Impact of Prone Position in COVID-19 Patients on Extracorporeal Membrane Oxygenation*

OBJECTIVES: Prone positioning and venovenous extracorporeal membrane oxygenation (ECMO) are both useful interventions in acute respiratory distress syndrome (ARDS). Combining the two therapies is feasible and safe, but the effectiveness is not known. Our objective was to evaluate the potential survival benefit of prone positioning in venovenous ECMO patients cannulated for COVID-19-related ARDS.

DESIGN: Retrospective analysis of a multicenter cohort.

PATIENTS: Patients on venovenous ECMO who tested positive for severe acute respiratory syndrome coronavirus 2 by reverse transcriptase polymerase chain reaction or with a diagnosis on chest CT were eligible.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: All patients on venovenous ECMO for respiratory failure in whom prone position status while on ECMO and in-hospital mortality were known were included. Of 647 patients in 41 centers, 517 were included. Median age was 55 (47–61), 78% were male and 95% were prone before cannulation. After cannulation, 364 patients (70%) were prone and 153 (30%) remained in the supine position for the whole ECMO run. There were 194 (53%) and 92 (60%) deaths in the prone and the supine groups, respectively. Prone position on ECMO was independently associated with lower in-hospital mortality (odds ratio = 0.49 [0.29–0.84]; p = 0.010). In 153 propensity score-matched pairs, mortality rate was 49.7% in the prone position group versus 60.1% in the supine position group (p = 0.085). Considering only patients alive at decannulation, propensity-matched prone patients had a significantly lower mortality rate (22.4% vs 37.8%; p = 0.029) than nonproned patients.

CONCLUSIONS: Prone position may be beneficial in patients supported by venovenous ECMO for COVID-19–related ARDS but more data are needed to draw definitive conclusions.

KEY WORDS: acute respiratory distress syndrome; critical care; extracorporeal membrane oxygenation; mechanical ventilation; mortality; prone position

Prone positioning is a key nonpharmacological intervention in moderate to severe acute respiratory distress syndrome (ARDS) patients (Pao₂/Fio₂ < 150 mm Hg) (1) and is an early intervention in National Institutes of Health COVID-19 treatment guidelines (https://www.covid19treatment-guidelines.nih.gov/). Prone position improves gas exchange by reducing ventilation/perfusion mismatch and allows for a reduction of ventilator-induced lung injury (VILI) by promoting more homogeneous parenchymal aeration (2). Other beneficial effects include improved lung recruitability, enhanced secretion drainage, and reduced right ventricular strain.

Venovenous extracorporeal membrane oxygenation (ECMO) is considered a rescue therapy in ARDS but has been used extensively in the COVID-19

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pandemic (3). Venovenous ECMO provides adequate gas exchange when normal pulmonary gas exchange is compromised, and allows for an ultraprotective ventilation strategy, reducing VILI.

Whether the combination of prone position and venovenous ECMO is beneficial in COVID-19 remains unknown. Available evidence, mainly from observational studies in non-COVID ARDS, demonstrates that prone position on venovenous ECMO is safe and feasible and is associated with a potential improvement in survival (4–7). The available data in COVID-19–related ARDS are more limited, with one recent report suggesting a potential survival advantage (8), but several meta-analyses that combined COVID and non-COVID patients showing conflicting results (9–11).

As prone positioning on ECMO is a resource-intensive task, defining its impact on survival is critical, especially in a period of resource constraints (12). Thus, the objective of our study was to evaluate the survival benefit of prone position in venovenous ECMO patients cannulated for COVID-19–related ARDS in a large multicenter nationwide cohort. We hypothesized that prone position while on ECMO would be associated with improved in-hospital survival.

**MATERIALS AND METHODS**

The Extracorporeal Membrane Oxygenation for Respiratory Failure and/or Heart failure related to Severe Acute Respiratory Syndrome Coronavirus 2 (ECMOSARS) registry was launched in April 2020 (ClinicalTrials.gov Identifier: NCT04397588, ECMO and Severe Acute Respiratory Syndrome Coronavirus 2: ECMOSARS registry, principal investigators: N.N., A.V., date of registration: May 21, 2020) and is currently recruiting (13). The registry includes 47 centers, academic or nonacademic, which represent 374 (77%) of the 485 ECMO consoles available in France at the beginning of the pandemic.

