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

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*Anesthesiology 2022; 136:732–48

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 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.

(E)arly 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)
pandemic demonstrated the value of ECMO support for patients with severe ARDS related to influenza.\textsuperscript{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.\textsuperscript{7–9}

Several early retrospective case series showed encouraging results of ECMO support in COVID-19–related respiratory failure.\textsuperscript{10–12} 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.\textsuperscript{14} Recently, a similar mortality rate was reported in a multicenter cohort study of 190 critically ill adults with Extracorporeal Membrane Oxygenation and COVID-19
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_ARStdf-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 Critical Care and Anesthesia (Anesthésie-Réanimation Cœur-Thorax-Vaisseaux [ARCOTHOVA], Paris, France), and the French Society of Thoracic and Cardiovascular Critical Care and Anesthesia (Anesthésie-Réanimation Cœur-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) × PaCO₂ (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, PaCO₂ at cannulation, Pao₂/Fio₂ 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, Pao₂/Fio₂ 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 venaarterio-venous ECMO (fig. 1). No patients were initially supported by venaarterio-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).
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 Fio2, 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 PaCO2, 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

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

| Characteristics | No. | Full Cohort (n = 429) | Nonsurvivors (n = 219) | Survivors (n = 210) | P Value |
|-----------------|-----|----------------------|------------------------|---------------------|---------|
| Age             | 428 | 54 (46–60)           | 56 (49–62)             | 51 (43–58)          | < 0.001 |
| < 40 yr         | 56  | 19 of 218 (9)        | 37 of 210 (18)         |                     |         |
| 40–49 yr        | 96  | 38 of 218 (17)       | 58 of 210 (28)         |                     |         |
| 50–59 yr        | 160 | 85 of 218 (39)       | 75 of 210 (36)         |                     |         |
| 60–69 yr        | 103 | 66 of 218 (30)       | 37 of 210 (18)         |                     |         |
| > 70 yr         | 13  | 10 of 218 (5)        | 3 of 210 (1)           |                     |         |
| Sex             | 429 | 38 of 219 (17)       | 53 of 210 (25)         |                     |         |
| Female          | 91  | 181 of 219 (83)      | 157 of 210 (75)        |                     | 0.046   |
| Male            | 338 | 29 (27–34)           | 31 (28–35)             |                     | 0.132   |
| Body mass index | 413 | 28 of 206 (14)       | 25 of 207 (12)         |                     |         |
| < 25 kg/m²      | 53  | 79 of 206 (38)       | 68 of 207 (33)         |                     |         |
| 25–30 kg/m²     | 147 | 61 of 206 (30)       | 60 of 207 (29)         |                     |         |
| 30–35 kg/m²     | 121 | 20 of 206 (10)       | 36 of 207 (17)         |                     |         |
| > 40 kg/m²      | 36  | 18 of 206 (9)        | 18 of 207 (9)          |                     |         |
| Comorbidities   |     |                      |                        |                     |         |
| Hypertension    | 429 | 83 of 219 (38)       | 82 of 210 (39)         |                     | 0.807   |
| Diabetes        | 425 | 70 of 218 (32)       | 57 of 207 (28)         |                     | 0.303   |
| Chronic obstructive pulmonary disease | 429 | 8 of 219 (4)        | 6 of 210 (3)           |                     | 0.643   |
| Chronic respiratory failure | 429 | 7 of 219 (3)        | 6 of 210 (3)           |                     | 0.838   |
| Congestive heart failure | 308 | 1 of 169 (1)       | 2 of 169 (1)           |                     | 0.591   |
| Coronary artery disease | 429 | 10 of 219 (6)       | 11 of 139 (8)          |                     | 0.747   |
| Chronic kidney disease | 309 | 7 of 171 (4)       | 4 of 138 (3)           |                     | 0.760   |
| Malignancy      |     |                      |                        |                     |         |
| Cancer          | 306 | 6 of 168 (4)         | 0 of 138 (0)           |                     | 0.034   |
| Hematological malignancy | 306 | 1 of 168 (1)       | 2 of 138 (1)           |                     | 0.591   |
| Active smoker   | 423 | 10 of 216 (5)        | 7 of 207 (3)           |                     | 0.514   |
| Alcohol abuse   | 301 | 3 of 166 (2)         | 5 of 135 (4)           |                     | 0.474   |
| History of venous thromboembolism | 306 | 7 of 168 (4)       | 4 of 138 (3)           |                     | 0.760   |
| Pre-ECMO medications |     |                      |                        |                     |         |
| Steroids (corticotherapy) | 307 | 10 of 169 (6)       | 7 of 138 (5)           |                     | 0.748   |
| Nonsteroidal anti-inflammatory drugs | 307 | 4 of 167 (2)      | 3 of 140 (2)           | > 0.999          |
| Angiotensin-converting enzyme inhibitors | 305 | 14 of 167 (8)     | 15 of 138 (11)         |                     | 0.461   |
| Angiotensin receptor blockers | 306 | 23 of 168 (14)     | 21 of 138 (15)         |                     | 0.705   |

