ANESTHESIOLOGY

Extracorporeal Membrane Oxygenation for Respiratory Failure Related to COVID-19: A Nationwide Cohort Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Venovenous extracorporeal membrane oxygenation is increasingly used for managing severe respiratory failure; however, the characteristics, management, and patient outcomes continue to be determined
- Determining factors associated with in-hospital mortality for both COVID-19 and non–COVID-19 patients are important factors to consider in patient management

What This Article Tells Us That Is New

- In this investigation, most patients were cannulated by a mobile extracorporeal membrane oxygenation unit without a negative impact on mortality
- Based on this report, venovenous extracorporeal membrane oxygenation support should be considered within the first week of mechanical ventilation initiation for optimal outcomes

ABSTRACT

Background: Despite expanding use, knowledge on extracorporeal membrane oxygenation support during the COVID-19 pandemic remains limited. The objective was to report characteristics, management, and outcomes of patients receiving extracorporeal membrane oxygenation with a diagnosis of COVID-19 in France and to identify pre-extracorporeal membrane oxygenation factors associated with in-hospital mortality. A hypothesis of similar mortality rates and risk factors for COVID-19 and non–COVID-19 patients on venovenous extracorporeal membrane oxygenation was made.

Methods: The Extracorporeal Membrane Oxygenation for Respiratory Failure and/or Heart failure related to Severe Acute Respiratory Syndrome-Coronavirus 2 (ECMOSARS) registry included COVID-19 patients supported by extracorporeal membrane oxygenation in France. This study analyzed patients included in this registry up to October 25, 2020, and supported by venovenous extracorporeal membrane oxygenation for respiratory failure with a minimum follow-up of 28 days after cannulation. The primary outcome was in-hospital mortality. Risk factors for in-hospital mortality were analyzed.

Results: Among 494 extracorporeal membrane oxygenation patients included in the registry, 429 were initially supported by venovenous extracorporeal membrane oxygenation and followed for at least 28 days. The median (interquartile range) age was 54 yr (46 to 60 yr), and 338 of 429 (79%) were men. Management before extracorporeal membrane oxygenation cannulation included prone positioning for 411 of 429 (96%), neuromuscular blockage for 419 of 427 (98%), and NO for 161 of 401 (40%). A total of 192 of 429 (45%) patients were cannulated by a mobile extracorporeal membrane oxygenation unit. In-hospital mortality was 219 of 429 (51%), with a median follow-up of 49 days (33 to 70 days). Among pre-extracorporeal membrane oxygenation modifiable exposure variables, neuromuscular blockage use (hazard ratio, 0.286; 95% CI, 0.101 to 0.81) and duration of ventilation (more than 7 days compared to less than 2 days; hazard ratio, 1.74; 95% CI, 1.07 to 2.83) were independently associated with in-hospital mortality. Both age (per 10-yr increase; hazard ratio, 1.27; 95% CI, 1.07 to 1.50) and total bilirubin at cannulation (6.0 mg/dl or more compared to less than 1.2 mg/dl; hazard ratio, 2.65; 95% CI, 1.09 to 6.5) were confounders significantly associated with in-hospital mortality.

Conclusions: In-hospital mortality was higher than recently reported, but nearly half of the patients survived. A high proportion of patients were cannulated by a mobile extracorporeal membrane oxygenation unit. Several factors associated with mortality were identified. Venovenous extracorporeal membrane oxygenation support should be considered early within the first week of mechanical ventilation initiation.

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Early reports of severe manifestations of COVID-19 such as acute respiratory distress syndrome (ARDS) and acute myocardial injury have suggested a possible role for extracorporeal membrane oxygenation (ECMO) support.[1] Recent experience during the influenza A (H1N1)

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pandemic demonstrated the value of ECMO support for patients with severe ARDS related to influenza.[2–6] Additionally, a recent meta-analysis of patients from two major randomized controlled trials on ECMO support in severe ARDS patients showed a significant benefit of the technique for improving both morbidity and mortality.[7–9]

Several early retrospective case series showed encouraging results of ECMO support in COVID-19–related respiratory failure.[10–13] However, these case series were limited in sample size (fewer than 90 patients) and restricted to few centers. Consequently, the international report from the Extracorporeal Life Support Organization (Ann Arbor, Michigan) registry, gathering 1,035 ECMO patients from 213 centers in 36 countries, was an important landmark. The study showed an estimated in-hospital mortality of less than 40% for critically ill adults with COVID-19 treated with ECMO in a collection of self-selected and experienced centers worldwide.[14] Recently, a similar mortality rate was reported in a multicenter cohort study of 190 critically ill adults with

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COVID-19 who received ECMO at 35 sites across the United States.[15]

In France, 485 ECMO consoles are available in 103 academic or nonacademic, public, or private centers due to the wide interest in the technique in the country. During the first wave of the pandemic, a central system was established to coordinate national ECMO resources in France. Regional coordinators met weekly to check the national availability of consoles and circuits. Specific recommendations and algorithms were issued on ECMO indications and organization in the context of the outbreak (https://www.iledefrance.ars.sante.fr/system/files/2020-12/038_ARSIdF-CRAPS_2020-12-02_Doctrine_ECMO.pdf).[16] Collecting data on this initiative is essential to evaluate the results of our organization, to inform clinicians, and to adapt our response to the future developments of the outbreak. Therefore, the goals of our study were (1) to report characteristics, management, and outcomes of patients receiving ECMO with a diagnosis of COVID-19 in France and (2) to identify potentially modifiable variables associated with in-hospital mortality. We hypothesized that the mortality rate and risk factors would be similar for COVID-19 and non–COVID-19 patients on venovenous ECMO.

Materials and Methods

The ECMOSARS registry was launched in April 2020 (ClinicalTrials.gov Identifier: NCT04397588, Extracorporeal Membrane Oxygenation for Respiratory Failure and/or Heart failure related to Severe Acute Respiratory Syndrome-Coronavirus 2 [ECMOSARS] registry, principal investigators: Nicolas Nesseler and André Vincentelli, date of registration: May 21, 2020) and is currently still recruiting. The registry includes 47 centers, academic or nonacademic, which represent 77% of the ECMO consoles available in France. The registry has been endorsed by the French Society of Thoracic and Cardiovascular (Société Française de Chirurgie Thoracique et Cardio-Vasculaire [SFCTCV], Paris, France), the French Society of Thoracic and Cardiovascular Critical Care and Anesthesia (Anesthésie-Réanimation Coeur-Thorax-Vaisseaux [ARCOTHOVA], Paris, France), and the French Society of Anesthesiology and Critical Care Medicine (Société Française d'Anesthésie-Réanimation [SFAR], Paris, France) research network.