Data were collected by research assistants from each patient's medical record using an electronic case report form. Automatic checks were generated for missing or incoherent data, and additional consistency tests were performed by data managers. The nationwide objective of our registry included the collection of all available data of ECMO patients with COVID-19 in France, including some patients who have been included in published retrospective studies or case series (3, 14–16). The registry has been approved by the University Hospital of Rennes ethics committee (n° 20.43) on April 18, 2020. The procedures were followed in accordance with the ethical standard of the University Hospital of Rennes ethics committee and with the Helsinki Declaration of 1975. According to French legislation, written consent is waived because of the observational design of the study. After information, only nonopposition of patients or their legal representative was obtained for the use of the data.

**ECMOSARS Registry Inclusion Criteria**

All patients who tested positive for severe acute respiratory syndrome coronavirus 2 by reverse transcriptase polymerase chain reaction (RT-PCR) (nasopharyngeal swabs, sputum, endotracheal aspiration, bronchoalveolar lavage, or stool sample), or with a diagnosis based on chest CT (17), and who were supported by venovenous, venaarterial, or vena-arterio-venous ECMO were included in the registry.

**Data Collection**

Data were collected prospectively in the ECMOSARS registry, except for patients who were cannulated for ECMO...
before April 21, 2020, which were collected retrospectively. Collected data included patient characteristics and comorbidities, management of COVID-related ARDS before ECMO cannulation, patient characteristics at ECMO cannulation and the day after, therapeutics, complications, and patient outcomes on ECMO (Table S1, http://links.lww.com/CCM/H234, for the definition of the main variables). Center experience was classified in two groups according to their experience in ECMO management before the pandemic: high-volume ECMO center if they managed more than 30 ECMO (≥ 30) patients annually and low-volume ECMO center if they managed fewer than 30 ECMO (< 30) patients annually (15).

**Study Population**

For the present study, we analyzed all consecutive patients included in the registry up to June 29, 2021, supported by venovenous ECMO for respiratory failure, and in whom prone position status while on ECMO (yes/no) and hospital mortality were known. The analysis followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

**Outcomes**

Our primary outcome was in-hospital mortality. Secondary outcomes were length of ECMO support, ECMO-free days and ventilator-free days to day 90, number of days alive from cannulation to day 90, acquired infection, thrombosis, limb ischemia, and hemorrhage. ECMO-free days or ventilator-free days are composite outcomes, which combine survival and ECMO support duration or survival and length of ventilatory support (13, 18, 19). The number of ECMO-free days or ventilator-free days were calculated as 90 minus the number of days on ECMO or with mechanical ventilatory support during the first 90 days after ECMO cannulation. Patients who died within 90 days after cannulation were assigned the worst possible outcome of zero ECMO-free days or ventilator-free days.

**Statistical Analysis**

A statistical analysis plan was made prior to accessing the data. No, a priori statistical power calculation was conducted. Categorical variables were expressed as n (%) and continuous variables as median and interquartile range. When appropriate, the chi-square test and the Fisher exact test were used to compare categorical variables. The Mann-Whitney U test and the Wilcoxon test were used to compare continuous variables. Overall, 143 (28%) patients had missing data. For the purpose of the multivariable analysis, multiple imputations were used to replace missing data using the “MICE” R package (R Foundation for Statistical Computing, Vienna, Austria).

Survival was analyzed using log-rank test and logistic regression. A directed acyclic graph was constructed using DAGitty software (Fig. S1, http://links.lww.com/CCM/H234) and association between the event (prone position during ECMO support) and the outcome (in-hospital death) was estimated with a multivariable logistic regression model including confounders identified with the directed acyclic graph (20, 21). In order to account for center-related effects, a mixed-effect multivariable logistic regression was performed with the variable center included as a random effect. Then, a propensity-score matched analysis was performed with in-hospital mortality as the outcome. Using the R package “MatchIt” (R Foundation for Statistical Computing), we generated two study groups with similar probabilities of prone positioning while on ECMO. This probability (propensity score) was calculated using a nonparsimonious model including all nonredundant baseline variables available in Tables 1 and 2 (i.e., age, sex, body mass index, comorbidities, period of enrollment, treatment before cannulation, delay from intubation to cannulation, Pao2/Fio2 at cannulation, Paco2 at cannulation, lung compliance, positive end-expiratory pressure, tidal volume, respiratory rate, other support at ECMO cannulation, details of cannulation, center experience). Then, patients who were not proned while on ECMO were matched with similar patients who underwent prone positioning with the closest propensity score. The balance between matched groups was evaluated by analysis of the standardized differences after weighting. A post-matching difference less than 0.2 was considered an optimal bias reduction.

