenation response was a strong predictor of mortality particularly in C-ARDS. The analysis of the relationship between the time to PP and the deterioration in \( \text{PaO}_2/\text{FiO}_2 \) from intubation to the time of proning in the two groups shows that C-ARDS had a higher \( \text{PaO}_2/\text{FiO}_2 \) ratio at baseline but greater deterioration, that is, lower value preproning. This finding is in agreement with the data showing that improvement in oxygenation after the first PP was a predictor of survival (23, 28). The relationship between timing of proning in relationship to hospital admission and severity of \( \text{PaO}_2/\text{FiO}_2 \) may be explained by the changing pathophysiology of hypoxemia that characterizes the different phases of disease (e.g., alteration of perfusion, worsening edema, etc.).
and atelectasis; vs the development of denser consolidation or fibrosis) (29).

These findings—together with the higher compliance seen in C-ARDS—may suggest that the main mechanism for improvement in oxygenation may be the redistribution of pulmonary perfusion from lower to higher ventilation/perfusion ratio areas, rather than that significant alveolar recruitment, given that the reduction in Paco₂ following PP, was significantly smaller in C-ARDS in agreement with what reported in other studies (30). According to the model by Riley and Cournand (31), arterial Paco₂ is a weighted average of the Pco₂ in the shunted blood (mixed venous blood perfusing nonaerated lung regions) and Pco₂ in the capillary blood in equilibrium with the alveolar Pco₂. Therefore, alveolar recruitment should lead to a reduction in dead space. This phenomenon was seen in the ARDS cohort consistently with previous studies (32). The higher compliance and, therefore, gas volume (1) and the higher PEEP used in C-ARDS may have worsened dead space ventilation regardless of disease severity (33) and are consistent with the reported dissociation between improvement in oxygenation and worsening indices of dead space with higher PEEP in COVID-19 (34). Prior systematic reviews and meta-analyses (7, 35) demonstrated that the combination of low tidal volumes and prone positioning improved survival (36). Differently from meta-analysis of earlier trials, which included patients ventilated with tidal volumes greater than 8 mL/kg PBW, our patients were ventilated with lower tidal volumes (6–6.5 mL/kg PBW) and driving pressures, and this might explain why tidal volume was not independently associated with outcome.

The mortality predictions based on SOFA, SAPS II, and APACHE II score underestimated the mortality in COVID-19, similar to that reported in a U.S. cohort of mechanically ventilated patients based on the pre-intubation SOFA (37). Given that a lower proportion of patients with severe C-ARDS received vasopressors or renal replacement therapy, the excess mortality likely derives from respiratory mortality and possibly the effect of mechanical ventilatory support. Indeed, the mechanical power delivered to these patients was higher (27–29 J/min) than the threshold reported to be associated with mortality when mechanical power was higher than 17.0 J/min regardless of driving pressure and low tidal volumes (38).

This study has several strengths that derive from being a large multicenter physiologic study and, therefore, possessing greater external validity, and the fact that it compares the C-ARDS with ARDS highlighting the determinants of response to PP and their potential differences. However, this study presents several limitations due to its retrospective, observational design. Specifically, data included in the database were collected for clinical purposes and may occur at different time intervals before and after PP. Some important data—including the total duration of symptoms prior to hospital admission—have not been routinely collected. In addition, there was no prespecified sample size for the cohort enrolled, despite the fact that all COVID-19 patients who had a documented proning session were included in the study. Additional limitations relate to potential inclusion bias, as the initiation of prone positioning may ultimately reflect the practice of the treating clinical team. Furthermore, differences in patient selection among centers reflect potentially different resources at a time of pandemics. The issues of staffing, burden of patients, and ICU occupancy may have affected the timeliness of delivery of PP and the use of NIV prior to intubation. This leads to another potential limitation of the study, which is understanding to what extent the difference noted is intrinsic to C-ARDS or reflects the constraints of a healthcare system engaged in dealing with a pandemic. Finally, the comparisons refer only to the first proning session. In this cohort, the median number of PP session was two (ranging from one to five). Therefore, to ensure homogeneity of the data, we concentrated on the first session as this will allow to compare the entire cohort of patients.

**CONCLUSIONS**

PP, particularly when delivered early, achieves a significant oxygenation response in almost 80% of patients with severe C-ARDS. The response is similar to ARDS. Response to PP was independently associated with improved survival.

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