The data were collected by research assistants using an electronic case report form from each patient's medical record. Automatic checks were generated for missing or incoherent data, and additional consistency tests were performed by data managers. The nationwide objective of our registry implied the collection of all available data of ECMO patients in France, including data for some patients already published in retrospective studies or case series.[12,14,17] Two studies focused on a specific French area (*e.g.*, the city of Strasbourg or the Greater Paris area), and one study included only a fraction of French patients in an international cohort, which involved only self-selected and experienced centers.

The registry has been approved by the University Hospital of Rennes ethics committee (approval No. 20.43). According to French legislation, written consent is waived because of the study's observational design that does not imply any modification of existing diagnostic or therapeutic strategies. After the information was provided, only non-opposition of patients or their legal representative was obtained for use of the data.

ECMOSARS Registry Inclusion Criteria

All patients, adults or children, tested positive by reverse transcription–polymerase chain reaction for SARS-CoV2 (nasopharyngeal swabs, sputum, endotracheal aspiration, bronchoalveolar lavage, or stool sample) and/or with a diagnosis of COVID-19 made on chest computed tomography findings and supported by venovenous, venoarterial, or venoarterio-venous ECMO can be included in the registry. Patients or proxies who refused consent were excluded from the study, as were legally protected adults.

Data Collection

The data were collected prospectively in the ECMOSARS registry, except for patients whose ECMO was implanted before April 21, 2020. Those data 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, management, complications, and patient outcomes on ECMO (see Supplemental Digital Content 1, table S1, http://links.lww.com/ALN/C809, for the definition of the main variables).

Study Population

For the current study, we analyzed all patients included in the registry up to October 25, 2020, initially supported by venovenous ECMO for respiratory failure and with a minimum follow-up of 28 days after ECMO cannulation for alive patients.

Outcomes

Our primary outcome was in-hospital mortality. Secondary outcomes were mortality at day 28, mortality at day 90, ECMO-free days, and intensive care unit (ICU)–free days to day 28. ECMO-free days or ICU-free days are composite outcomes that combine survival and ECMO support duration or survival and ICU length of stay. The numbers of ECMO-free days or ICU-free days were calculated as 28 minus the number of days on ECMO or in the ICU during the first 28 days after ECMO cannulation. Patients who died were assigned the worst possible outcome of 0 ECMO-free days or ICU-free days.

Statistical Analysis

Patient characteristics are expressed as number and percentage for categorical variables and median with interquartile

range for continuous variables. For bivariate comparison between deceased and alive patients, a chi-square test or a Fisher exact test was used for categorical variables, and an independent *t* test or a Wilcoxon rank sum test was used for continuous variables. Blood gases values and ventilator settings before and after ECMO cannulation were compared using a repeated measures ANOVA model. The ventilatory ratio was defined as [minute ventilation (ml/min) × $Paco_2$ (mmHg)]/(predicted body weight × 100 × 37.5).[18]

A statistical analysis plan was made before accessing the data. No *a priori* statistical power calculation was conducted. Regarding the primary outcome, no minimum clinically meaningful hazard ratio was defined before data access. In accordance with reviewers' recommendations, modeling and variable selection strategies were modified and are thus considered *post hoc* analyses. Only pre-ECMO variables were included in these analyses to prevent competing risk bias.

A directed acyclic graph was used to describe the associations between pre-ECMO modifiable exposure variables, patient-related confounders, pre-ECMO hospitalization-related confounders, and in-hospital mortality using DAGitty software (Supplemental Digital Content 1, fig. S1, http://links.lww.com/ALN/C809).[19] No variables were analyzed as effect modifiers. Pre-ECMO modifiable exposure variables comprised anticoagulation, antibiotic therapy, antiviral therapy, noninvasive ventilation, selective digestive decontamination, neuromuscular blocking agents, prone position, high-flow oxygen therapy, cannulation mode, inotropes use, vasopressors use, renal replacement therapy, ECMO cannulation, inhaled NO, positive end-expiratory pressure, tidal volume at cannulation, and ventilation duration before ECMO. The set of pre-ECMO confounders sufficient for adjustment comprised patient-related confounders (sex, age, body mass index, diabetes, chronic obstructive pulmonary disease, chronic respiratory failure, congestive heart failure, chronic kidney disease, malignancy, and previous corticotherapy) and pre-ECMO hospitalization-related confounders (septic shock, total bilirubin at cannulation, pH at cannulation, $Paco_2$ at cannulation, Pao_2/fractional inspired oxygen tension (Fio_2) ratio at cannulation, driving pressure, left ventricular ejection fraction, ventilator-associated pneumonia, and delay from hospitalization to ICU admission).

To estimate hazard ratios between exposure variables and in-hospital mortality, we fitted a univariate and multivariable Cox proportional hazards model including exposure variables and confounders identified using the directed acyclic graph. Four different models were built, for sensitivity analysis (see Supplemental Digital Content 1, table S2, http://links.lww.com/ALN/C809). Model 1 was a univariable Cox model; model 2 was a multivariable Cox model of modifiable exposure variables, adjusted for patient-related confounders; model 3 was a multivariable Cox model of modifiable exposure variables, adjusted for pre-ECMO hospitalization-related confounders; and model 4 was a multivariable Cox model of modifiable exposure variables, fully adjusted for all confounders. Centers were included as a random effect using a γ frailty model. Patients who were still hospitalized were censored at the time of the database lock, and those who were discharged alive were censored at the time of their discharge date. Proportional hazard assumption was assessed using simultaneous time-dependent covariates. To comply with log-linearity assumptions, several continuous variables (body mass index, pH, left ventricular ejection fraction, delay from hospitalization to ICU admission, driving pressure, positive end-expiratory pressure, tidal volume, and ventilation duration before ECMO) were split into categorical variables in accordance with previously published works and guidelines.[8,20–26]

Multiple imputation was used to account for missing values in variables (Supplemental Digital Content 1, table S3, http://links.lww.com/ALN/C809). We used fully specified chained equations in the SAS multiple imputation procedure (SAS Institute, USA). For continuous variables, the regression method was used to impute missing values, and discriminant function methods were used for binary and categorical variables. Passive imputation was used for the derived variables (body mass index, tidal volume, Pao_2/Fio_2 ratio, anticoagulation before ECMO, and malignancy), meaning that each variable needed for the calculation was imputed before the calculation of the derived variable. A total of 50 imputed data sets were created and combined using standard between/within-variance techniques. All tests used a two-tailed hypothesis. Statistical significance was achieved for $P < 0.05$. Statistical analyses were computed with SAS version 9.4 software (SAS Institute, USA).

Results

At the time of the database lock, 38 centers had included 494 patients in the ECMOSARS registry, of whom 462 patients were followed for at least 28 days after ECMO cannulation; 429 patients were initially supported by venovenous ECMO, and 33 were supported by venoarterial ECMO (fig. 1). No patients were initially supported by venoarterio-venous ECMO.

