Survival and Long-Term Functional Status of COVID-19 Patients Requiring Prolonged Extracorporeal Membrane Oxygenation Support

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Abstract

Rationale: Severe cases of acute respiratory distress syndrome (ARDS) may require prolonged (>28 d) extracorporeal membrane oxygenation (ECMO). In nonresolving disease, recovery is uncertain, and lung transplant may be proposed.

Objectives: This study aims to identify the variables influencing survival and to describe the functional status of these patients at 6 months.

Methods: This was a retrospective, multicenter, observational cohort study including patients requiring ECMO support for coronavirus disease (COVID-19)-related ARDS for >28 days. Multivariate analysis was performed using Cox regression in preselected variables and in least absolute shrinkage and selection operator selected variables. In a *post hoc* analysis to account for confounders and differences in awake strategy use by centers, treatment effects of the awake strategy were estimated using an augmented inverse probability weighting estimator with robust standard errors clustered by center.

Results: Between March 15, 2020 and March 15, 2021, 120 patients required ECMO for >28 days. Sixty-four patients (53.3%) survived decannulation, 62 (51.7%) were alive at hospital discharge, and 61 (50.8%) were alive at 6-month follow-up. In the multivariate analysis, age (1.09; 95% confidence interval [CI], 1.03–1.15; $P = 0.002$) and an awake ECMO strategy (defined as the patient being awake, cooperative, and performing rehabilitation and physiotherapy with or without invasive mechanical ventilation at any time during the extracorporeal support) (0.14; 95% CI, 0.03–0.47; $P = 0.003$) were found to be predictors of hospital survival. At 6 months, 51 (42.5%) patients were at home, 42 (84.3%) of them without oxygen therapy. A cutoff point of 47 ECMO days had a 100% (95% CI, 76.8–100%) sensitivity and 60% (95% CI, 44.3–73.6%) specificity for oxygen therapy at 6 months, with 100% specificity being found in 97 days.

Conclusions: Patients with COVID-19 who require ECMO for >28 days can survive with nonlimiting lung impairment. Age and an awake ECMO strategy may be associated with survival. Longer duration of support correlates with need for oxygen therapy at 6 months.

Keywords: acute respiratory distress syndrome; respiratory failure; awake; lung transplantation

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The coronavirus disease 2019 (COVID-19) has posed an unprecedented challenge to healthcare systems around the world (1). The most severe cases may require extracorporeal membrane oxygenation (ECMO). According to data from the Extracorporeal Life Support Organization Registry, more than 14,000 patients have required ECMO for COVID-19 since the pandemic began (2). The experiences described in various countries regarding the use of extracorporeal respiratory support in patients with COVID-19 typically report a longer ECMO run than in acute respiratory distress syndrome (ARDS) due to other causes. Reported survival rates also range widely, from 37.1% to 75% (3–7). This difference is due to the variations in healthcare organization systems, indication criteria, and pre-ECMO and ECMO management (8).

Variability is also evident in the measurement or interpretation of lung resilience, and this has led to the application of very different criteria for the withdrawal of extracorporeal support. According to a European survey of European ECMO centers' perceptions of the topic, definitions of prolonged treatment duration varied widely: 34% considered a duration of 14–21 days as prolonged, 30% one of 21–28 days, and 28% one of >28 days. At some centers, futility was considered after >21 days of treatment without a positive progression (9), which led to ECMO withdrawal or bridge-to-destination therapy. Bharat and colleagues recently described a series of 12 patients with COVID-19 requiring ECMO treated at five centers, for a median of 46 (interquartile range [IQR], 35–62) days of support. Patients were considered candidates for lung transplantation 4 weeks after the onset of ARDS and when a multidisciplinary team agreed on the absence of lung recovery. However, no specific signs have been identified that define a case as irreversible, and some of the explanted lungs showed potentially reversible diffuse alveolar damage rather than fibrotic changes (10). Patients requiring ECMO often present with physical and psychological limitations at 6–12 months (11, 12); however, considering the median survival of 6.2 years (13) after lung transplantation and the associated morbidity (14, 15), the overall benefits of lung transplantation in the acute phase may not outweigh the disadvantages.

