ORIGINAL ARTICLE

# One-Year Mental and Physical Health Assessment in Survivors after Extracorporeal Membrane Oxygenation for COVID-19–related Acute Respiratory Distress Syndrome

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## Abstract

**Rationale:** Long-term outcomes of patients with coronavirus disease (COVID-19)–related acute respiratory distress syndrome treated with extracorporeal membrane oxygenation (ECMO) are unknown.

**Objectives:** To assess physical examination, pulmonary function tests, anxiety, depression, post-traumatic stress disorder and quality of life at 6 and 12 months after ECMO onset.

**Methods:** Multicenter, prospective study in patients who received ECMO for COVID-19 acute respiratory distress syndrome from March to June 2020 and survived hospital discharge.

**Measurements and Main Results:** Of 80 eligible patients, 62 were enrolled in seven French ICUs. ECMO and invasive mechanical ventilation duration were 18 (11–25) and 36 (27–62) days, respectively. All were alive, but only 19/50 (38%) returned to work and 13/42 (31%) had recovered a normal sex drive at 1 year. Pulmonary function tests were almost normal at 6 months, except for $D_{LCO}$, which was still impaired at 12 months. Mental health, role-emotional, and role-physical were the most impaired domain compared with patients receiving ECMO who did not have COVID-19. One year after ICU admission, 19/43 (44%) patients had significant anxiety, 18/43 (42%) had depression symptoms, and 21/50 (42%) were at risk for post-traumatic stress disorders.

**Conclusions:** Despite the partial recovery of the lung function tests at 1 year, the physical and psychological function of this population remains impaired. Based on the comparison with long-term follow-up of patients receiving ECMO who did not have COVID-19, poor mental and physical health may be more related to COVID-19 than to ECMO in itself, although this needs confirmation.

**Keywords:** venovenous–extracorporeal membrane oxygenation; quality of life; follow-up studies; COVID-19; acute respiratory distress syndrome

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Venovenous (VV) extracorporeal membrane oxygenation (ECMO) is now well established as a part of the management of severe acute respiratory distress syndrome (ARDS) (3–5). This technology applied early in a selected population is associated with a reduction in mortality if combined with ultraprotective ventilation (4, 5). Before the ongoing coronavirus disease (COVID-19) pandemic, long-term assessment of the quality of life (QoL) and pulmonary function of these patients with severe disease were considered almost similar to patients with ARDS without ECMO (3, 6–8), although QoL was consistently lower than the general age-matched population (9, 10). During the initial COVID-19 outbreak in 2020, worldwide ICUs had to handle a surge of critically ill patients (11). Among them, a small proportion needed ECMO for severe ARDS refractory to conventional care, including prone positioning. In highly selected patients, national and international cohorts reported that the survival of ECMO-rescued extremely sick patients with COVID-19 was similar to that reported in recent studies on ECMO support for non-COVID severe ARDS (1, 2). However, in contrast with other causes of ARDS, ECMO duration and ICU and hospital length of stay were much longer. For instance, mean (interquartile range) ECMO support and ICU length of stay were 20 (10–40) and 36 (23–60) days, respectively, in a single-university cohort of 83 patients on ECMO (1). In that context, a long-term follow-up seems essential.

Indeed, patients who recovered from COVID-19 were found to improve lung and physical capacity during the first year, although these studies involved very few patients on mechanical ventilation and no patients on ECMO (12, 13). For these patients, we also need to evaluate COVID-19's potential pulmonary, physical, and psychological sequelae. Herein, we report the long-term pulmonary, physical, and psychological functions of these survivors who underwent the most severe forms of COVID-19–related ARDS.

## Methods

### Settings of the Study

This study was performed during 14 months in seven ICUs, including four in Paris and the greater area, in six French University Hospitals. The Sorbonne-University Ethics Committee (CER-2021-01) approved the protocol. Agreement from the patient to use demographic, physiological, hospital-outcome, QoL assessment, and pulmonary function data was obtained. All consecutive adult patients with severe ARDS supported by VV-ECMO during the first outbreak of COVID-19 (from March 1 to June 15, 2020) and alive at hospital discharge were included.