The first venovenous ECMO included in the analysis was implanted on February 25, 2020, and the last venovenous ECMO included in the analysis was implanted on September 17, 2020. Most of the patients (257 [59.9%]) were admitted from another hospital. Venovenous ECMO was cannulated in-hospital by mobile ECMO units in 192 (45%) patients, of whom 79% were transferred subsequently to a referral ECMO center. In total, 13 centers included fewer than 5 patients, 12 centers included between 5 and 10 patients, 5 centers included between 10 and 20 patients, 2 centers included between 20 and 30 patients, 3 centers included between 30 and 40 patients, and 1 center included 124 (26.8%) patients (see Supplemental Digital Content 1, figs. S2 and S3, http://links.lww.com/ALN/C809).

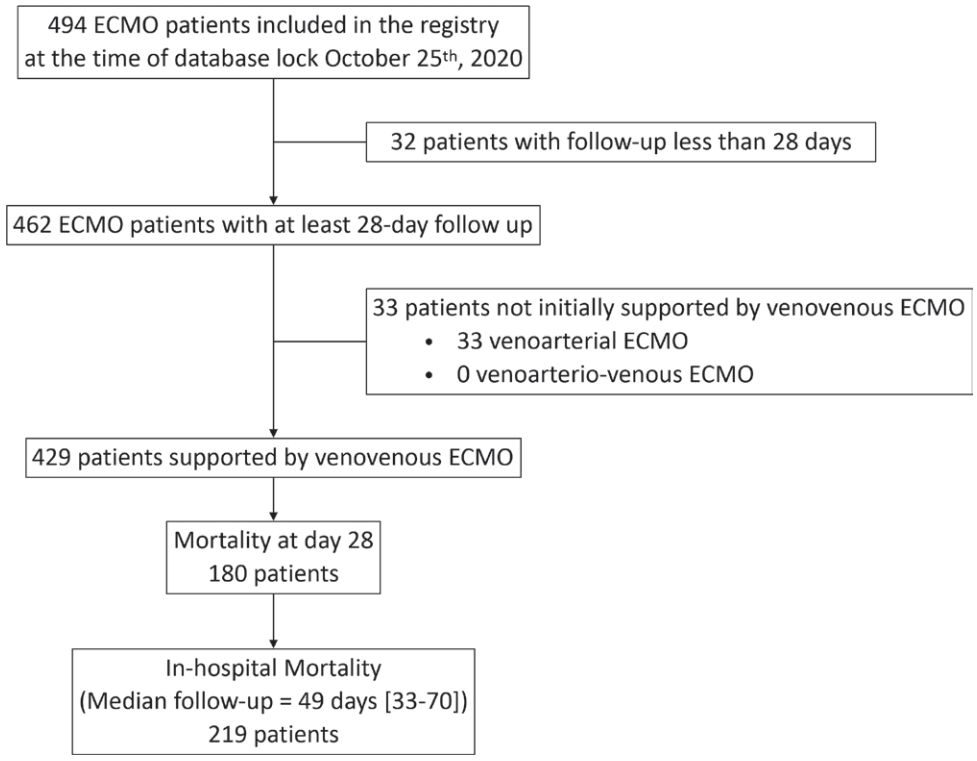

Fig. 1. Flow chart of extracorporeal membrane oxygenation (ECMO) patients included in the study.

Study Population

The median age was 54 (46 to 60) years, 79% of the patients were men, and the median body mass index was 30 (27 to 34). Management before ECMO cannulation included prone positioning (96% [411 of 429]), neuromuscular blocking agent (98% [419 of 427]), and NO (40% [161 of 401]; table 1). Median ventilation duration before ECMO was 5.0 (3.0 to 8.0) days. The median total Sequential Organ Failure Assessment (SOFA) score at cannulation (n = 395) was 9 (8 to 12), and 51% (216 of 422) of the patients had a cardiovascular SOFA score of 3 or higher. The blood lactate level was 1.7 (1.2 to 2.3) mmol/l (n = 366), and 12% (51 of 423) of the patients were on renal replacement therapy. Finally, 99% of the patients met the Berlin ARDS criteria at ECMO cannulation (table 2).

The ventilation settings at the time of the cannulation and the day after the cannulation are shown in table 3. ECMO cannulation was associated with reduced tidal volume, respiratory rate, and F_{IO_2}, as well as lower plateau and driving pressures. A tracheostomy was performed in 21% (90 of 424) of the patients.

Complications on ECMO

Hemorrhagic complications on ECMO were observed in 40% (169 of 426) of the patients, while thrombosis occurred in 37% (159 of 427), and neurologic complications occurred in 11% (47 of 425), including 38 hemorrhagic strokes (table 4). Renal replacement therapy was required in 35%. Bacteremia and cannula site infection were observed in 41% (176 of 428) and 8% (36 of 428) of the patients, respectively. According to cannulation by mobile ECMO units (see Supplemental Digital Content 1, table S4, http://links.lww.com/ALN/C809), cannula site infections were observed significantly more frequently after cannulation by mobile ECMO units, but less cannula site bleeding, although nonsignificant, was observed.

Outcomes

In-hospital mortality was 219 of 429 (51%) with a median follow-up of 49 (33 to 70) days (see Supplemental Digital Content 1, fig. S4, http://links.lww.com/ALN/C809). The extent of missing data across all variables included in the statistical models is described in Supplemental Digital Content 1 (table S3, http://links.lww.com/ALN/C809). Mortality at days 28 and 90 was 42% (180 of 429) and 60% (215 of 357), respectively. At day 28, ventilator-free days (n = 425), ECMO-free days (n = 414), and ICU-free days (n = 412) were 0 (0 to 0), 0 (0 to 14), and 0 (0 to 0) days, respectively. More male patients died, and they were significantly older (table 1). At cannulation, pH was significantly lower, and the $Paco_2$, the ventilatory ratio, and the serum lactate levels were significantly higher in the patients who ultimately died (table 2). Patients who died also had a significantly higher