The main aim of this investigation was to identify the variables that influence morbidity and survival without transplantation in patients who received prolonged ECMO support at four high-volume ECMO centers in France, Sweden, Portugal, and Spain.

Methods

Study Design and Population

This retrospective multicenter observational cohort study included data from four ECMO services (for descriptions, *see* Table E1 in the data supplement). All consecutive adult patients with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, documented by real-time reverse transcriptase–polymerase chain reaction on nasopharyngeal swabs or lower respiratory tract aspirates and admitted to the intensive care unit (ICU) with a prolonged ECMO run (i.e., ECMO for >28 days) for ARDS from March 15, 2020 to March 15, 2021, were identified from medical charts and institutional ECMO databases. The criteria for ECMO indication were those in use in the respective local protocols at each center and did not significantly differ from the EOLIA (ECMO to Rescue Lung Injury in Severe ARDS criteria) (16). Only patients requiring ECMO for ARDS were included in the analysis; those needing circulatory support and those needing respiratory support for reasons other than ARDS were excluded. Patients were followed until 6 months after the start of ECMO.

Ethical Issues and Informed Consent

The study protocol was approved by the local ethics committees at all the participating centers. The need for informed consent was waived because of the retrospective nature of the analysis and because only data available in the medical records or files were collected.

Data Collection, Variables Studied, and Objectives of the Investigation

Researchers at each participating center collected data by manual chart review and used a standardized case report form to enter data on a secure, web-based platform. Data included information on demographics, comorbidities, pre-ECMO clinical conditions, ECMO management, complications, and outcomes. Definitions of all the study variables are presented in Table E2. An awake ECMO strategy was defined as the patient being awake (Richmond Agitation Sedation Scale, 0 or −1), cooperative, and performing rehabilitation and physiotherapy with or without invasive mechanical ventilation at any time during the extracorporeal support. The main objective was to identify variables correlated with hospital survival. As secondary outcomes, we evaluated patients' functional status at 6 months and the possible relationship between ECMO duration on the need for oxygen therapy at 6 months.

Statistical Analysis

An initial descriptive analysis was performed. Variables were described using mean (standard deviation [SD]), median (IQR), or frequency (percentage). A comparative analysis was performed between survivors and nonsurvivors at hospital discharge. Differences between continuous variables were analyzed using the Kruskal-Wallis test. Differences between categorical variables were assessed using the χ^2 test or Fisher's exact test. Global survival analysis was performed using the Kaplan-Meier estimator, from ECMO initiation to 6-month follow-up. For qualitative variables, a Kaplan-Meier survival curve was estimated for each category, and a log-rank test was used to assess differences between categories. Quantitative variables were adjusted to a univariate Cox model.

For multivariate analysis, Cox regression was used including the following variables selected on the basis of the literature: age at ECMO initiation, immunocompromised status, mechanical ventilation duration before ECMO initiation, driving pressure before ECMO initiation, and awake strategy (11, 17–19). To account for bias in variable selection, the regression was repeated using a least absolute shrinkage and selection operator (LASSO) analysis, which was cross-validated and subjected to a final LASSO analysis to select the optimal variables among those completed in >90% of patients.

A *post hoc* descriptive analysis of patients who were treated with an awake strategy against the rest of the population was performed with the same methodology as the initial descriptive analysis. To account for both confounders and differences in awake strategy usage by centers, treatment effects of the awake strategy were estimated using an augmented inverse probability weighting estimator with robust standard errors clustered by center: the differences in the baseline characteristics of the awake and nonawake group were used for fitting a propensity score model for treatment

assignment, and the LASSO selected variables were used for the outcome model for both treated and untreated patients. Each outcome was then weighted by the propensity score from the previous step to produce a weighted average of both models.

To analyze the predictive power of ECMO duration to anticipate the need for oxygen therapy at 6 months, a receiver operating characteristic curve analysis was performed. A cutoff point was obtained using Youden's index (point of maximal sensitivity and specificity). An adequate area under the curve (AUC) was considered to be ⩾70%. Statistical analyses were performed using the statistical program R (R version 4.1.3, 2022-03-10, The R Foundation for Statistical Computing) or Stata (Stata/BE 17.0, StataCorp LLC). Significance was defined as a P value < 0.05.

