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

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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>).

Clinical Trial NCT04397588, date of registration: May 21, 2020.

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 proned before cannulation. After cannulation, 364 patients (70%) were proned 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 proned 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 (Pao 2 / 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-19a rescue therapy in ARDS but has been used extensively in the COVID-19 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 re- mains 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 veno- venous, venoarterial, or venoarterio-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 prone 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 prone 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.

RESULTS

Population

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 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

TABLE 1.
Baseline Characteristics of Study Patients

Baseline Variables	No. of Patient With Missing Data (in Prone Group/Supine Group)	Whole Population, <i>n</i> = 517	Prone Positioning While On ECMO, <i>n</i> = 354	No Prone Positioning While On ECMO, <i>n</i> = 153	<i>p</i>
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, <i>n</i> (%)	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, <i>n</i> (%)					
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, <i>n</i> (%)					
	0				0.68
Spring 2020		424 (82)	303 (86)	121 (79)	
Summer 2020		24 (5)	15 (4)	9 (6)	
Fall 2020		51 (10)	33 (9)	18 (12)	
Winter 2020		12 (2)	8 (2)	4 (3)	
Spring 2021		6 (1)	5 (1)	1 (1)	
Treatment before cannulation, <i>n</i> (%)					
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, <i>n</i> = 517	Prone Positioning While On ECMO, <i>n</i> = 354	No Prone Positioning While On ECMO, <i>n</i> = 153	<i>p</i>
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), <i>n</i> (%)	13 (10/3)	495 (98)	347 (98)	148 (99)	1
Pao ₂ /Fio ₂ 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	
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
Paco ₂ , mm Hg	19 (8/11)	55 (46–65)	54 (45–64)	55 (48–67)	0.13
Lung compliance, mL/cm H ₂ O	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 H ₂ O	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 H ₂ O	99 (76/33)	30 (26–32)	30 (26–32)	30 (26–32)	0.90
Other support at ECMO cannulation, <i>n</i> (%)					
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, <i>n</i> (%)					
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).