### Initial Hospitalization

Demographic information, including the type of work, family status, marital status, patient medical history, illness evolution, and treatment received during ICU stay were collected from the medical records. Briefly, we collected ECMO duration, ICU and hospital length of stay, pre-ECMO Sequential Organ Function Assessment score, tracheostomy, and prone positioning during ECMO.

### Long-Term Follow-Up

All patients were contacted by phone by theirreferring physician or their pulmonary service to plan their 6- and 12-month follow-up. Two medical consultations in theambulatory setting were performed 6–8months and 12–14 months after ICU admission (i.e., from October 1 to December 20, 2020, and from March 1 to July 17, 2021), respectively.

***General assessment.*** A general clinical examination was performed at 6 and 12 months by a pulmonologist or an intensivist. Patients were asked whether they complain about symptoms relative to dyspnea, fatigue, pain, physical limitations, sexual dysfunction, or psychological issues. If any, patients were asked whether symptoms existed before COVID-19 infection. The return to their initial work (i.e., pre-COVID infection) and sports practice were also assessed at 6 and 12 months, respectively. The general physical examination also focused on ECMO or prone positioning–related complications, such as a peripheral neurologic deficit, nerve compression, vascular complication, or physical scars with severe physical, psychological, and social consequences. Patients were evaluated for their QoL with the French version of the 36-Item Short-Form Health Survey questionnaire (SF-36) (14). For the eight items, higher scores denote a better health-related QoL. The eight domains were summarized into two overall domains, total physical component summary and mental component summary. Fatigue was assessed with the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) (15). A higher FACIT-F score indicates less fatigue (15). Sexual dysfunction was assessed with a simple yes or no question: "Is your sex drive the same as before ICU admission?" Due to several prolonged lockdowns and movement restrictions in our country during the study period, the questionnaires could be completed by phone if the patient was unable to come to the hospital.

***Pulmonary assessment.*** Standard pulmonary function tests, including spirometry, $D_{LCO}$, and a 6-minute-walk test (16), were performed. In addition, long-term survivors' pulmonary symptoms were

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Data sharing: Individual patient data reported in this article will be shared after deidentification (text, tables, figures, and appendices), beginning 6 months and ending 2 years after article publication, to researchers who provide a methodologically sound proposal and after approval of the COVID-ICU internal scientific committee. Proposals should be addressed to matthieu.schmidt@aphp.fr. To gain access, data requestors will need to sign a data access agreement.

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

## At a Glance Commentary

**Scientific Knowledge on the Subject:** The long-term pulmonary, physical, and psychological functions of those survivors with the most severe forms of COVID-19–related ARDS treated with ECMO are unknown.

**What This Study Adds to the Field:** Despite the partial recovery of lung function tests at 1 year, the physical and psychological function of 62 patients supported by ECMO for severe ARDS during the first surge of the pandemic was still impaired, with consequences on their quality of life. Noticeably, almost 50% of them reported persistent long-term psychological and emotional sequelae, only 40% had returned to work, and only one-third had recovered a normal sex drive. Based on the comparison with long-term follow-up of patients without COVID-19 receiving ECMO, poor mental and physical health may be more related to COVID-19 than to ECMO in itself, although this needs confirmation.

evaluated with the St. George's Respiratory Questionnaire (SGRQ) (17). With a score ranging from 0 to 100, a higher SGRQ score indicated more limitations in three respective domains (activity, impact, and symptoms) (17). As part of the standard of care, chest computed tomography (CT) was performed at 6 months and 1 year. An experienced thoracic radiologist (S.B.), blinded to the time of assessment, patient clinical information, laboratory findings, or clinical progress, reviewed all CT scans at the end of the study period. CT scans were assessed based on key features defined by the Fleischner Society (18) to describe and quantify the lung patterns. Distribution of persistent ground-glass opacity, an extension of pulmonary opacities, and fibrosis-like lesions was evaluated over time, respectively, on ECMO, at 6 and 12 months (19). Details of the CT analysis are provided in the supplementary data.