Results

Characteristics of Study Patients

During the study period, among the total of 352 patients with COVID-19 supported with ECMO at the four centers, 124 (35.2%) required extracorporeal respiratory support for >28 days. Of these, three underwent lung transplantation and were excluded (Figure E1), and one was excluded because of missing follow-up data. Finally, a total of 120 patients were included in the analysis. The overall temporal distribution of cases by initiation date and center during the study period can be seen in Figure E2.

Baseline characteristics of the whole population are summarized in Table 1. One hundred eleven patients (92.5%) were supported with venovenous ECMO. Three patients were supported with venoarterial ECMO with a jugulo-femoral configuration, four required conversion to venovenoarterial ECMO because of acute cor pulmonale, and two were initially cannulated as venoarterial for instability and later converted to venovenous. The most frequent cannulation strategy was femoro-jugular (82 patients, 68.3%), followed by femoro-femoral (24 patients, 20%) and jugulo-femoral (13 patients, 10.8%). Single-site double-lumen cannulae were not used. Median ECMO duration was 46 (IQR, 35–62) days, with the longest ECMO run lasting 197 days. Hemorrhagic complications were frequent, with 94 (78.3%) patients presenting bleeding that required intervention or transfusion. Twenty-four (20%) suffered from hemorrhagic shock. Infectious complications were also frequent, with 112 (93.3%) patients having at least one episode of ventilator-associated pneumonia and 65 (54.2%) having at least one episode of bacteremia during the ECMO run. Regarding therapies provided during ECMO, 63 (52.5%) patients were proned on ECMO, 60 (51.7%) required at least one circuit change (averaging 1.5 [SD, 2.5] circuit changes per patient), and an awake ECMO strategy was implemented in 33 (27.5%). In these patients, Richmond Agitation Sedation Scale 0 was achieved for the first time after a mean of 24 (IQR, 10–41) days of support. Regarding the ventilation status of patients receiving an awake ECMO strategy, the majority (28; 84.8%) remained under mechanical ventilation during the ECMO run, three were never intubated, and two were completely released from mechanical ventilation before ECMO decannulation.

Table 1. Main characteristics of our study population

Variable	(*N* = 120) median (IQR) *n* (%)
Age, yr	52.8 (46–60)
Sex, male	94 (78.3%)
BMI	29.4 (26.7–32.8)
Hypertension	56 (46.7%)
Diabetes	39 (32.5%)
Preexisting cardiac disease and/or ischemic myocardiopathy	7 (5.8%)
Preexisting respiratory disease, COPD, or asthma	11 (9.2%)
Immunocompromise	10 (8.3%)
Preexisting renal insufficiency	2 (1.7%)
MV duration before ECMO	5 (2–8)
Prone before ECMO	108 (92.3%)
P/F ratio before ECMO	65 (54–80)
pH before ECMO	7.3 (7.2–7.4)
Pco_2 before ECMO	57 (49–65)
Driving pressure before ECMO	18 (16–21)
Respiratory rate before ECMO	29.5 (25.8–30)
PEEP before ECMO	12 (9–14)
Bacterial respiratory coinfection before ECMO	65 (54.2%)
Severe bleeding	24 (20%)
New-onset VAP	112 (93.3%)
Median time on-ECMO, d	46 (35.2–62)
Hospital survival	62/120 (51.7%)

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; ECMO = extracorporeal membrane oxygenation; IQR = interquartile range; MV = mechanical ventilation; PEEP = positive end-expiratory pressure; P/F = arterial partial pressure of oxygen to fraction of inspired oxygen ratio; VAP = ventilator-associated pneumonia.

Survival

The overall ECMO results for all patients with COVID-19 requiring ECMO at the participating centers during the study period are displayed in Table E3. Of the 120 patients needing a prolonged ECMO run, 64 (53.3%) survived decannulation, 62 (51.7%) were alive at hospital discharge, and 61 (50.8%) were alive at 6-month follow-up. In the multivariate analysis, age and an awake ECMO strategy were found to be associated with hospital survival (Table 2 and statistical supplement in the data supplement). Comparisons between the patients with an awake strategy and the rest of the cohort can be seen in Table 3.

In the 56 patients on ECMO who died, the most common cause of death was septic shock (27; 48.2%), followed by support withdrawal due to refractory respiratory failure (15; 26.8%). Information about patients who died after withdrawal of the support is shown in Table E4.