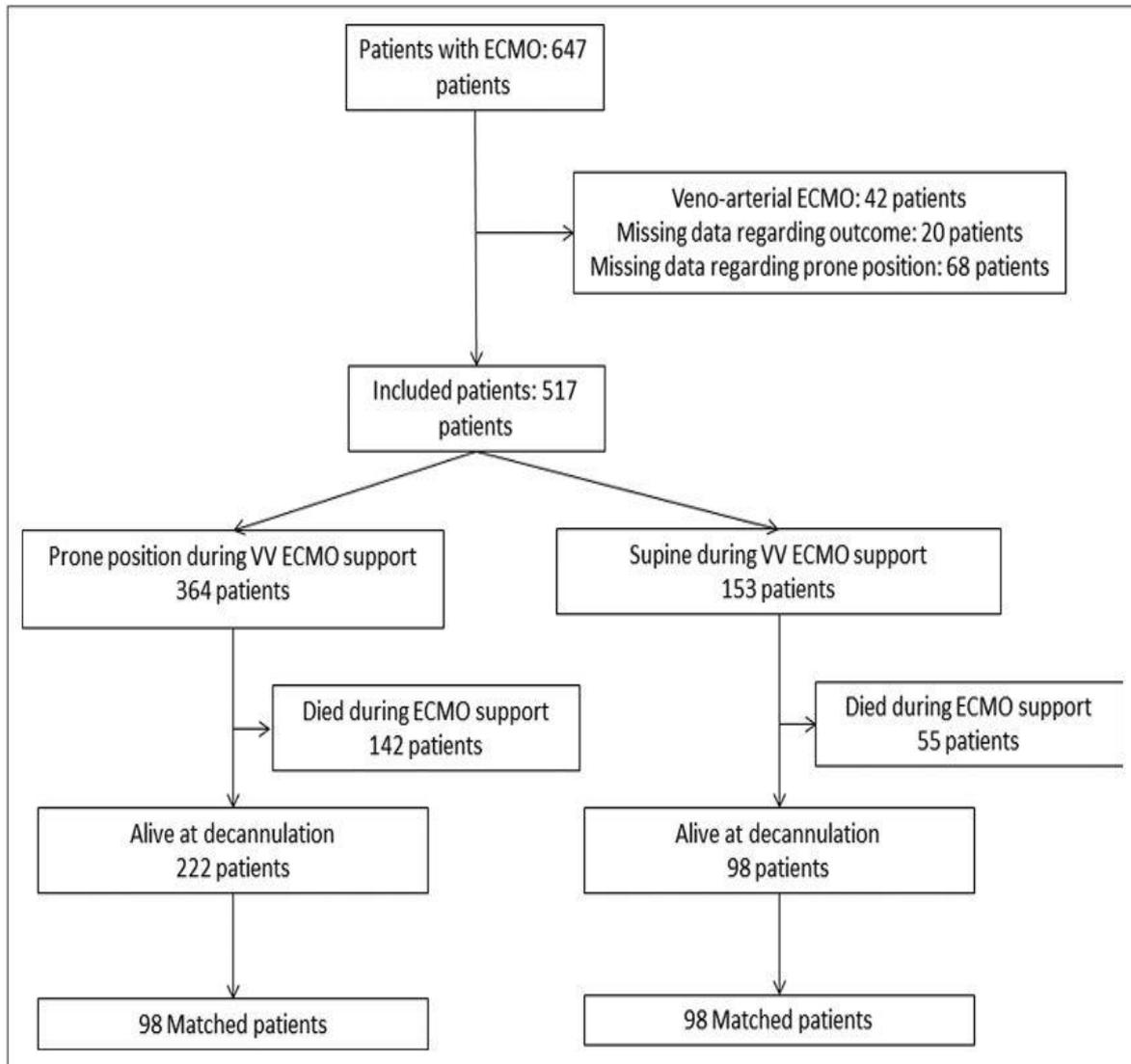


Figure 1. Flow chart.

ECMO = extracorporeal membrane oxygenation, VV = venovenous.

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] 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.

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 un-related complications that increase mortality but are not affected by prone positioning. Our data also high- light 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