***Physical assessment.*** The evaluation of muscle strength by the Medical Research Council scale (MRC) (20) was performed at 6 and 12 months.

***Psychological assessment.*** Anxiety and depression symptoms were assessed with the Hospital Anxiety and Depression Scale (HADS) (21), with respective HADS-anxiety and HADS-depression subscale scores ⩾8/21 considered clinically significant (21). Post-traumatic stress disorder (PTSD)-related symptoms were assessed with the PTSD Checklist for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Post-Traumatic Stress Disorder Checklist for DSM-5 (PCL-5) (22). A patient with a PCL-5 score ⩾38/80 was considered at risk for PTSD (22).

### Comparison with Other Cohorts

Our patients' characteristics, outcomes, long-term QoL, and psychological assessments were compared with 67 survivors of non-COVID ARDS on ECMO evaluated 17 months after ECMO initiation. Among these 67 patients, hospitalized in three French ICUs between 2008 and 2012, ARDS etiologies were bacterial infection (42%), 2009 A($H_1N_1$) influenza (31%), peri-/postoperative (19%), and other (8%). Detailed characteristics and outcomes of the latter cohort are published elsewhere (10). In addition, SF-36 scores were also compared with 51 patients with COVID-19–related ARDS without ECMO at 12 months (23). In this latter cohort, Latronico and colleagues followed 114 patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) wild type (23). Fifty (44%) and 41 (36%) patients had moderate and severe ARDS. One-year outcomes were obtained in 51 of them.

### Data Analyses

Comparisons of anxiety, depression, PTSD, and QoL at 12 months in our population with a cohort of non–COVID-19–related ARDS treated with ECMO (10) were performed using Student's *t* or Mann-Whitney tests, as appropriate. To assess potential correlations between $D_{LCO}$, TLC, and FEV with SF-36 domains (vitality, pain), SGRQ sections (symptoms, activity, and impact), and fatigue, bivariate Spearman correlation tests were performed. $P$ value $<$ 0.05 was considered statistically significant, and tests were two-sided. Results were expressed as median (interquartile range) or *n* (%). Analyses were performed using Prism 7.0 (GraphPad Software) software.

## Results

### Study Population

During the first surge of COVID-19 in France, 132 patients were treated with ECMO in the seven participating ICUs. Fifty-two (39%) died during their hospital stay. Among the 80 patients discharged alive from the hospital, 62/80 (78%) were assessed for long-term follow-up at 6 and 12 months (*see* Figure E1 in the online supplement). Among the 18 patients not included in the follow-up, 12 refused to participate and 6 were limited by travel restrictions and curfews. Characteristics of the 62 patients included and those from the 18 patients not included at ECMO initiation are given in Tables 1 and E1, respectively. Baseline characteristics did not differ between these two groups except for hospital length of stay. Briefly, their median age was 47 (interquartile range, 40–61) years, median body mass index was 32 (28–36) kg/$m^2$, and median Simplified Acute Physiology Score II was 45 (32–54) at ICU admission. Most patients had no major comorbidity, and all except two had a full-time job before ICU admission. During their ICU stay, 59 (95%) patients were proned on ECMO, and 20 (32%) underwent renal replacement therapy. ECMO duration was 18 (11–25) days, and they spent 43 (33–62) and 85 (29–112) days in ICU and the hospital, respectively. Noticeably, two patients were still hospitalized in an acute rehabilitation center at 6 months, whereas only one remained at 12 months.