Table 1. Patient Characteristics before Hospitalization

Characteristics	No.	Full Cohort (n = 429)	Vital Status		*P* Value
			Nonsurvivors (n = 219)	Survivors (n = 210)	
Age	428	54 (46–60)	56 (49–62)	51 (43–58)	< 0.001
< 40 yr		56 (13)	19 of 218 (9)	37 of 210 (18)	
40–49 yr		96 (22)	38 of 218 (17)	58 of 210 (28)	
50–59 yr		160 (37)	85 of 218 (39)	75 of 210 (36)	
60–69 yr		103 (24)	66 of 218 (30)	37 of 210 (18)	
> 70 yr		13 (3)	10 of 218 (5)	3 of 210 (1)	
Sex	429				0.046
Female		91 (21)	38 of 219 (17)	53 of 210 (25)	
Male		338 (79)	181 of 219 (83)	157 of 210 (75)	
Body mass index	413	30 (27–34)	29 (27–34)	31 (28–35)	0.132
< 25 kg of m^2		53 (13)	28 of 206 (14)	25 of 207 (12)	
25–30 kg of m^2		147 (36)	79 of 206 (38)	68 of 207 (33)	
30–35 kg of m^2		121 (29)	61 of 206 (30)	60 of 207 (29)	
35–40 kg of m^2		56 (14)	20 of 206 (10)	36 of 207 (17)	
> 40 kg of m^2		36 (9)	18 of 206 (9)	18 of 207 (9)	
Comorbidities					
Hypertension	429	165 (38)	83 of 219 (38)	82 of 210 (39)	0.807
Diabetes	425	127 (30)	70 of 218 (32)	57 of 207 (28)	0.303
Chronic obstructive pulmonary disease	429	14 (3)	8 of 219 (4)	6 of 210 (3)	0.643
Chronic respiratory failure	429	13 (3)	7 of 219 (3)	6 of 210 (3)	0.838
Congestive heart failure	308	3 (1)	1 of 169 (1)	2 of 169 (1)	0.591
Coronary artery disease	429	21 (5)	10 of 219 (5)	11 of 139 (8)	0.747
Chronic kidney disease	309	11 (4)	7 of 171 (4)	4 of 138 (3)	0.760
Malignancy					
Cancer	306	6 (2)	6 of 168 (4)	0 of 138 (0)	0.034
Hematological malignancy	306	3 (1)	1 of 168 (1)	2 of 138 (1)	0.591
Active smoker	423	17 (4)	10 of 216 (5)	7 of 207 (3)	0.514
Alcohol abuse	301	8 (3)	3 of 166 (2)	5 of 135 (4)	0.474
History of venous thromboembolism	306	11 (4)	7 of 168 (4)	4 of 138 (3)	0.760
Pre-ECMO medications					
Steroids (corticotherapy)	307	17 (6)	10 of 169 (6)	7 of 138 (5)	0.748
Nonsteroidal anti-inflammatory drugs	307	7 (2)	4 of 167 (2)	3 of 140 (2)	> 0.999
Angiotensin-converting enzyme inhibitors	305	29 (10)	14 of 167 (8)	15 of 138 (11)	0.461
Angiotensin receptor blockers	306	44 (14)	23 of 168 (14)	21 of 138 (15)	0.705

The results are presented as n (%) or median (interquartile range).
ECMO, extracorporeal membrane oxygenation.

SOFA score at cannulation, with significantly more patients with a liver (6.0 mg/dl bilirubin or more) and cardiovascular scores of 3 or higher and significantly more patients with renal replacement therapy than patients who survived. While on ECMO, patients who ultimately died experienced significantly more hemorrhagic complications, membrane lung failure, acute kidney injury, and neurologic complications than patients who survived (table 4).

Effect of Pre-ECMO Modifiable Exposure Variables on In-hospital Mortality

Among pre-ECMO modifiable exposure variables, neuromuscular blockage use (hazard ratio, 0.286; 95% CI, 0.101 to 0.81) and duration of ventilation (more than 7 days compared to less than 2 days; hazard ratio, 1.74; 95% CI, 1.07 to 2.83) were independently associated with in-hospital mortality (table 5). Among patient-related and pre-ECMO hospitalization-related confounders, age (per 10-yr increase; hazard ratio, 1.27; 95% CI, 1.07 to 1.50) and total bilirubin at cannulation (6.0 mg/dl or more compared to less than 1.2 mg/dl; hazard ratio, 2.65; 95% CI, 1.09 to 6.5) were both significantly associated with in-hospital mortality. These results remained consistent after sensitivity analysis in two distinct models: (1) modifiable exposure variables and patient-related baseline characteristics and (2) modifiable exposure variables and pre-ECMO hospitalization-related variables (see Supplemental Digital Content 1, table S2, http://links.lww.com/ALN/C809). In the latter model, septic shock (hazard ratio, 1.69; 95% CI, 1.03 to 2.77) at cannulation and pH lower than 7.25 at cannulation (hazard ratio, 1.56; 95% CI, 1.05 to 2.31) were also associated with in-hospital mortality.

Discussion

Our study reports, at a nationwide level, the characteristics, management, and outcomes of COVID-19 patients treated with venovenous ECMO for respiratory failure. We found an in-hospital mortality of 51%, numerically higher