As a sensitivity analysis and to limit the impact of confounders that might affect both the chance of being proned and mortality, we considered only the patients alive at decannulation (22, 23). Statistical analysis were performed with the statistical software R 4.1.1 (R Foundation for Statistical Computing). All tests were two-sided, and a p value of less than 0.05 was considered statistically significant.
Of the 647 patients included in the ECMOSARS registry in 41 centers at the time of data extraction, 42 had venoarterial ECMO only and 88 others had missing data regarding prone position status ($n = 68$) or in-hospital death ($n = 20$), leaving 517 patients in the analysis (Fig. 1). Median age was 55 (47–61), 78% were male and most patients (82%) were included in the spring of 2020 (Table 1). Median Simplified Acute Physiology Score II was 35 (24–52) and Sequential

| Baseline Variables | No. of Patient With Missing Data (in Prone Group/Supine Group) | Whole Population, $n = 517$ | Prone Positioning While On ECMO, $n = 354$ | No Prone Positioning While On ECMO, $n = 153$ | $p$ |
|-------------------|---------------------------------------------------------------|-----------------------------|------------------------------------------|------------------------------------------|-----|
| Simplified Acute Physiology Score II | 0 | 35 (24–52) | 36 (24–53) | 33 (24–43) | 0.18 |
| Age, yr | 2 (1/1) | 55 (47–61) | 54 (48–61) | 56 (46–62) | 0.54 |
| Male sex, n (%) | 0 | 402 (78) | 282 (77) | 120 (78) | 0.90 |
| Body mass index, kg/m$^2$ | 17 (10/7) | 30.1 (27.5–34.3) | 30.1 (27.1–34.0) | 30.1 (27.5–35.0) | 0.88 |
| Comorbidities, n (%) | | | | | |
| Chronic respiratory failure | 0 | 17 (3) | 13 (4) | 4 (3) | 0.77 |
| Chronic cardiac failure | 120 (88/32) | 4 (1) | 4 (1) | 0 | 0.32 |
| Coronary artery disease | 0 | 26 (5) | 17 (5) | 9 (6) | 0.72 |
| Chronic kidney failure | 119 (88/31) | 18 (5) | 13 (5) | 5 (4) | 0.99 |
| Cirrhosis | 6 (5/1) | 1 (0) | 1 (0) | 0 (0) | 0.31 |
| Solid cancer | 122 (90/32) | 7 (2) | 5 (2) | 2 (2) | 1 |
| Hematologic malignancy | 122 (90/32) | 4 (1) | 3 (1) | 1 (1) | 1 |
| Active smoker | 6 (5/1) | 20 (4) | 12 (3) | 8 (5) | 0.44 |
| Alcohol abuse | 127 (94/33) | 10 (3) | 7 (3) | 3 (3) | 1 |
| Period of enrollment, n (%) | 0 | 424 (82) | 303 (86) | 121 (79) | 0.68 |
| Spring 2020 | 24 (5) | 15 (4) | 9 (6) | | |
| Summer 2020 | 51 (10) | 33 (9) | 18 (12) | | |
| Fall 2020 | 12 (2) | 8 (2) | 4 (3) | | |
| Winter 2020 | 6 (1) | 5 (1) | 1 (1) | | |
| Antiviral | 124 (91/33) | 197 (50) | 137 (50) | 60 (50) | 1 |
| Antibiotic | 123 (91/32) | 365 (93) | 252 (92) | 113 (93) | 0.87 |
| Therapeutic anti-coagulation | 128 (94/34) | 361 (93) | 250 (93) | 111 (93) | 0.98 |
| Neuromuscular blocking agent | 2 (2/0) | 500 (97) | 353 (98) | 147 (96) | 0.55 |
| Prone positioning before cannulation | 0 | 490 (95) | 349 (96) | 141 (92) | 0.087 |