Functional Status at 6 Months

Among 61 6-month survivors, 43 (70.5%) were at home without any respiratory support (Table 4). Dyspnea according to the Medical Research Council Dyspnoea Scale was reported in 34 patients (55.7%); 12 (35.3%) presented no or mild dyspnea, and five (14.7%) presented severe dyspnea. Return-to-work information was obtained for 48 patients, and 8 (16.7%) were actively working. Data on neuropsychological status were obtained in 31 patients. Of those, 15 (48.4%) reported sequelae, varying from

Table 2. Prediction models for hospital mortality according to statistical or clinical criteria

LASSO-selected Variables				Predefined Variables (Common in the Literature)			
Predictor	**Hazard Ratio**	**CI**	***P* Value**	**Predictor**	**Hazard Ratio**	**CI**	***P* Value**
Age	1.066	1.03–1.10	0.001	Age	1.09	1.03–1.15	0.002
P/F ratio before ECMO	0.98	0.97–1	0.064	Immunosuppressed	2.56	0.33–22.93	0.368
Driving pressure	1.03	0.96–1.10	0.398	Driving pressure	1.07	0.97–1.19	0.206
V_T before ECMO	1	0.99–1	0.197	Duration of MV before ECMO	1.04	0.94–1.15	0.417
Awake strategy	0.3	0.10–0.87	0.027	Awake strategy	0.14	0.03–0.47	0.003
Observations, 99; R^2 Nagelkerke, 0.255				Observations, 103; R^2 Tjur, 0.230			

Definition of abbreviations: CI = confidence interval; ECMO = extracorporeal membrane oxygenation; LASSO = least absolute shrinkage and selection operator; MV = mechanical ventilation; P/F = arterial partial pressure of oxygen to fraction of inspired oxygen ratio; V_T = tidal volume.

anxiety to peripheric neuropathy and ataxia. Respiratory function tests were performed in 38 patients and are detailed in Table E5.

Duration of ECMO Support and Oxygen Therapy at 6 Months

Duration of ECMO support was found to be a good predictor of oxygen therapy requirement at 6 months, with an AUC of 0.837 (95% confidence interval [CI], 0.735–0.939) (Figure 1). A cutoff point of 47 ECMO days had a 100% (95% CI, 76.8–100)

Table 3. Comparisons between patients who received and did not receive an awake strategy

	Awake Strategy (*n* = 33) *n* (%) median (IQR) mean (SD)	**Rest of the Population (*n* = 87) *n* (%) median (IQR) mean (SD)**	***n***
Age	53 (45–59)	54 (48–60)	120
Sex, male	29 (87.9%)	66 (75.9%)	120
BMI	29.3 (26–32.3)	29.7 (27–33.6)	120
Hypertension	16 (48.5%)	39 (44.8%)	120
Diabetes mellitus	6 (18.2%)	33 (37.9%)	120
Ischemic cardiomyopathy	5 (15.2%)	2 (2.3%)	120
COPD or asthma	3 (9.1%)	8 (9.2%)	120
Immunocompromise	5 (15.2%)	5 (5.8%)	120
Chronic kidney disease	2 (6.1%)	0	120
MV days before ECMO	4 (1–7)	6 (2–9)	119
Prone position before ECMO	25 (83.3%)	84 (95.4%)	117
P/F ratio before ECMO	65 (52–85)	63.5 (55–80)	120
pH before ECMO	7.32 (0.1)	7.31 (0.1)	112
P_{CO_2} before ECMO	55.5 (45.8–64)	58 (49–67.9)	113
Driving pressure before ECMO	18 (6.5)	19.2 (4.4)	103
Respiratory rate before ECMO	30 (26–35)	29.5 (25–30)	116
PEEP before ECMO	11 (8–14)	12 (10–14)	111
Lactate before ECMO	1.5 (1–1.9)	1.6 (1.3–2.5)	102
Hemodynamic component of SOFA score	3 (1–4)	1 (0–4)	120
AKI before ECMO	6 (18.2%)	27 (31%)	120
Required RRT before ECMO	2 (6.1%)	2 (2.3%)	120
Coinfection	14 (42.4%)	42 (48.3%)	120
Bleeding during ECMO	26 (78.8%)	67 (77%)	120
Hemorrhagic shock	11 (33.3%)	13 (14.9%)	120
RRT during ECMO	16 (48.5%)	30 (34.5%)	120
Prone position during ECMO	3 (9.1%)	61 (69.3%)	120
VAP during ECMO	29 (87.9%)	83 (95.4%)	120
Bacteremia	14 (42.4%)	52 (59.7%)	120
Required a circuit change	27 (81.8%)	33 (37.9%)	120
Accidental decannulation	0	2 (2.3%)	120
ECMO duration	50 (41–64)	44.5(34–61)	120
MV duration	76 (50–98)	59 (45–77)	120
ICU length of stay	78 (64–107)	61 (49–82)	120
Hospital survival	26 (78.8%)	36 (41.4%)	120
Required discharge to a rehabilitation center	15 (68.2%)	29 (80.6%)	58