Table 2. Clinical Condition and Management before ECMO

Condition/Management	No.	Full Cohort (n = 429)	Vital Status		*P* Value
			Nonsurvivors (n = 219)	Survivors (n = 210)	
Delay from hospitalization to ICU admission	428	0 (0–0)	0 (0–0)	0 (0–0)	0.622
< 24 h		329 (77)	169 of 218 (78)	160 of 210 (76)	
24–48 h		52 (12)	30 of 218 (14)	22 of 210 (10)	
> 72 h		47 (11)	19 of 218 (9)	28 of 210 (13)	
ECMO cannulation	426				0.141
Referral center		234 (55)	128 of 216 (59)	106 of 210 (50)	
Mobile ECMO unit, no transfer		41 (10)	21 of 216 (10)	20 of 210 (10)	
Mobile ECMO unit, transfer to referral center		151 (35)	67 of 216 (31)	84 of 210 (40)	
ARDS (Berlin criteria) at cannulation	421	417 (99)	210 of 213 (99)	207 of 208 (100)	0.623
Noninvasive ventilation	426	104 (24)	64 of 217 (29)	40 of 209 (19)	0.013
High-flow oxygen therapy	307	125 (41)	74 of 168 (44)	51 of 139 (37)	0.192
Ventilation duration before ECMO	428	5 (3–8)	6 (3–8)	5 (3–7)	0.057
< 2 days		94 (22)	43 of 218 (20)	51 of 210 (24)	
2–7 days		221 (52)	105 of 218 (48)	116 of 210 (55)	
> 7 days		113 (26)	70 of 218 (32)	43 of 210 (20)	
pH at cannulation	408	7.33 (7.25–7.39)	7.31 (7.22–7.37)	7.35 (7.29–7.41)	< 0.001
$Paco_2$ at cannulation, mmHg	406	55 (46–65)	57 (48–68)	54 (45–62)	0.005
Pao_2 of Fio_2 ratio at cannulation, mmHg	404	67 (57–82)	67 (58–84)	67 (57–81)	0.625
PEEP at cannulation, cm H_2O	385	12 (10–14)	12 (10–14)	12 (10–14)	0.747
V_T at cannulation	353	5.9 (5.2–6.3)	5.8 (5.1–6.2)	5.9 (5.3–6.3)	0.244
< 6 ml/kg ideal body weight		216 (61)	113 of 178 (63)	103 of 175 (59)	
6–8 ml/kg ideal body weight		132 (37)	63 of 178 (35)	69 of 175 (39)	
> 8 ml/kg ideal body weight		5 (1)	2 of 178 (1)	3 of 175 (2)	
Respiratory rate at cannulation, breaths/min	348	28 (20–30)	28 (22–30)	28 (20–30)	0.321
Ventilatory ratio*	315	2.2 (1.5–3.0)	2.4 (1.7–3.1)	2.1 (1.5–2.9)	< 0.001
Plateau pressure at cannulation, cm H_2O	331	30 (27–32)	30 (26–33)	30 (27–32)	0.414
Driving pressure at cannulation, cm H_2O	327	17 (14–20)	17 (13–21)	17 (14–20)	0.297
Neuromuscular blocking agents	427	419 (98)	213 of 218 (98)	206 of 209 (99)	0.725
Prone position	429	411 (96)	207 of 219 (95)	204 of 210 (97)	0.176
Inhaled NO	401	161 (40)	90 of 206 (44)	71 of 195 (36)	0.137
Renal replacement therapy	423	51 (12)	34 of 213 (16)	17 of 210 (8)	0.013
Antiviral therapy	305	179 (59)	96 of 168 (57)	83 of 137 (61)	0.544
Remdesivir		7 (2)	4 of 168 (2)	4 of 137 (3)	> 0.999
Lopinavir/ritonavir		58 (19)	36 of 168 (21)	36 of 137 (26)	0.130
Hydroxychloroquine		102 (33)	52 of 168 (31)	52 of 137 (38)	0.360
Interferon-β		4 (1)	4 of 168 (2)	4 of 137 (3)	0.125
Others		59 (19)	34 of 168 (20)	34 of 137 (25)	0.486
Antibiotic therapy	305	296 (97)	162 of 168 (96)	134 of 137 (98)	0.522
Anticoagulation	294				0.033
No		19 (6)	5 of 161 (3)	14 of 133 (11)	
Curative		139 (47)	77 of 161 (48)	62 of 133 (47)	
Prophylactic		136 (46)	79 of 161 (49)	57 of 133 (43)	
Selective digestive decontamination	304	13 (4)	10 of 166 (6)	3 of 138 (2)	0.099
SOFA score at cannulation	395	9 (8–12)	11 (8–13)	9 (8–12)	0.004
Septic shock	312	35 (11)	25 of 172 (15)	10 of 140 (7)	0.040
Cardiovascular SOFA ≥ 3 at cannulation	422	216 (51)	126 of 215 (59)	90 of 207 (43)	0.002
Left ventricular ejection fraction, %	191	60 (60–65)	60 (55–60)	60 (60–65)	0.722
Vasoactive/inotropic drugs					
Norepinephrine	306	176 (58)	103 of 168 (61)	73 of 138 (53)	0.139
Epinephrine	304	10 (3)	8 of 166 (5)	2 of 138 (1)	0.119
Dobutamine	304	8 (3)	5 of 166 (3)	3 of 137 (2)	0.732
Lactatemia at cannulation, mmol/l	366	1.7 (1.2–2.3)	1.7 (1.3–2.4)	1.6 (1.2–2.1)	0.012
Total bilirubin at cannulation	409				0.023
< 1.2 mg/dl		291 (71)	147 of 207 (71)	144 of 202 (71)	
1.2–1.9 mg/dl		50 (12)	20 of 207 (10)	30 of 202 (15)	
2.0–5.9 mg/dl		57 (14)	30 of 207 (14)	27 of 202 (13)	
≥ 6.0 mg/dl		11 (3)	10 of 207 (5)	1 of 202 (0)	

The results are presented as n (%) or median (interquartile range).

*The ventilatory ratio is defined as [minute ventilation (ml/min) × $Paco_2$ (mmHg)]/(predicted body weight × 100 × 37.5).

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; Fio_2, fractional inspired oxygen tension; ICU, intensive care unit; PEEP, positive end-expiratory pressure; SOFA, Sequential Organ Failure Assessment; V_T, tidal volume.

Table 3. Blood Gases and Ventilator Settings Pre-ECMO the Day of Implantation and the Day after Cannulation

	Nonsurvivors (n = 219)					Survivors (n = 210)				
	Pre-ECMO Day of Cannulation		Post-ECMO Day 1			Pre-ECMO Day of Cannulation		Post-ECMO Day 1		
Blood Gases/Settings	No.	Median (Interquartile Range)	No.	Median (Interquartile Range)	*P* Value	No.	Median (Interquartile Range)	No.	Median (Interquartile Range)	*P* Value
pH	207	7.31 (7.22–7.37)	209	7.40 (7.34–7.45)	0.010	201	7.35 (7.29–7.41)	206	7.42 (7.37–7.47)	< 0.001
Pa_{O_2}, mmHg	208	64 (57–77)	209	79 (65–101)	0.001	199	65 (54–73)	206	83 (70–106)	< 0.001
$Paco_2$, mmHg	206	57 (48–68)	206	44 (40–50)	< 0.001	200	54 (45–62)	206	45 (39–50)	< 0.001
Fio_2, %	210	100 (100–100)	210	70 (50–100)	< 0.001	201	100 (100–100)	206	60 (50–80)	< 0.001
Pa_{O_2}/Fio_2 ratio, mmHg	208	67 (58–84)	209	116 (90–160)	< 0.001	196	67 (57–81)	204	134 (104–208)	< 0.001
PEEP, cm H_2O	201	12 (10–14)	199	12 (10–14)	0.134	184	12 (10–14)	182	12 (10–14)	0.176
V_T, ml/kg ideal body weight	178	5.8 (5.1–6.2)	178	3.2 (2.2–4.5)	< 0.001	175	5.9 (5.3–6.3)	185	3.5 (2.6–4.5)	< 0.001
Respiratory Rate, breaths/min	183	28 (22–30)	190	16 (12–20)	< 0.001	165	28 (20–30)	184	18 (12–20)	< 0.001
Plateau pressure, cm H_2O	173	30 (26–33)	171	26 (24–28)	< 0.001	158	30 (27–32)	166	25 (23–28)	< 0.001
Driving pressure, cm H_2O	171	17 (13–21)	168	14 (11–16)	< 0.001	156	17 (14–20)	159	12 (11–15)	< 0.001

The results are presented as median (interquartile range). The *P* values are for bivariate analysis between pre- and post-ECMO.