ECMO = extracorporeal membrane oxygenation.
Variables are presented as n (%) or median (interquartile range).
TABLE 2.
Characteristics at Extracorporeal Membrane Oxygenation Cannulation

| Baseline Variables | No. of Patient With Missing Data (in Prone Group/Supine Group) | Whole Population, n = 517 | Prone Positioning While On ECMO, n = 354 | No Prone Positioning While On ECMO, n = 153 | p  |
|--------------------|---------------------------------------------------------------|--------------------------|------------------------------------------|--------------------------------------------|----|
| **Characteristics at ECMO cannulation**                                           |                                                                           |                           |                                          |                                            |    |
| Delay from intubation to cannulation, d                                           | 17 (10/7)                                                                | 5 (3–8)                   | 6 (3–8)                                  | 5 (2–8)                                    | 0.40|
| ARDS criteria (Berlin criteria), n (%)                                            | 13 (10/3)                                                                | 495 (98)                  | 347 (98)                                 | 148 (99)                                   | 1   |
| PaO₂/FiO₂ before cannulation, mm Hg                                               | 24 (13/11)                                                               | 63 (54–76)                | 64 (54–76)                               | 61 (52–75)                                 | 0.54|
| ARDS severity                                                                      |                                                                           |                           |                                          |                                            | 0.81|
| Mild ARDS                                                                         | 1 (0)                                                                    | 1 (0)                     | 0                                        |                                            | 0   |
| Moderate ARDS                                                                     | 40 (8)                                                                   | 28 (9)                    | 12 (8)                                   |                                            |    |
| Severe ARDS                                                                       | 476 (92)                                                                 | 335 (95)                  | 141 (92)                                 |                                            |    |
| Respiratory ECMO Survival Prediction score                                         | 0                                                                        | 2 (0–3)                   | 2 (0–3)                                  | 2 (0–3)                                    | 0.33|
| Sequential Organ Failure Assessment score                                         | 0                                                                        | 9 (7–12)                  | 9 (8–12)                                 | 9 (7–13)                                   | 0.72|
| PaO₂, mm Hg                                                                        | 19 (8/11)                                                                | 55 (46–65)                | 54 (45–64)                               | 55 (48–67)                                 | 0.13|
| Lung compliance, mL/cm H₂O                                                         | 137 (94/43)                                                              | 21.4 (16.2–29.2)          | 21.5 (16.4–30)                           | 21.2 (15.7–27.7)                           | 0.40|
| Positive end-expiratory pressure, cm H₂O                                          | 48 (31/17)                                                               | 12 (10–14)                | 12 (10–14)                               | 12 (10–14)                                 | 0.10|
| Tidal volume, mL                                                                  | 69 (43/26)                                                               | 380 (320–427)             | 380 (320–422)                            | 380 (320–434)                              | 0.59|
| Tidal volume, mL/kg ideal body weight                                             | 82 (50/32)                                                               | 5.6 (5.2–6.3)             | 5.9 (5.1–6.3)                            | 5.9 (5.5–6.4)                              | 0.24|
| Respiratory rate, per min                                                         | 84 (59/25)                                                               | 28 (20–30)                | 28 (18–30)                               | 27 (23–30)                                 | 0.62|
| Plateau pressure, cm H₂O                                                          | 99 (76/33)                                                               | 30 (26–32)                | 30 (26–32)                               | 30 (26–32)                                 | 0.90|
| **Other support at ECMO cannulation, n (%)**                                      |                                                                           |                           |                                          |                                            |    |
| Inhaled nitric oxide                                                              | 28 (18/10)                                                               | 196 (40)                  | 140 (40)                                 | 56 (39)                                    | 0.87|
| Dobutamine                                                                        | 123 (91/32)                                                              | 8 (2)                     | 6 (2)                                    | 2 (2)                                      | 1   |
| Epinephrine                                                                       | 123 (91/32)                                                              | 11 (3)                    | 6 (2)                                    | 5 (4)                                      | 0.32|
| Norepinephrine                                                                    | 122 (90/32)                                                              | 225 (57)                  | 153 (56)                                 | 72 (59)                                    | 0.57|
| Renal replacement therapy                                                         | 5 (4/1)                                                                  | 63 (12)                   | 40 (11)                                  | 23 (15)                                    | 0.26|
| **Details of cannulation, n (%)**                                                 |                                                                           |                           |                                          |                                            |    |
| Femoro-jugular vs others                                                          | 13 (11/2)                                                                | 456 (90)                  | 313 (89)                                 | 143 (95)                                   | 0.051|
| Cannulation by a mobile ECMO team                                                  | 3 (2/1)                                                                  | 163 (32)                  | 121 (33)                                 | 42 (28)                                    | 0.24|
| **Center experience**                                                             | 0                                                                        |                           |                                          |                                            | 0.046|
| High volume                                                                       | 471 (91)                                                                 | 338 (95)                  | 133 (87)                                 |                                            |    |
| Low volume                                                                        | 36 (7)                                                                   | 16 (5)                    | 20 (13)                                  |                                            |    |