### General, Respiratory, and Physical Assessments

The general, physical, and respiratory assessments are presented in Table 2 and Figure 1. At 6 months, only 13/62 (20%) of the patients had returned to their initial work (19/50 [38%] at 12 mo), and only 16/42 (38%) reported a sex drive similar to before COVID-19 (13/42 [31%] at 1 yr). Twenty-two of 35 (63%) and 21/41 (51%) survivors suffered from significant fatigue (i.e., FACIT-F ⩽ 35). Lung function, expressed by FVC, FEV, and FEV/FVC, was almost normal 6 months after ICU admission. However, $D_{LCO}$ was still impaired at 12 months, despite a slight improvement compared with the 6-month evaluation. Only two patients still suffered from obstructive airway disease at 6 months, which persisted at 1 year. Briefly, after 1 year

**Table 1.** Clinical Characteristics of the 62 Survivors of ECMO Enrolled in the Long-Term Follow-Up Assessment, 67 Patients with Non–COVID-19–related ARDS on ECMO (10), and 51 Patients with COVID-19–related ARDS without ECMO (23)

| | Original Cohort | Cohorts Previously Published | |
|---|---|---|---|
| | COVID-ARDS on ECMO (*n* = 62) | Non-COVID ARDS on ECMO (*n* = 67) (10) | COVID-ARDS without ECMO (*n* = 114)* (23) |
| Age, yr | 47 (40–55) | 37 (28–50) | 60 (52–66) |
| Male | 45 (72) | 41 (61) | 88 (77) |
| Single status | 10 (16) | — | — |
| Full-time job before hospitalization | 60 (98) | 57 (85) | — |
| Body mass index, kg/m$^2$ | 32 (28–36) | 29 (25–36) | 27 (24–31) |
| Comorbidities | | | |
| Hypertension | 22 (34) | — | — |
| Diabetes | 17 (26) | 4 (6) | — |
| Immunocompromised status | 2 (2) | 10 (15) | — |
| Chronic respiratory disease (i.e., asthma/COPD) | 8 (11) | 11 (16) | — |
| Ischemic cardiomyopathy | 3 (3) | — | — |
| Berlin ARDS definition | | | |
| Mild | 0 | 0 | 4 (4) |
| Moderate | 0 | 0 | 50 (44) |
| Severe | 62 (100) | 67 (100) | 41 (36) |
| In ICU | | | |
| SAPS II | 45 (32–54) | 51 (40–61) | 29 (25–35) |
| Pre-ECMO SOFA score | 11 (8–12) | 12 (9–14) | — |
| Time from intubation to ECMO, d | 4 (2–6) | 5 (1–9) | — |
| Tracheostomy | 29 (46) | 49 (73) | 36 (32) |
| Renal replacement therapy | 20 (32) | 29 (43) | — |
| Adjunct ARDS therapies before ECMO | | | |
| Prone position | 59 (95) | 39 (58) | 17 (16) |
| Continuous neuromuscular blockades | 60 (97) | 61 (91) | — |
| Inhaled nitric oxide | 19 (31) | 61 (91) | 4 (4) |
| Almitrine | 1 (2) | 7 (10) | — |
| Adjunct ARDS therapies during ECMO | | | |
| High-dose corticosteroids† | 15 (24) | 12 (18) | — |
| Prone position | 50 (81) | 0 (0) | — |
| Continuous neuromuscular blockades | 62 (100) | 67 (100) | — |
| Outcomes, d | | | |
| ECMO duration | 18 (11–25) | 15 (8–30) | — |
| Invasive mechanical ventilation duration | 36 (27–62) | 42 (25–69) | 10 (8)‡ |
| ICU length of stay | 43 (33–62) | 45 (29–72) | 12 (7–21) |
| Hospital length of stay | 85 (29–112)§ | 74 (43–112) | 29 (20–45) |

*Definition of abbreviations*: ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease; ECMO = extracorporeal membrane oxygenation; SAPS II = Simplified Acute Physiology Score II; SOFA = Sequential Organ-Function Assessment.

Data are presented as median (interquartile range) or *n* (%) unless otherwise noted.

*A total of 51/114 patients were followed at 1 year.

†High-dose corticosteroids: methylprednisolone >1 mg/kg.

‡Mean (SD).