ECMO, extracorporeal membrane oxygenation; Fio_2, fractional inspired oxygen tension; PEEP, positive end-expiratory pressure; V_T, tidal volume.

than that reported in two recent studies of venovenous ECMO use in COVID-19 patients.[14,15] The international Extracorporeal Life Support Organization study reported an estimated cumulative incidence of in-hospital mortality 90 days after ECMO initiation of 37%.[13] The Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 study reported a 60-day mortality rate of 33% in the United States.[15] Similarly, the ECMO to Rescue Lung Injury in Severe ARDS trial reported a mortality of 35% at 60 days in non–COVID-19 ARDS patients supported by venovenous ECMO.[8]

Several factors may explain the higher mortality rate observed in this study. First, this population was older than the populations in the Extracorporeal Life Support Organization or the Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 studies (median age, 54 [interquartile range, 46 to 60] yr *vs.* 49 [41 to 57] yr in the Extracorporeal Life Support Organization or 49 [41 to 57] years in the Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 cohort). Second, this population had more severe ARDS at the time of cannulation. In addition, 99% of the patients in this study met the Berlin criteria for ARDS, compared with only 79% in the Extracorporeal Life Support Organization study.[14] Patients in this study tended to have been mechanically ventilated for longer before ECMO cannulation (median 6 days *vs.* 4 days in the Extracorporeal Life Support Organization and 2 days in the Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19), which is known to be associated with worse outcomes.[24] Our patients were also more likely to have been proned (96% *vs.* 60% in the Extracorporeal Life Support Organization or 71% in the Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 cohort) and/or paralyzed before ECMO cannulation (98% *vs.* 72% or 78%), both suggesting the use of ECMO later in the disease process. Finally, this study included patients from a wide range of both high- and low-volume centers, reflecting the broad use of ECMO in France during the COVID-19 pandemic.[9]

We found several factors independently associated with in-hospital mortality in our cohort, including older age, liver failure (6 mg/dl bilirubin or more) at ECMO cannulation, and a duration of ventilation before ECMO cannulation of more than 7 days; in contrast, only neuromuscular blocking agent use before ECMO was found as a protective factor. These findings were consistent with previous studies[14,24,27,28] and could be useful to the bedside clinician. First, they emphasize the value of early consideration of ECMO when indicated. This finding is particularly important as it can be easily modifiable at the bedside. In our cohort, 26% of the patients were canulated after 7 days of mechanical ventilation. Thus, the clinicians should be strongly encouraged to consider ECMO within 7 days after mechanical ventilation initiation. Second, these findings emphasize that ECMO support seems less beneficial in the sickest patients, as previously described for non–COVID-19 ARDS patients.[24,27,28] In our cohort, liver failure at cannulation appears to be an especially strong marker of severity, which should alert the clinicians before considering ECMO support. Of course, only a limited number of patients presented liver failure, which underlined that the majority of clinicians are already fully aware of the poor results of ECMO support in the sickest patients. Third, the data from this study again emphasize the comparatively poorer outcomes in older patients who received ECMO for COVID-19. Notably, patients of more than 70 yr of age were excluded from the U.S. Study of

Table 4. Outcomes and Complications on ECMO

Outcomes and Complications	No.	Full Cohort (n = 429)	Vital Status		*P* Value
			Nonsurvivors (n = 219)	Survivors (n = 210)	
Total ECMO duration, days		12 (8–21)	11 (6–21)	13 (8–21)	0.751
ECMO-free days at day 28, days	414	0 (0–14)	0 (0–0)	14 (6–19)	< 0.001
Conversion to venoarterial-venous ECMO	429	9 (2)	8 of 219 (4)	1 of 210 (0)	0.038
Cannulation mode	425				0.823
Femoro-jugular		388 (91)	196 of 217 (90)	192 of 208 (92)	
Femoro-femoral		27 (6)	16 of 217 (7)	11 of 208 (5)	
Bicaval dual lumen		6 (1)	2 of 217 (1)	4 of 208 (2)	
Not specified		4 (1)	3 of 217 (1)	1 of 208 (0)	
Total ventilation duration, days	390	27 (16–41)	18 (12–34)	31 (24–46)	< 0.001
Ventilator-free days at day 28, days	425	0 (0–0)	0 (0–0)	0 (0–4)	< 0.001
Tracheostomy	424	90 (21)	11 of 217 (5)	79 of 207 (38)	< 0.001
Prone position	425	301 (71)	145 of 216 (67)	156 of 209 (75)	0.089
Respiratory ECMO Survival Prediction score	240	1 (0–3)	1 (0–3)	2 (0–4)	< 0.001
Vasoactive/inotropic drugs					
Norepinephrine	304	255 (84)	154 of 167 (92)	101 of 137 (74)	< 0.001
Epinephrine	305	15 (5)	13 of 168 (8)	2 of 137 (1)	0.012
Dobutamine	304	16 (5)	11 of 167 (7)	5 of 137 (4)	0.254
Hemorrhagic complications	426	169 (40)	107 of 217 (49)	62 of 209 (30)	< 0.001
Cannula site bleeding		77 (18)	54 of 107 (50)	23 of 62 (37)	
Gastrointestinal bleeding		26 (6)	20 of 107 (19)	6 of 62 (10)	
Pulmonary hemorrhage		37 (9)	27 of 107 (25)	10 of 62 (16)	
Retroperitoneal bleeding		4 (1)	3 of 107 (3)	1 of 62 (2)	
Massive hemorrhage		20 (5)	15 of 107 (14)	5 of 62 (8)	
Number of packed red blood cells transfused	300	4 (2–8)	6 (3–10)	3 (0–6)	< 0.001
Thrombotic complications	427	159 (37)	84 of 217 (39)	75 of 210 (36)	0.522
Deep vein thrombosis		33 (8)	9 of 84 (11)	24 of 75 (32)	
Pulmonary embolism		48 (11)	28 of 84 (33)	20 of 75 (27)	
Circuit clot		66 (15)	32 of 84 (38)	34 of 75 (45)	
Circuit change		56 (13)	32 of 84 (38)	24 of 75 (32)	
Membrane lung failure		35 (8)	25 of 84 (30)	10 of 75 (13)	
Neurologic complications	425	47 (11)	41 of 216 (19)	6 of 209 (3)	< 0.001
Seizures		2 (0)	2 of 41 (5)	0 of 6 (0)	
Ischemic stroke		5 (1)	3 of 41 (7)	2 of 6 (33)	
Hemorrhagic stroke		38 (9)	35 of 41 (85)	3 of 6 (50)	
Acute limb ischemia	424	4	4 (100)	0 (0)	0.124
Acute mesenteric ischemia	427	4	4 (100)	0 (0)	0.123
Acute kidney injury on ECMO	424	192 (45)	134 of 216 (62)	58 of 208 (28)	< 0.001
Renal replacement therapy		149 (35)	104 of 134 (78)	45 of 58 (78)	
Extracorporeal blood purification device	326	50 (15)	34 of 178 (19)	16 of 148 (11)	0.039
Ventilator-associated pneumonia	426	277 (65)	137 of 219 (63)	140 of 210 (67)	0.405
Timing of ventilator-associated pneumonia	169				0.235
Before ECMO		83 (49)	50 of 94 (53)	33 of 75 (44)	
After ECMO		86 (51)	44 of 94 (47)	42 of 75 (56)	
Infectious complications	428	235 (55)	112 of 218 (51)	123 of 210 (59)	0.135
Bacteremia		176 (41)	87 of 112 (78)	89 of 123 (72)	
Cannula site infection		36 (8)	16 of 112 (14)	20 of 123 (16)	
Infection under ECMO-free days, days*	323	9 (3–21)	7 (2–12)	13 (5–28)	< 0.001
ICU duration, days	411	35 (17–54)	18 (10–34)	34 (26–54)	< 0.001
ICU-free days at day 28, days	412	0 (0–0)	0 (0–0)	0 (0–2)	< 0.001
Hospitalization duration, days	395	35 (17–54)	21 (12–36)	52 (37–71)	< 0.001

The results are presented as n (%) or median (interquartile range).