ARDS = acute respiratory distress syndrome, ECMO = extracorporeal membrane oxygenation.
Variables are presented as n (%) or median (interquartile range).
Organ Failure Assessment (SOFA) score at cannulation was 9 (7–12) (Table 2). Ninety-eight percent of the patients met Berlin criteria for ARDS, with a Pao₂/Fio₂ ratio of 63 mm Hg (54–76 mm Hg) at cannulation and lung compliance of 21.4 mL/cm H₂O (16.2–29.2 mL/cm H₂O). Almost all patients were treated with antibiotics (93%), therapeutic anticoagulation (93%), neuromuscular blocking agents (NMBAs) (97%) and were prone before cannulation (95%). Among survivors, median follow-up was 47 days (35–70 d). Of the 517 included patients, 493 (95%) had a positive RT-PCR, while the remainder (24, 5%) were diagnosed with chest CT.

After cannulation, 364 patients (70%) were prone at least once, while 153 (30%) remained in the supine position for the whole ECMO run. The 12 patients who were not prone before nor during ECMO support were all cannulated in low-volume centers, had high SOFA scores (10 [6–14] at cannulation) and high mortality (10/12 died, 83%). Patients admitted to high-volume centers were more likely to be prone (71%) than those admitted to low-volume centers (44%) while on ECMO (odds ratio [OR], 2.41 [0.97–6.13]; p = 0.059) but no variables were significantly associated with prone position in multivariable analysis (Table 1; and Table S2, http://links.lww.com/CCM/H234).

**Primary Analysis**

Two hundred eighty-six patients died (55%) in the hospital, 194 patients (53%) in the prone position group and 92 (60%) in the supine group (log rank = 0.01; Fig. S2 and Table S3 [http://links.lww.com/CCM/H234]). Prone position on ECMO was found to be independently associated with lower in-hospital mortality (OR = 0.49 [0.29–0.84]; p = 0.010; Table S4, http://links.lww.com/CCM/H234). Interestingly, prone position before cannulation was also found to be independently
associated with lower in-hospital mortality (OR = 0.31 [0.10–0.98]; \( p = 0.047 \)). In a dataset of 153 propensity score matched patient pairs (Table S5, http://links.lww.com/CCM/H234), patients in the prone position group had a longer ECMO runs (17 d [9–29 d] vs 8 d [5–16 d]; \( p < 0.001 \)), more days alive after cannulation (90 d [30–90 d] vs 32 d [12–90 d]; \( p < 0.001 \)), and a higher occurrence rate of acquired infection (60.1% vs 42.5%; \( p = 0.003 \)). The mortality rate was 49.7% in the prone position group compared with 60.1% in the supine position group \( (p = 0.085) \) (Fig. 2 and Table 3).

**Sensitivity Analysis**

The potential bias that clinicians may be less inclined to prone sicker patients might have led to an overestimation of the benefits of prone positioning on ECMO in the whole population. Thus, we performed a pre-planned sensitivity analysis including only patients alive at ECMO decannulation. In this subgroup, proned patients alive at decannulation \((n = 222)\) were matched with supine patients alive at decannulation \((n = 98)\), based on the likelihood of being proned. The matching process resulted in 98 pairs of patients in whom baseline characteristics were well balanced (Table S5, http://links.lww.com/CCM/H234). Patients in the prone position group had a significant lower mortality rate (22.4% vs 37.8%; \( p = 0.029 \); Fig. 2). Other outcomes of matched pairs are reported in Table 3. Interestingly, prone position while on ECMO was associated with longer ECMO runs \((15 d [10–24 d] \text{ vs } 10 d [7–16 d]; \ p < 0.001)\).

**DISCUSSION**

Our study suggests a potential survival benefit of prone position while on ECMO for COVID-19 patients treated for respiratory failure in a nationwide cohort.