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

ECMO, extracorporeal membrane oxygenation.
## Table 2. Clinical Condition and Management before ECMO

| Condition/Management | No. | Full Cohort (n = 429) | Nonsurvivors (n = 219) | Survivors (n = 210) | P Value |
|----------------------|-----|-----------------------|------------------------|---------------------|---------|
| 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) | 26 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 | 210 of 213 (99) | 207 of 208 (100) | | |
| Noninvasive ventilation | 125 (41) | 74 of 168 (44) | 51 of 139 (37) | | 0.623 |
| Ventilation duration before ECMO | 428 | 6 (6–8) | 5 (6–7) | 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 |
| PaO$_2$/FiO$_2$ at cannulation, mmHg | 405 | 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$_2$O | 385 | 12 (10–14) | 12 (10–14) | 12 (10–14) | 0.747 |
| Vt at cannulation | 353 | 5.9 (5.2–6.3) | 5.8 (5.1–6.2) | 5.3 (5.3–6.3) | 0.244 |
| 6–8 ml/kg ideal body weight | 113 (26) | 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 | 347 | 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$_2$O | 331 | 113 of 178 (63) | 103 of 175 (59) | | |
| Driving pressure at cannulation, cm H$_2$O | 327 | 11 (9–13) | 10 (9–12) | 0.013 |
| Neumonous blocking agents | 427 | 210 of 219 (95) | 204 of 210 (97) | 0.176 |
| Prone position | 429 | 207 of 219 (95) | 204 of 210 (97) | 0.176 |
| Inhaled NO | 401 | 90 of 206 (44) | 71 of 195 (36) | 0.137 |
| Renal replacement therapy | 423 | 3 of 168 (2) | 4 of 137 (3) | > 0.999 |
| Antiviral therapy | 305 | 52 of 168 (31) | 52 of 137 (38) | 0.360 |
| Antibiotic therapy | 305 | 10 of 166 (6) | 3 of 138 (2) | 0.099 |
| Anticoagulation | 294 | 5 of 161 (3) | 14 of 133 (11) | 0.033 |
| NO | 19 (6) | 2 of 161 (1) | 3 of 158 (2) | 0.032 |
| Curative | 139 (47) | 13 of 161 (8) | 2 of 133 (1) | 0.130 |
| Prophylactic | 136 (46) | 3 of 161 (2) | 1 of 133 (1) | 0.032 |
| Selective digestive decontamination | 304 | 10 of 166 (6) | 3 of 138 (2) | 0.032 |
| SOFA score at cannulation | 395 | 11 (8–13) | 9 (8–12) | 0.004 |
| Septic shock | 312 | 15 (9–17) | 10 of 140 (7) | 0.040 |
| Cardiovascular SOFA ≥ 3 at cannulation | 422 | 90 of 207 (43) | 0.002 |
| Left ventricular ejection fraction, % | 191 | 60 (55–65) | 60 (55–65) | 0.722 |
| Vasoactive/inotropic drugs | | | | | |
| Norepinephrine | 306 | 103 of 168 (61) | 73 of 138 (53) | 0.139 |
| Epinephrine | 304 | 8 of 166 (5) | 2 of 138 (1) | 0.119 |
| Dobutamine | 304 | 5 of 166 (3) | 3 of 137 (2) | 0.732 |
| Lactateemia at cannulation, mmol/l | 366 | 1.7 (1.2–2.3) | 1.6 (1.2–2.1) | 0.012 |
| Total bilirubin at cannulation | 409 | 1.2 (1.2–2.3) | 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) × PaO$_2$ (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; Vt, tidal volume.