§Available in 61 patients, as 1 patient was still in an acute rehabilitation center at 12 months.

of follow-up, 2/38 (5%) had an obstructive syndrome (FEV/FVC < 70%), 8/38 (21%) patients had a restrictive syndrome (TLC < 80% predicted), and 22/38 (58%) had a decreased $D_{L_{CO}}$ (<80%). Noticeably, four and three patients still needed oxygen at 6 and 12 months, respectively. Respiratory-related QoL assessed by SGRQ did not improve significantly over time (Figure 1), and SGRQ values reported in our patients with COVID-19 were not different from those reported by 67 patients with non-COVID ARDS treated by ECMO (Table E2).

One year after ICU discharge, TLC and FEV were inversely correlated with SGRQ symptoms (including dyspnea and cough) ($\rho = -0.68$; $P < 0.001$, and $\rho = -0.66$; $P < 0.001$, respectively). Impaired $D_{L_{CO}}$ was significantly correlated with fatigue symptoms ($\rho = 0.6$; $P = 0.001$) and SF-36 Pain ($\rho = 0.65$; $P < 0.001$), whereas fatigue was correlated with SGRQ symptoms ($\rho = -0.40$; $P = 0.02$), SF-36 Pain ($\rho = 0.69$; $P < 0.001$), and SF-36 Vitality ($\rho = 0.82$; $P < 0.001$).

Forty-six and 35 patients had CT at 6 and 12 months, respectively. The distribution of the number of patients with specific patterns on CT is reported in Figure 2. Briefly, the extent of any pulmonary opacities and ground-glass opacities decreased in quantity after ICU discharge in most of the patients. CT scan evolution of an illustrative patient is shown in Figure E2. Noticeably, fibrotic-like changes were the predominant CT pattern observed at 6 and 12 months.

Muscle recovery assessed by the MRC scale was good at the 6-month evaluation (MRC score, 60 [57–60]) as well as the distance measured during the 6-minute-walk test. However, seven and four patients still

**Table 2.** General, Physical, and Pulmonary Assessments at 6 and 12 Months in ECMO-rescued Patients with Severe ARDS due to COVID-19

| | At 6 mo ($n = 62$) | At 12 mo ($n = 62$) |
|---|---|---|
| Still in an acute rehabilitation center | 2 (3) | 1 (2) |
| Back to their initial work | 13 (20)* | 19 (38)† |
| Sport practice | 9 (14)* | 11 (23)‡ |
| Oxygen requirement | 4 (6)* | 3 (5)* |
| Evaluation of muscle strength (MRC scale) | 60 (57–60)§ | 60 (57–60)§ |
| Similar sex drive as before COVID-19 | 16 (38)‖ | 13 (31)‖ |
| Lung function tests | | |
| TLC, % predicted | 84 (68–98)¶ | 87 (79–103)** |
| TLC < 80% predicted | 18 (37)¶ | 8 (21)** |
| FVC, % predicted | 84 (70–96)¶ | 88 (78–102)** |
| FVC < 80% predicted | 15 (31)¶ | 8 (21)** |
| $D_{LCO}$, % predicted | 65 (48–80)¶ | 68 (50–84)** |
| $D_{LCO}$ < 80% predicted | 22 (46)¶ | 22 (58)** |
| FEV, % predicted | 85 (77–98)¶ | 87 (78–99)** |
| FEV/FVC, % predicted | 85 (82–89)¶ | 83 (78–86)** |
| FEV/FVC < 70% predicted | 2 (4)¶ | 2 (5)** |
| Six-minute walking test, % predicted | 81 (67–90)‡ | 88 (73–91)†† |

*Definition of abbreviations*: ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease; ECMO = extracorporeal membrane oxygenation; MRC = Medical Research Council.
Data are expressed as median (interquartile range) or *n* (%).
*Available in 62 patients.
†Available in 50 patients.
‡Available in 47 patients.
§Available in 45 patients.
‖Available in 42 patients.
¶Available in 48 patients.
**Available in 38 patients.
††Available in 23 patients.

suffered from plexus or nerve injury at 6 and 12 months, respectively. Last, four patients spontaneously complained about esthetic discomfort due to physical scars related to prone positioning, endotracheal tube, or ECMO cannulation (Figure E3).