Definition of abbreviations: AKI = acute kidney injury; BMI = body mass index; COPD = chronic obstructive pulmonary disease; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IQR = interquartile range; MV = mechanical ventilation; P_{CO_2} = carbon dioxide partial pressure; PEEP = positive end expiratory pressure; P/F = arterial partial pressure of oxygen to fraction of inspired oxygen ratio; RRT = renal replacement therapies; SD = standard deviation; SOFA = Sepsis-related Organ Failure Assessment; VAP = ventilator-associated pneumonia.

sensitivity and 60% (95% CI, 44.3–73.6) specificity for oxygen therapy requirement at 6 months, whereas 100% specificity was found at 97 days (Figure E3). Interestingly, the duration of ECMO support was not a good predictor of mortality (AUC, 0.515; 95% CI, 0.42–0.604).

Discussion

We present a multicenter observational study on patients with COVID-19 needing prolonged ECMO support. Our results show that more than half of this population may be alive at 6 months and that younger age and an awake ECMO strategy may be associated with survival to 6 months.

Critically ill patients with COVID-19 receiving ECMO therapy usually need a longer period of extracorporeal support than other patients with ARDS (20), with a significant percentage of the population needing prolonged ECMO. After >4 weeks of support, doubts arise about the potential of the lung to recover, and a lung transplant may be seen as the only option for survival. A recent study described the experience of six high-volume transplant centers in this context (10). Results after lung transplantation were regarded as acceptable, with all the patients except one alive after a mean follow-up of 3 months. However, major concerns remain about the criteria used for defining irreversible lung impairment, even if performed by a multidisciplinary team in a population of patients with severe ARDS lasting >4 weeks. Lung transplant recipients require chronic immunosuppression and close ambulatory follow-up and present a high risk of hospital readmission and reduced life expectancy and quality of life (14). In our study, we show that a considerable proportion of patients with COVID-19 who required ECMO for >4 weeks can be successfully decannulated and discharged home. The majority of them did not require oxygen support at 6 months and presented a nonlimiting respiratory function (defined as Global Initiative for Chronic Obstructive Lung Disease > 2 in 32 of 38 survivors with available respiratory function tests). At follow-up, 8 of 48 patients (16.7%) had returned to work, a notably high rate in view of the long hospital stay (102 [IQR, 76–131] d). In comparison, in lung transplant recipients, rates of return to work at any point after transplantation ranges between 7.4 and 50.8% (21) but is only 4.9% during the first year (22).

Fifteen of our patients died of refractory respiratory failure, and another 14 still required respiratory support or supplementary oxygen at 6 months. Even though lung resilience appears to be greater than previously hypothesized, some of the patients who require prolonged ECMO support are likely to develop terminal lung disease. Early identification of these patients is clinically important, as the only long-term

Table 4. Status at 6 months

Status at 6 mo	*n* (%)
Deceased	59 (49.2)
Still on MV	
ICU	1 (0.8)
Subacute care center	2 (1.7)
Conventional ward or rehabilitation center	
With oxygen support	3 (2.5)
Without oxygen support	4 (3.3)
Home	
With oxygen support	8 (6.7)
Without oxygen support	43 (35.8)

Definition of abbreviations: ICU = intensive care unit; MV = mechanical ventilation.