![Figure 2. Survival curves of the matched patient pairs. ECMO = extracorporeal membrane oxygenation.](image-url)
Mortality was lower in prone positioned patients (53%) compared with supine patients (60%) and prone position was independently associated with a lower in-hospital mortality on multivariable analysis. However, when propensity matching was used in the entire population, the mortality difference did not reach statistical significance. Of note, a pre-planned sensitivity analysis in propensity-matched patients who survived to decannulation showed that propensity-matched patients in the proned group had significantly lower in-hospital mortality than nonproned patients (22.4% vs 37.8%; \( p = 0.029 \)). The mortality benefit associated with matched patients who survived to decannulation, but not in the entire population, may suggest that patients on ECMO for COVID-19 ARDS who do not survive to ECMO decannulation are so severely ill that they derive less benefit from prone positioning or that they develop other disease manifestations or unrelated complications that increase mortality but are not affected by prone positioning. Our data also highlight a rapid increase in the use of prone positioning for patients on ECMO in French ICUs that appears to have accompanied the COVID-19 pandemic.

Several case series have already shown the feasibility and the safety of combining prone position and ECMO support in ARDS patients (24, 25). However, whether the combination is beneficial for ARDS patients remains unclear. Both ECMO and prone positioning aim to decrease VILI but their effects could be synergistic or competitive. Several recent studies suggested

### TABLE 3.
Outcomes of the Matched Patients

| Outcomes                           | Matched Patients From Complete Population | Matched Patients From Those Alive at Decannulation |
|------------------------------------|------------------------------------------|---------------------------------------------------|
|                                   | Supine, \( n = 153 \) | Prone, \( n = 153 \) | \( p \) | Supine, \( n = 98 \) | Prone, \( n = 98 \) | \( p \) |
| Acquired infection, \( n (\%) \)   | 65 (42.5) | 92 (60.1) | 0.003 | 42 (42.9) | 53 (54.1) | 0.153 |
| Ventilator-associated pneumonia, \( n (\%) \) | 102 (66.7) | 107 (69.9) | 0.623 | 72 (73.5) | 64 (65.3) | 0.278 |
| Bloodstream infection, \( n (\%) \) | 64 (41.8) | 90 (58.8) | 0.004 | 41 (41.8) | 50 (51.0) | 0.252 |
| Surgical site infection, \( n (\%) \) | 4 (2.6) | 10 (6.5) | 0.171 | 4 (4.1) | 5 (5.1) | 1.000 |
| Thrombosis, \( n (\%) \)          | 48 (31.6) | 61 (39.9) | 0.164 | 33 (34.0) | 38 (38.8) | 0.588 |
| Deep vein thrombosis               | 16 (10.5) | 14 (9.2) | 0.848 | 12 (12.2) | 9 (9.2) | 0.644 |
| Pulmonary embolism                 | 8 (5.2) | 16 (10.5) | 0.137 | 7 (7.1) | 13 (13.3) | 0.238 |
| Limb ischemia, \( n (\%) \)       | 73 (48.7) | 67 (44.1) | 0.494 | 3 (3.1) | 1 (1.0) | 0.606 |
| Hemorrhage, \( n (\%) \)          | 3 (2.0) | 0 (0.0) | 0.246 | 39 (39.8) | 33 (33.7) | 0.459 |
| Number of days alive from cannulation to day 90 | 32 (12–90) | 90 (30–90) | <0.001 | 90 (30–90) | 90 (90–90) | <0.001 |
| Length of ECMO support, \( d \)   | 8 (5–16) | 17 (9–29) | <0.001 | 10 (6–16.25) | 15 (10–24) | <0.001 |
| Survivor at day 90                 | 10 (7–15) | 16 (10–23) | <0.001 | 9 (7–15) | 16 (11–25) | <0.001 |
| Dead before day 90                 | 7 (3–16) | 17 (9–39) | <0.001 | 13 (6–20) | 12 (6–18) | 0.92 |
| ECMO-free days within 90 d of cannulation | 2 (0–77) | 40 (0–75) | 0.526 | 73 (7–82) | 70.50 (36.25–78.75) | 0.915 |
| Ventilatory-free days within 90 d of cannulation | 2 (0–67) | 20 (0–63) | 0.727 | 61 (7–72) | 51 (16–66.75) | 0.459 |
| Length of ICU stay after decannulation, \( d \) | 7 (0–19) | 8 (0–21) | 0.682 | 17.50 (9–27.75) | 17 (10–35.50) | 0.592 |
| In-hospital death, \( n (\%) \)    | 92 (60.1) | 76 (49.7) | 0.085 | 37 (37.8) | 22 (22.4) | 0.029 |

ECMO = extracorporeal membrane oxygenation. Variables are presented as \( n (\%) \) or median (interquartile range).
a potential benefit of prone position on ECMO weaning and survival (4, 5, 7), while another group did not find any benefit on weaning or survival (6). However, the retrospective design and the limited sample size of these studies preclude definitive conclusions.