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than that reported in two recent studies of venovenous ECMO use in COVID-19 patients.\textsuperscript{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%.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 study. Second, these findings emphasize that ECMO should be considered within 7 days after mechanical ventilation, 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 Extracorporeal Membrane Oxygenation and COVID-19.

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

| Blood Gases/Settings | Nonsurvivors (n = 219) | Survivors (n = 210) |
|----------------------|----------------------|-------------------|
|                      | Pre-ECMO Day of Cannulation | Post-ECMO Day 1 | Pre-ECMO Day of Cannulation | Post-ECMO Day 1 |
|                      | Median (Interquartile Range) | No. | Median (Interquartile Range) | No. | P Value | Median (Interquartile Range) | No. | Median (Interquartile Range) | No. | 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 |
| PaO\(_2\), 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 |
| Pao\(_2\)/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\(_2\)O    | 201 (12 (10–14)) | 199 | 12 (10–14) | 0.134 | 184 | 12 (10–14) | 182 | 12 (10–14) | 0.176 |
| Driving pressure, cm H\(_2\)O | 171 (17 (13–21)) | 168 | 14 (11–16) | < 0.001 | 156 | 17 (14–20) | 159 | 12 (11–15) | < 0.001 |
| Respiratory Rate, breaths/min | 183 (20 (15–30)) | 190 | 16 (12–20) | < 0.001 | 165 | 20 (15–30) | 184 | 18 (12–20) | < 0.001 |
| Plateau pressure, cm H\(_2\)O | 173 (30 (25–33)) | 171 | 26 (24–28) | < 0.001 | 158 | 30 (27–32) | 166 | 25 (23–28) | < 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\(_e\), tidal volume.

In our cohort, liver failure at 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.\textsuperscript{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\textsuperscript{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 cannulated 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.\textsuperscript{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
the Treatment and Outcomes in Critically Ill Patients with COVID-19. Finally, the favorable results in patients in this cohort who received neuromuscular blocking agent before ECMO cannulation are in line with previous work 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 4. Outcomes and Complications on ECMO