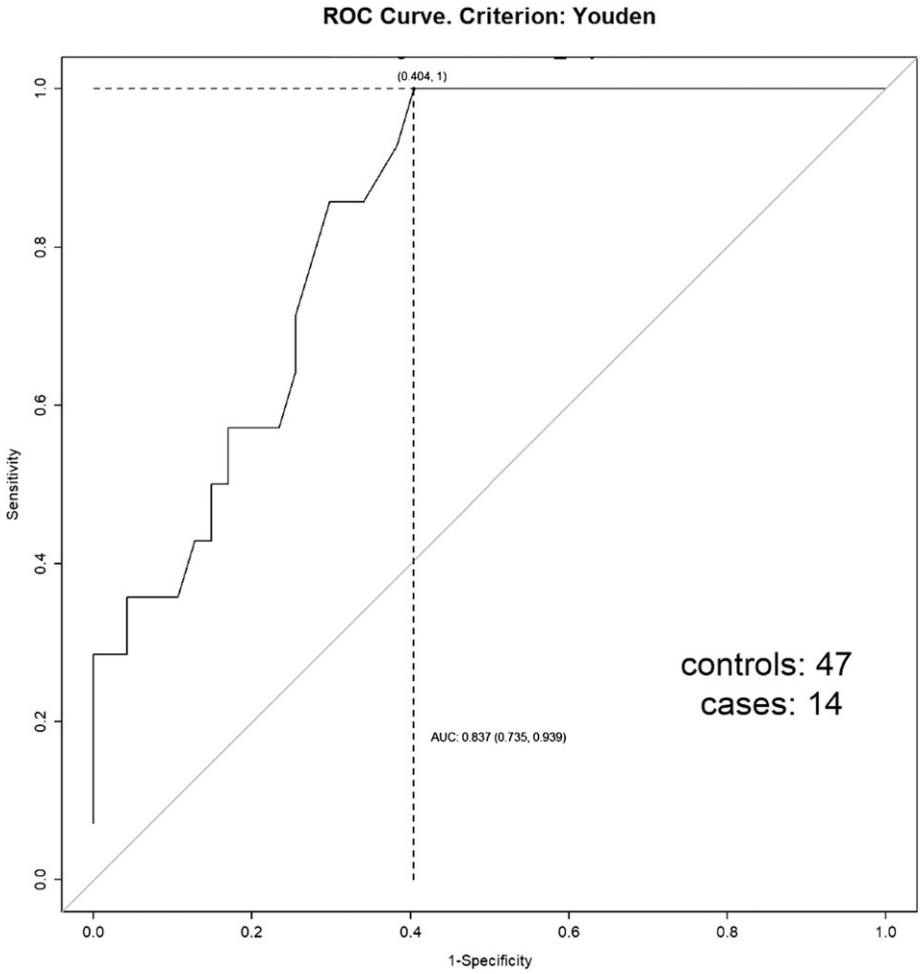

Figure 1. Receiver operator characteristic (ROC) curve for extracorporeal membrane oxygenation duration as a predictor of oxygen therapy at 6 months. Diagonal line indicates chance level. Vertical line indicates maximum value of Youden's index for the ROC curve. AUC = area under the curve.

survival option will be lung transplantation. However, in a case series of eight patients requiring ECMO support for >30 days who were formally presented as lung transplant candidates, four survived without transplantation (23). The clinical implications of lung transplantation have been discussed at length above, but there are also strong ethical implications. Mortality on the waiting list must be considered when including candidates with a significantly higher risk of worse outcomes after transplantation, as is the case here (24). This may be especially controversial in a pandemic period, in which the donor pool is notably reduced. In this regard, a potential improvement in the native lung function sufficient to allow hospital discharge and subsequent inclusion (if needed) in the conventional lung transplant evaluation should encourage clinicians to continue support. Interestingly, we found that patients who require ECMO for >47 days are likely to suffer longer-term respiratory impairment, with the need for home oxygen therapy at 6 months. In our view, this cutoff point should be used as a reminder of the possibility of nonrecovery and may be used as a trigger for initial contact with an experienced transplant team for assessment and advice. However, it must be noted that oxygen therapy in itself is not an indication for lung transplant and that complete recovery has been observed in patients supported with ECMO up to 97 days in this very same cohort.