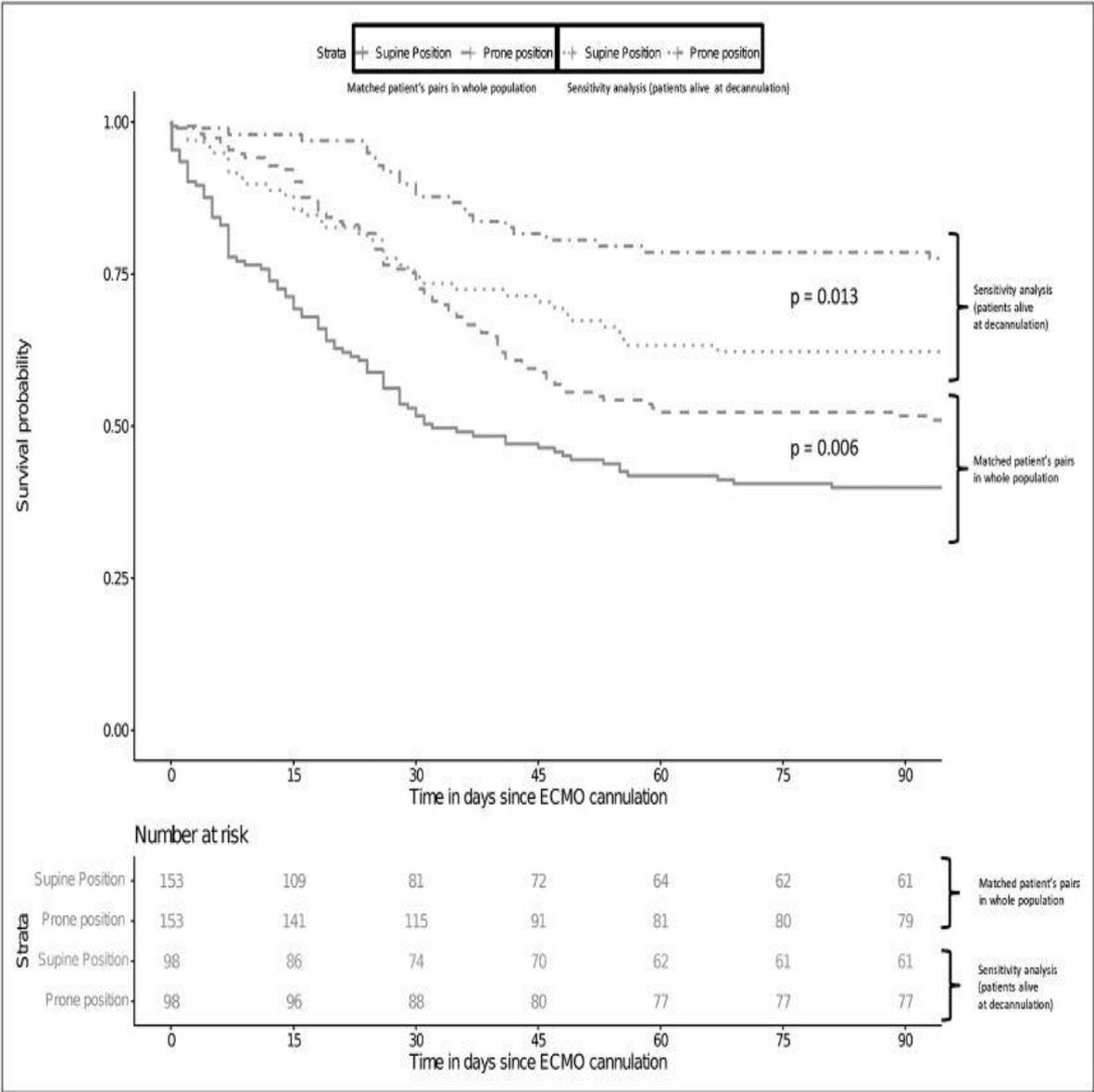


Figure 2. Survival curves of the matched patient pairs.

ECMO = extracorporeal membrane oxygenation

TABLE 3.
Outcomes of the Matched Patients

Outcomes	Matched Patients From Complete Population		<i>p</i>	Matched Patients From Those Alive at Decannulation		<i>p</i>
	Supine, <i>n</i> = 153	Prone, <i>n</i> = 153		Supine, <i>n</i> = 98	Prone, <i>n</i> = 98	
Acquired infection, <i>n</i> (%)	65 (42.5)	92 (60.1)	0.003	42 (42.9)	53 (54.1)	0.153
Ventilator-associated pneumonia, <i>n</i> (%)	102 (66.7)	107 (69.9)	0.623	72 (73.5)	64 (65.3)	0.278
Bloodstream infection, <i>n</i> (%)	64 (41.8)	90 (58.8)	0.004	41 (41.8)	50 (51.0)	0.252
Surgical site infection, <i>n</i> (%)	4 (2.6)	10 (6.5)	0.171	4 (4.1)	5 (5.1)	1.000
Thrombosis, <i>n</i> (%)	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, <i>n</i> (%)	73 (48.7)	67 (44.1)	0.494	3 (3.1)	1 (1.0)	0.606
Hemorrhage, <i>n</i> (%)	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, <i>n</i> (%)	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).

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 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 prone 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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Question:

Is prone position beneficial in venovenous extracorporeal membrane oxygenation (ECMO) patients cannulated for COVID-19–related acute respiratory distress syndrome (ARDS)?

Findings:

In a nationwide cohort study, prone position was found to be independently associated with lower in-hospital mortality in multivariable analysis. However, after propensity score matching there was no significant difference in mortality between proned and nonproned patients (49.7% vs 60.1%; $p = 0.085$).

Meaning:

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.

REFERENCES

1. Guérin C, Reignier J, Richard J-C, et al: Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; 368:2159–2168
2. Scholten EL, Beitler JR, Prisk GK, et al: Treatment of ARDS with prone positioning. *Chest* 2017; 151:215–224
3. Barbaro RP, MacLaren G, Boonstra PS, et al: Extracorporeal membrane oxygenation support in COVID-19: An international cohort study of the Extracorporeal Life Support Organization Registry. *Lancet* 2020; 396:1071–1078
4. Petit M, Fetita C, Gaudemer A, et al: Prone-positioning for severe acute respiratory distress syndrome requiring extracorporeal membrane oxygenation. *Crit Care Med* 2022;50:264–274
5. Guervilly C, Prud'homme E, Pauly V, et al: Prone positioning and extracorporeal membrane oxygenation for severe acute respiratory distress syndrome: Time for a randomized trial? *Intensive Care Med* 2019; 45:1040–1042
6. Rilinger J, Zotzmann V, Bemtgen X, et al: Prone positioning in severe ARDS requiring extracorporeal membrane oxygenation. *Crit Care* 2020; 24:397
7. Giani M, Martucci G, Madotto F, et al: Prone positioning during venovenous extracorporeal membrane oxygenation in acute respiratory distress syndrome. A multicenter cohort study and propensity-matched analysis. *Ann Am Thorac Soc* 2021; 18:495–501
8. Zaaqoq AM, Barnett AG, Griffie MJ, et al: Beneficial effect of prone positioning during venovenous extracorporeal membrane oxygenation for coronavirus disease 2019. *Crit Care Med* 2022; 50:275–285
9. Giani M, Rezoagli E, Guervilly C, et al: Prone positioning during venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: A pooled individual patient data analysis. *Crit Care* 2022; 26:8
10. Papazian L, Schmidt M, Hajage D, et al: Effect of prone positioning on survival in adult patients receiving venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: A systematic review and meta-analysis. *Intensive Care Med* 2022; 48:270–280
11. Poon WH, Ramanathan K, Ling RR, et al: Prone positioning during venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: A systematic review and meta-analysis. *Crit Care* 2021; 25:292
12. Barbaro RP, MacLaren G, Boonstra PS, et al: Extracorporeal membrane oxygenation for COVID-19: Evolving outcomes from the international Extracorporeal Life Support Organization Registry. *Lancet* 2021; 398:1230–1238
13. Nessler N, Fadel G, Mansour A, et al: Extracorporeal membrane oxygenation for respiratory failure related to COVID-19: A nationwide cohort study. *Anesthesiology* 2022; 136:732–748