*Infection under ECMO includes ventilator-associated pneumonia, bacteremia, and cannula site infection.

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

the Treatment and Outcomes in Critically Ill Patients with COVID-19.[15] Finally, the favorable results in patients in this cohort who received neuromuscular blocking agent before ECMO cannulation are in line with previous work[24] but should be interpreted with caution here as the vast majority of patients in our cohort received neuromuscular blocking agent before ECMO. Indeed, the very few patients who did not receive neuromuscular blocking agent before cannulation must be considered outliers whose management may have been out of the standard of care.

Table 5. Pre-ECMO Variables Associated with In-hospital Mortality in Multivariable Analysis

Variables	Hazard Ratio (95% CI)*
Neuromuscular blocking agents†	0.286 (0.101–0.81)
Ventilation duration before ECMO†	
< 2 days	1
2–7 days	1.37 (0.89–2.10)
> 7 days	1.74 (1.07–2.83)
Age (10-yr increase)‡	1.27 (1.07–1.50)
Total bilirubin at implantation‡	
< 1.2 mg/dl	1
1.2–1.9 mg/dl	0.88 (0.51–1.50)
2.0–5.9 mg/dl	1.16 (0.72–1.86)
≥ 6.0 mg/dl	2.65 (1.09–6.4)

*Hazard ratio with 95% CI, based on multivariable Cox model of exposure variables fully adjusted for all confounders, after multiple imputation (see model 4, Supplemental Digital Content 1, table S2, http://links.lww.com/ALN/C809). †Defined as pre-ECMO modifiable exposure variables in the model (see Supplemental Digital Content 1, fig. S1, http://links.lww.com/ALN/C809). ‡Defined as patient-related confounders and pre-ECMO hospitalization-related confounders in the model (see Supplemental Digital Content 1, fig. S1, http://links.lww.com/ALN/C809).

ECMO, extracorporeal membrane oxygenation.

While on ECMO, patients who ultimately died experienced significantly more hemorrhagic complications, neurologic complications (mainly hemorrhagic stroke), membrane lung failure, and acute kidney injury than patients who survived. We report more frequent bleeding complications than in the U.S. Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 study (28% *vs*. 40%) or in the Extracorporeal Life Support Organization study, including cannula site bleeding (18% *vs*. 7%, respectively), gastrointestinal hemorrhage (6% *vs*. 3%, respectively), and pulmonary hemorrhage (8% *vs.* 4%, respectively). Although our definitions of bleeding events were less restrictive, this might be also related to the contemporaneous publication of French guidelines on anticoagulation in COVID-19 patients, which recommended elevated unfractionated heparin targets in ECMO patients after early reports of prothrombotic state in COVID-19 patients.[29] Of note, the ECMO to Rescue Lung Injury in Severe ARDS trial reported 46% of bleeding leading to transfusion. Similarly, we observed a higher proportion of hemorrhagic stroke (9%) than previously reported (2, 4, and 6% in the ECMO to Rescue Lung Injury in Severe ARDS trial, the U.S. Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19, and the Extracorporeal Life Support Organization studies, respectively).

Membrane lung failures were higher than in the Extracorporeal Life Support Organization study (12% vs. 8%), and the higher proportion in the nonsurvivors might reflect the hypercoagulopathy pattern described in the more severe patients.[30] Interestingly, the proportion of acute kidney injury (AKI) requiring renal replacement therapy (35%) was higher than in the Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 study (22%) but lower than in the Extracorporeal Life Support Organization study (44%) or the ECMO to Rescue Lung Injury in Severe ARDS trial (52%). Nevertheless, as in in the Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 study, the proportion of AKI was significantly higher in the nonsurvivors, highlighting how the development of AKI might be a turning point in the trajectories of COVID-19 patients on ECMO.

Critically ill patients with COVID-19 have been found at high risk for hospital-acquired infections.[31] In non-ECMO critically ill patients with COVID-19, ventilator-associated pneumonia was found in 25 to 50%, and bacteremia was found in 15 to 34%.[31,32] However, few data are available in COVID-19 patients on ECMO. We found a high proportion of ventilator-associated pneumonia (51%) and bacteremia while on ECMO (41%). The Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 study reported 35% of ventilator-associated pneumonia and 18% of other documented infections. A similar proportion of 39% of ventilator-associated pneumonia on ECMO was reported in the ECMO to Rescue Lung Injury in Severe ARDS trial. The discrepancy between our study and other reports remains to be elucidated. One hypothesis might be the difficulty of applying infection control procedures in a context of increased workload and a shortage in healthcare workers related to the pandemic surge. Variations in ventilator-associated pneumonia definition applications and microbiologic sampling methods across ICUs and countries might also explain these differences, and further studies are mandated to explore these questions. In contrast, in our cohort, the cannula site infection proportion (8%) was lower than previously described in non–COVID-19 patients.[8,33]

A high proportion of patients were cannulated by mobile ECMO units in our cohort (45%), similar to the percentage previously reported in the Extracorporeal Life Support Organization study (47%). Cannulation by mobile ECMO unit was not found associated with higher mortality, highlighting the importance of mobile ECMO program to rescue patients hospitalized outside of the referral centers as previously suggested.[34] Of note, cannulation by a mobile ECMO unit was not associated with more cannula site bleeding, but more cannula site infections were observed.

Our study has several strengths. This cohort is one of the largest samples of patients supported by venovenous ECMO for COVID-19–related ARDS published to date. Second, the participating centers represented most of the ECMO sites available in France, giving this study a good representation of the ECMO activity between the end of February and September 2020. Additionally, a central system was established to coordinate national ECMO resources, allowing relocation of consoles and circuits, when needed, in the areas the most affected by the virus. Third, the wide adherence during the pre-ECMO period

to known medical interventions in ARDS patient management, such as protective ventilation, prone positioning, or neuromuscular blocking agent infusions, must be emphasized. These data strengthen the fact that in our cohort, ECMO support was proposed to highly severe patients as a rescue therapy after adequate management. Fourth, the multicenter design enables generalization of the data. Finally, the database quality was regularly assessed by dedicated data managers.