Age and an awake ECMO strategy were found to be associated with hospital mortality. Age has already been identified as a factor strongly related to mortality, which rises notably in patients >65 years old (20). This variable should be considered when deciding whether to continue or withdraw ECMO and whether to propose lung transplantation (at many centers, the eligibility of patients aged ⩾65 years for lung transplant is debated). For their part, the duration of mechanical ventilation before ECMO initiation and other common parameters of severity failed to predict death, as previously reported in the largest meta-analysis of ECMO in patients with COVID-19 to date (25). In contrast, an awake ECMO strategy was found to be associated with survival, as >75% of the cohort of patients receiving this treatment were alive at 6 months. Sedation withdrawal and active rehabilitation are feasible in patients with extracorporeal respiratory support, given that ECMO offers an efficient way of maintaining an adequate gas exchange with the potential of titrating the support according to the patient's oxygen consumption (26). In contrast, patients with the same degree of respiratory impairment and without extracorporeal support often need aggressive mechanical ventilation despite prone positioning and deep sedation (16). Heavy sedation and immobility in critically ill patients are associated with a higher risk of ICU death and poor functional recovery in survivors (27). Besides the possible benefits of the minimization of ventilator-associated pneumonia (e.g., the ability to cough) and ventilator-induced lung injury, an awake ECMO strategy has other positive effects that should not be underestimated. For instance, direct interaction with relatives optimizes cognitive status and minimizes the incidence of delirium (28). Furthermore, the ability to communicate with the patient opens up the possibility of diagnosing by exploring symptoms, thus refining the team's understanding of the clinical scenario and guiding the decision of whether or not to continue therapy.

Despite these advantages, an awake ECMO strategy has associated risks that have impeded its inclusion in the management of patients with ARDS requiring ECMO support (29). Besides cannula displacement, one of the most important risks of this strategy is an uncontrollably high respiratory drive and effort that may perpetuate or worsen lung inflammation even further (30). A recent short case series including 18 patients with COVID-19 with severe respiratory failure (mean partial pressure of oxygen to fraction of oxygen in inhaled air ratio of 64 mm Hg) who received ECMO support instead of full sedation and intubation reported that 78% had to be finally intubated for this reason and that these patients had lower survival than the overall cohort (19). However, the clinical setting of our study is different: we excluded the acute phase by focusing on patients needing prolonged ECMO support and defined an awake strategy as one in which the patient is cooperative and consciously performs physical therapy regardless of their mechanical ventilation status. In this way, we minimized selection bias by excluding patients who died during the first 28 days of support and would never have been awakened. Moreover, the first awake ECMO trial of patients receiving an awake strategy was performed before Day 28 in more than half of the patients, thus decreasing the risk of immortal time bias inherent to the observational nature of the study. Interestingly, we found that the severity of the initial clinical condition before cannulation of the two cohorts (with or without an awake ECMO strategy) was equivalent.

Strengths and Limitations

The main strengths of the study are its multicenter design, which allowed us to identify a high number of prolonged ECMO runs, and its solid internal validity, thanks to the use of detailed records from four high-volume centers. There are, however, some limitations. First, its observational and retrospective nature generates a risk of indication, selection, or other biases; in the specific case of patients receiving an awake strategy and the rest of the cohort, measures not necessarily represented by pre-ECMO severity of illness may play a confounder role, and survivor treatment bias may be present. Second, the follow-up data are heterogeneous, as most of the patients' follow-up was performed in the referring centers, and they are missing in almost half of the 6-month survivors. Third, the follow-up period was only 6 months; patients with severe disease and extended hospital admission will likely require longer for an accurate assessment of their final respiratory function. Last, these patients were treated at four centers with experience in the management of ARDS and ECMO, a circumstance that may limit the generalizability of our results, especially regarding the implementation of the awake ECMO strategy. In addition, COVID-19 results may not be generalizable to ARDS of other causes, and the predictor models used in the study have not been externally validated.

Conclusions

Nearly half of patients with COVID-19 who require ECMO support for >28 days can survive with nonlimiting lung impairment. Further research should be directed both at identifying the specific characteristics of patients in whom transplantation is the only salvage therapy and the optimal moment to implement it and at exploring in more detail the possible benefits of the awake ECMO strategy, in this and other clinical scenarios. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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