Similar to our findings, investigators of the COVID-19 Critical Care consortium found a decrease in mortality in 67 patients proned on ECMO compared with supine patients with a multistate model (hazard ratio, 0.31; 95% CI, 0.14–0.68) (8). The longer duration of ECMO support among prone position patients was also reported in previous studies (9). One possible explanation for this relationship may be that patients may not be evaluated for ECMO weaning during prone position sessions, which could delay decannulation. Another hypothesis is that prone position may be performed only for patients who did not improve quickly on ECMO and therefore might be expected to have longer ECMO runs independent of prone positioning.

We have observed a clear trend toward increased use of prone positioning in ARDS during the COVID-19 pandemic. This is reflected in the high proportion of patients in our study population who underwent prone positioning prior to ECMO cannulation. Despite the positive results of the Proning Severe ARDS Patients trial published in 2013, only 16% of non-ECMO ARDS patients were reported to be prone in a large international prospective observational study released in 2016 (1, 26). Similarly, in a recent international survey including 23 ECMO centers, prone positioning was applied in only 15% of the ARDS patients supported by ECMO (27). Strikingly, in the latter study, prone position was applied in only 26% of the patients before ECMO cannulation, compared with our cohort, where 95% of the patients had been prone before ECMO cannulation. Other studies conducted in the COVID-19 pandemic show similarly high rate of proning. In large multicenter cohort studies in Spain, France, and Italy, around 61% to 76% of the patients with severe ARDS related to COVID-19 were prone (28–30). Similarly, in the Extracorporeal Life Support Organization cohort, 61% of the patients with ARDS related to COVID-19 had been prone before ECMO initiation (3). Of note, we observed that prone position before ECMO was associated with a lower in-hospital mortality. However, data on the use of prone position of COVID-19 patients while on ECMO are very limited. The one recent observational international multicenter study from the COVID-19 Critical Care consortium, which involved 232 COVID-19 patients supported by venovenous ECMO in 72 institutions reported 29% use of prone positioning during ECMO support (8).

Our study has several strengths. This report is the largest study to evaluate prone position in venovenous ECMO for COVID-19–related ARDS published to date. Second, the participating centers represented most of the ECMO centers in France, improving external validity. Third, there was good adherence to national guidelines for ARDS patient management, such as lung protective ventilation, prolonged and repeated prone positioning, and NMBA infusions during the pre-ECMO period in all of the participating centers. This relative standardization of care across sites helps to address a common concern in multicenter studies of ECMO patients, of which patients are offered ECMO and at what stage of their disease. Finally, the database quality was regularly assessed by dedicated data managers.

However, our study has some limitations. First, this is a retrospective study with its inherent limitations. Second, 88 patients were excluded of the analysis because of missing data regarding prone position status or in-hospital death. Third, the time of initiation of prone position was not recorded in our database precluding any time-to-event analysis. Similarly, other information on prone position sessions, such as duration, tolerance, frequency, and number of sessions were not recorded in our database, although such elements are fundamental for the success of prone positioning (31). Fourth, indications for prone position were not standardized across the centers. Hence, whether prone position was systematically applied or only in case of refractory hypoxemia while on ECMO is unknown. Fifth, dexamethasone administration was also not collected in our database as data collection was started before publication of the Randomised Evaluation of COVID-19 Therapy trial (32) and at the time of study initiation steroids use was not recommended (33).

In conclusion, in a large nationwide cohort of patients supported by venovenous ECMO for severe ARDS related to COVID-19, prone positioning was extensively used during ECMO support. We found that prone positioning was associated with a mortality benefit in patients who survived to ECMO decannulation but not in the entire population. Therefore, while prone positioning may be beneficial in COVID-19
patients on ECMO, a randomized prospective study will be needed to identify which subset of patients might benefit from this combination therapy.

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Extracorporeal Membrane Oxygenation for Respiratory Failure and/or Heart failure related to Severe Acute Respiratory Syndrome Coronavirus 2 (ECMOSARS) Investigators are listed in the Appendix (http://links.lww.com/CCM/H234).

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