However, there are some limitations. Despite broad representation among French ECMO centers, the cohort did not include all ECMO centers, creating potential selection bias. Within our cohort, a significant proportion (26%) of patients came from a single center in Paris, which is a high-volume ECMO center and is also located in an area that was severely affected by the pandemic. In addition, at the time of the database lock, 34 patients (8%) were still hospitalized, leading to a possible underestimation of the in-hospital mortality. Further, as an observational study relying on patients' medical records, this study might be subject to information bias. There were no specific recommendations on cannulation or management of ECMO, introducing variability in management across the study population. However, because we anticipated regional differences in the burden of the pandemic, as well as expertise disparities between participating centers, centers were included as a random effect using a γ frailty model in the Cox model. Additionally, considering that the vast majority of patients in our cohort received neuromuscular blocking agent before ECMO, we underline that the association found between neuromuscular blocking agent use and survival must be interpreted with caution. Finally, it is worth remembering that our study analyzed only patients already receiving ECMO, and thus the results obtained might not be fully relevant in a general population of severe COVID-19 patients.

In conclusion, this analysis of the ECMOSARS registry provides results and outcomes of COVID-19–related respiratory failure patients supported by venovenous ECMO between February and September 2020 in France. In-hospital mortality was higher than recently reported in a multicenter international cohort, but nearly half of the patients survived. A high proportion of patients were cannulated by mobile ECMO unit without negative impact on mortality. Several factors associated with mortality were identified, which may help to guide future clinical decision-making. In particular, venovenous ECMO support should be considered early, within the first week of mechanical ventilation initiation.

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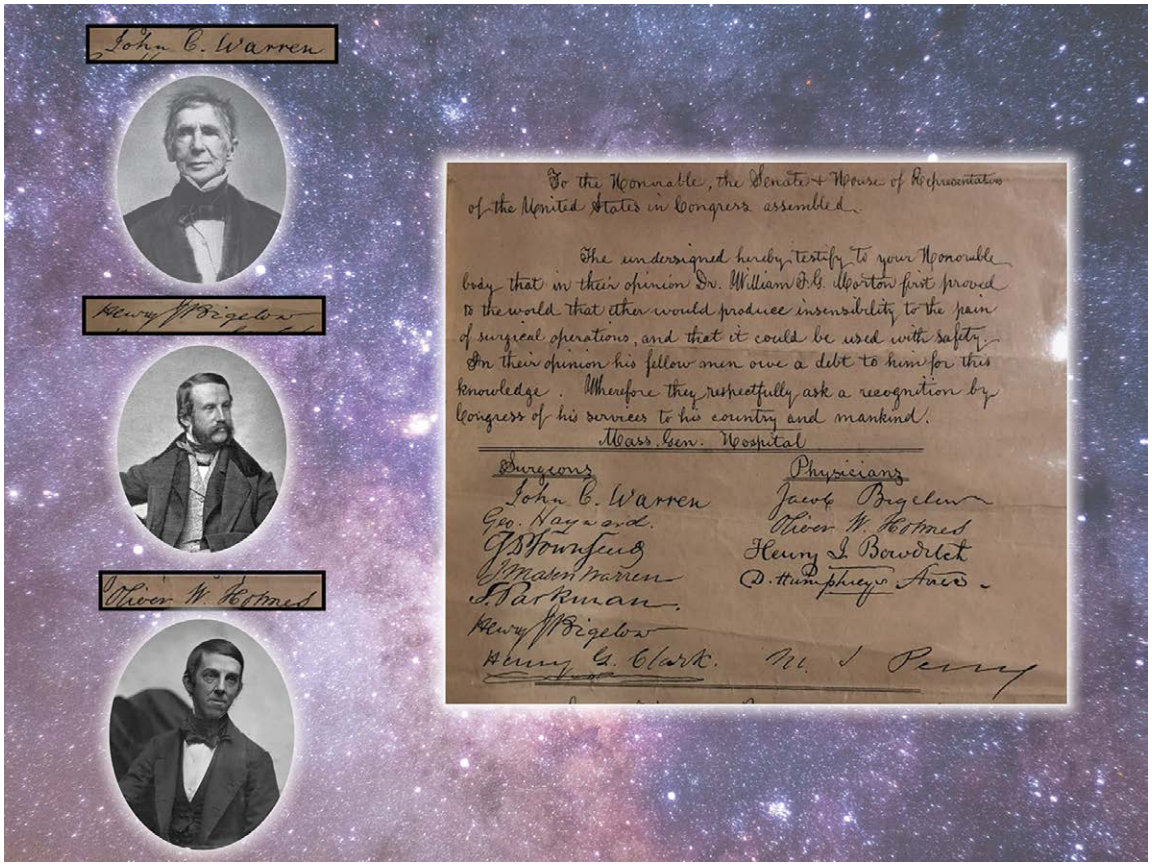
Anne Olland, M.D., Ph.D., University Hospital of Strasbourg, Strasbourg, France, collected data, provided and cared for study patients
Marion Villard, M.D., University Hospital of Strasbourg, Strasbourg, France, collected data, provided and cared for study patients
Fanny Bounes, M.D., University Hospital of Toulouse, Toulouse, France, collected data, provided and cared for study patients

Vincent Minville, M.D., Ph.D., University Hospital of Toulouse, Toulouse, France, collected data, provided and cared for study patients
Antoine Guillon, M.D., University Hospital of Tours, Tours, France, collected data, provided and cared for study patients
Yannick Fedun, M.D., Bretagne Atlantique Hospital, Vannes, France, collected data, provided and cared for study patients
James T. Ross, M.D., University of California Davis, Sacramento, California, provided critical revisions of the manuscript

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

The Stars Align in Support of Morton's "Anaesthesia"



"Never before…did such a brilliant galaxy of medical and surgical talent unite on any one measure." Penned by the brightest stars of Massachusetts General Hospital in 1852, a petition to the United States Congress (*right*) shined a favorable light on Morton, who in a quest for recognition had ignited a national controversy over primacy for the discovery of surgical anesthesia. These medical luminaries declared "that, in their opinion, Dr. William T.G. Morton first proved to the world that ether would produce insensibility to the pain of surgical operations… [and asked for] recognition by [U.S.] Congress of his services to his country and mankind." Among these leading lights were John C. Warren, M.D. (*upper left*), founding father of Massachusetts General Hospital and senior surgeon on Ether Day; Henry J. Bigelow, M.D. (*middle left*), surgeon and organizer of that celebrated day; and Oliver W. Holmes, M.D. (*lower left*), physician-poet who bestowed the name "anaesthesia" onto this new discovery. Whether this was a true endorsement of Morton or the medical discovery that elevated surgical practice may be lost among the stars. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology. www.woodlibrarymuseum.org)

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