| Outcomes and Complications | No. | Full Cohort (n = 429) | Nonsurvivors (n = 219) | Survivors (n = 210) | P Value |
|----------------------------|-----|-----------------------|------------------------|---------------------|---------|
| Total ECMO duration, days  | 12  | 8 (6–21)              | 13 (6–21)              | 14 (6–19)           | < 0.001 |
| 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 | Femoro-jugular        | 388 (91)               | 196 of 217 (90)     | 0.751   |
|                           |     | Femoro-femoral        | 27 (6)                 | 16 of 217 (7)       | < 0.001 |
|                           |     | Bicaval dual lumen    | 6 (1)                  | 2 of 217 (1)        | < 0.001 |
|                           |     | Not specified         | 4 (1)                  | 3 of 217 (1)        | < 0.001 |
| Total ventilation duration, days | 390 | 27 (16–41)            | 19 (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)            | < 0.001 |
|                           |     | Epinephrine           | 305                    | 15 (5)              | 0.012   |
|                           |     | Dobutamine            | 304                    | 16 (5)              | 0.254   |
| Hemorrhagic complications  | 426 | 169 (40)              | 107 of 217 (49)        | 62 of 209 (30)      | < 0.001 |
| Cannula site bleeding     | 77  | 18 (17–30)            | 54 of 107 (50)         | 23 of 62 (37)       | < 0.001 |
| Gastrointestinal bleeding | 26  | 6 (0–26)              | 20 of 107 (19)         | 6 of 62 (10)        | < 0.001 |
| Pulmonary hemorrhage      | 37  | 9 (1–41)              | 27 of 107 (25)         | 10 of 62 (16)       | < 0.001 |
| Retropitoneal bleeding    | 4   | 1 (0–1)               | 3 of 107 (3)           | 1 of 62 (2)         | < 0.001 |
| Massive hemorrhage        | 20  | 5 (0–10)              | 15 of 107 (14)         | 5 of 62 (8)         | < 0.001 |
| 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  | 9 (4–19)              | 9 of 84 (11)           | 24 of 75 (32)       | < 0.001 |
| Pulmonary embolism        | 48  | 11 (0–31)             | 28 of 84 (33)          | 20 of 75 (27)       | < 0.001 |
| Circuit clot              | 66  | 15 (0–32)             | 32 of 84 (38)          | 34 of 75 (45)       | < 0.001 |
| Circuit change            | 56  | 13 (0–10)             | 32 of 84 (38)          | 24 of 75 (32)       | < 0.001 |
| Membrane lung failure     | 35  | 8 (0–29)              | 25 of 84 (30)          | 10 of 75 (13)       | < 0.001 |
| Neurologic complications  | 425 | 47 (11)               | 41 of 216 (19)         | 6 of 209 (3)        | < 0.001 |
| Seizures                  | 2   | 0 (0–1)               | 2 of 41 (5)            | 0 of 6 (0)          | < 0.001 |
| Ischemic stroke           | 5   | 1 (0–1)               | 3 of 41 (7)            | 2 of 6 (3)          | < 0.001 |
| Hemorrhagic stroke        | 38  | 9 (0–53)              | 35 of 41 (85)          | 3 of 6 (0)          | < 0.001 |
| Acute limb ischemia       | 424 | 4                     | 4 (0–100)              | 0 (0)               | 0.124   |
| Acute mesenteric ischemia | 427 | 4                     | 4 (0–100)              | 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 (11–64)            | 104 of 134 (78)        | 45 of 58 (78)       | < 0.001 |
| 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 | 4                     | 4 (0–100)              | 0 (0)               | 0.235   |
| Before ECMO               | 83  | 49 (50–94)            | 50 of 94 (53)          | 33 of 75 (44)       | < 0.001 |
| After ECMO                | 86  | 51 (44–94)            | 44 of 94 (47)          | 42 of 75 (56)       | < 0.001 |
| Infectious complications  | 428 | 235 (55)              | 112 of 218 (51)        | 123 of 210 (59)     | 0.135   |
| Bacteremia                | 176 | 41 (17–70)            | 87 of 112 (78)         | 89 of 123 (72)      | < 0.001 |
| Cannula site infection    | 36  | 8 (0–31)              | 16 of 112 (14)         | 20 of 123 (16)      | < 0.001 |
| 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.
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 prothrombolic 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.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.

Research Support

Supported by a grant from the University Hospital of Rennes (Appel à Projets CFTR2; Rennes, France) and by a grant from the Société Française de Chirurgie Thoracique et Cardiovasculaire (Paris, France), Bourse Marc Laskar.

Competing Interests

Dr. Mongardon received consultant fees from Amomed (Vienna, Austria). Dr. Gaudard received payment from Abiomed (Aachen, Germany), Air Liquide Santé (Gentilly, France), and Abbot (Chicago, Illinois) and consultancy fees from Amomed. Dr. Matthay received payment for his institution from Roche-Genentech (San Francisco, California), from Citius Pharmaceuticals (Cranford, New Jersey) for consulting for ARDS trial design, from Novartis (Baé, Switzerland) for consulting for ARDS trial design, and from Johnson & Johnson (New Brunswick, New Jersey) and Pliant Therapeutics (San Francisco, California) for ARDS consultation. The other authors declare no competing interests.

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Appendix: ECMOSAR Investigators

Marc Pierrot, M.D., University Hospital of Angers, Angers, France, collected data, provided and cared for study patients
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Claire Fogerou-Leurent, Pharm.D., University Hospital of Rennes, Rennes, France, critically reviewed the study proposal
Yoann Launey, M.D., Ph.D., University Hospital of Rennes, Rennes, France, provided and cared for study patients
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Fanny Bounes, M.D., University Hospital of Toulouse, Toulouse, France, collected data, provided and cared for study patients
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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