14. Falcoz P-E, Monnier A, Puyraveau M, et al: Extracorporeal membrane oxygenation for critically ill patients with COVID-19-related acute respiratory distress syndrome: Worth the effort? *Am J Resp Crit Care* 2020; 202:460–463
15. Lebreton G, Schmidt M, Ponnaiah M, et al: Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: A multicentre cohort study. *Lancet Respir Med* 2021; 9:851–862
16. Garcia B, Cousin N, Bourel C, et al: Prone positioning under VV-ECMO in SARS-CoV-2-induced acute respiratory distress syndrome. *Crit Care* 2020; 24:428
17. Ye Z, Zhang Y, Wang Y, et al: Chest CT manifestations of new coronavirus disease 2019 (COVID-19): A pictorial review. *Eur Radiol* 2020; 30:4381–4389
18. Jäckel M, Rilinger J, Lang CN, et al: Outcome of acute respiratory distress syndrome requiring extracorporeal membrane oxygenation in Covid-19 or influenza: A single-center registry study. *Artif Organs* 2020; 45:593–601
19. Yehya N, Harhay MO, Curley MAQ, et al: Reappraisal of ventilator-free days in critical care research. *Am J Resp Crit Care* 2019; 200:828–836
20. Lederer DJ, Bell SC, Branson RD, et al: Control of confounding and reporting of results in causal inference studies. Guidance for authors from editors of respiratory, sleep, and critical care journals. *Ann Am Thorac Soc* 2018; 16:22–28
21. Textor J, van der Zander B, Gilthorpe MS, et al: Robust causal inference using directed acyclic graphs: The R package “dagitty.” *Int J Epidemiol* 2017; 45:1887–1894
22. Massart N, Mansour A, Flecher E, et al: Clinical benefit of extubation in patients on venoarterial extracorporeal membrane oxygenation. *Crit Care Med* 2022; 50:760–769
23. Vail EA, Gershengorn HB, Wunsch H, et al: Attention to immortal time bias in critical care research. *Am J Resp Crit Care* 2021; 203:1222–1229
24. Guervilly C, Hraiech S, Gariboldi V, et al: Prone positioning during veno-venous extracorporeal membrane oxygenation for severe acute respiratory distress syndrome in adults. *Minerva Anesthesiol* 2013; 80:307–313
25. Kimmoun A, Roche S, Bridey C, et al: Prolonged prone positioning under VV-ECMO is safe and improves oxygenation and respiratory compliance. *Ann Intensive Care* 2015; 5:35
26. Bellani G, Laffey JG, Pham T, et al: Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016; 315:788–800
27. Schmidt M, Pham T, Arcadipane A, et al: Mechanical ventilation management during extracorporeal membrane oxygenation for acute respiratory distress syndrome. An international multicenter prospective cohort. *Am J Resp Crit Care* 2019; 200:1002–1012

28. Schmidt M, Hajage D, Demoule A, et al: Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: A prospective cohort study. *Intensive Care Med* 2020; 47:60–73
29. Ferrando C, Suarez-Sipmann F, Mellado-Artigas R, et al: Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS. *Intensive Care Med* 2020; 46:2200–2211
30. Langer T, Brioni M, Guzzardella A, et al: Prone position in intubated, mechanically ventilated patients with COVID-19: A multi-centric study of more than 1000 patients. *Crit Care* 2021; 25:128
31. Papazian L, Munshi L, Guérin C: Prone position in mechanically ventilated patients. *Intensive Care Med* 2022; 48: 1062–1065
32. Group RC, Horby P, Lim WS, et al: Dexamethasone in hospitalized patients with Covid-19. *New Engl J Med* 2020; 384:693–704
33. Matthay MA, Aldrich JM, Gotts JE: Treatment for severe acute respiratory distress syndrome from COVID-19. *Lancet Respir Med* 2020; 8:433–434