***Psychological assessment.*** The psychological impact of these prolonged ICU and hospital stays is reported in Figure 1. All patients completed these tests on a face-to-face consultation, except four who performed them by phone at 1 year. A total of 19/43 (44%) and 18/43 (42%) survivors, respectively, exhibited significant anxiety and depression symptoms (i.e., scores ⩾ 8/21) 1 year after ICU admission. However, our patients' percentages of significant anxiety and/or depression were comparable to those of 67 patients with non-COVID ARDS treated by ECMO (Table E2). Interestingly, 21/50 (42%) patients were at risk for PTSD (i.e., PCL-5 ⩾ 38) at 12 months. This rate was significantly higher than patients with non-COVID ARDS treated by ECMO ($P = 0.04$) (Table E2).

SF-36 assessment of QoL is reported in Table E2 and Figure 3. Mental health, role-emotional, and role-physical were the most impaired domains compared with patients without COVID-19 receiving ECMO (10) and patients with COVID-19 treated without ECMO (23). Of note, these SF-36 domain scores did not improve at 1 year and were still severely impaired over time.

## Discussion

To the best of our knowledge, we report the largest analysis to date of long-term follow-up of the most severe forms of COVID-19 rescued by VV-ECMO. Interestingly, respiratory function improved over time, but $D_{LCO}$ remained impaired in more than half of the patients at 1 year. The psychological impact of the prolonged ICU and hospital stays was worrisome, with frequent symptoms of anxiety, depression, PTSD, and severe impairment of the QoL in mental domains. These psychological sequelae were significantly more frequent than those reported by patients without COVID-19 treated by ECMO.

To date, information on long-term follow-up in patients treated with ECMO for ARDS is limited (8, 9, 24–26). However, several case series have shown that the long-term pulmonary function of non-COVID ARDS on ECMO was almost similar to patients treated for ARDS without ECMO (7, 26). COVID-19–related ARDS, especially in the most severe forms, is characterized by a slow pulmonary recovery with unusually long ECMO and mechanical ventilation durations and prolonged ICU and hospital length of stay. A significant proportion of patients with COVID-19 on ECMO did not meet the classic weaning criteria defined by the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial (4) and underwent facilitative weaning when lung mechanics were still severely impaired (27). Despite low mortality and almost normal lung function recovery after 6 months, these patients had longer mechanical ventilation duration and ICU stay than those who strictly fulfilled classic weaning criteria (27).

Despite an almost normalized FEV and FVC, most patients had an impaired $D_{LCO}$ at 1 year, which was highly correlated with fatigue, thus indicating some residual pulmonary damage. These results concur with findings reported in patients with less severe COVID-19 (27–29) and 27 ECMO survivors after COVID-19–related ARDS (30). The persistence of fibrotic lesions 6 months after severe ARDS on ECMO is common in patients without COVID-19 and seems to be fixed after 6 months (31–33). However, it is reassuring to observe that the initial severity and prolonged mechanical ventilation in patients with COVID-19 do not prevent progressive lung recovery. Ultraprotective ventilation, applied during ECMO to all of our patients, could have markedly contributed to lung recovery (34).

Specific pulmonary sequelae of ARDS include mild restrictive disease, modestly reduced diffusion capacity, and some degree of pulmonary fibrosis, mainly in nondependent areas of the lung (35). For the 16 ECMO-rescued survivors of ARDS studied at 26 months by Lindén and colleagues (36), CT scan abnormalities included a reticular pattern, combined with interstitial fibrosis and ground-glass opacities with architectural distortion and a total extent of pathological lung parenchyma limited to 10%. However, the clinical significance and the impact on daily life activities of these structural pulmonary sequelae are questionable. Interestingly, respiratory symptoms evaluated by the SGRQ were modest in our population, although physical limitations with an impact on activities persisted (37). Given that the

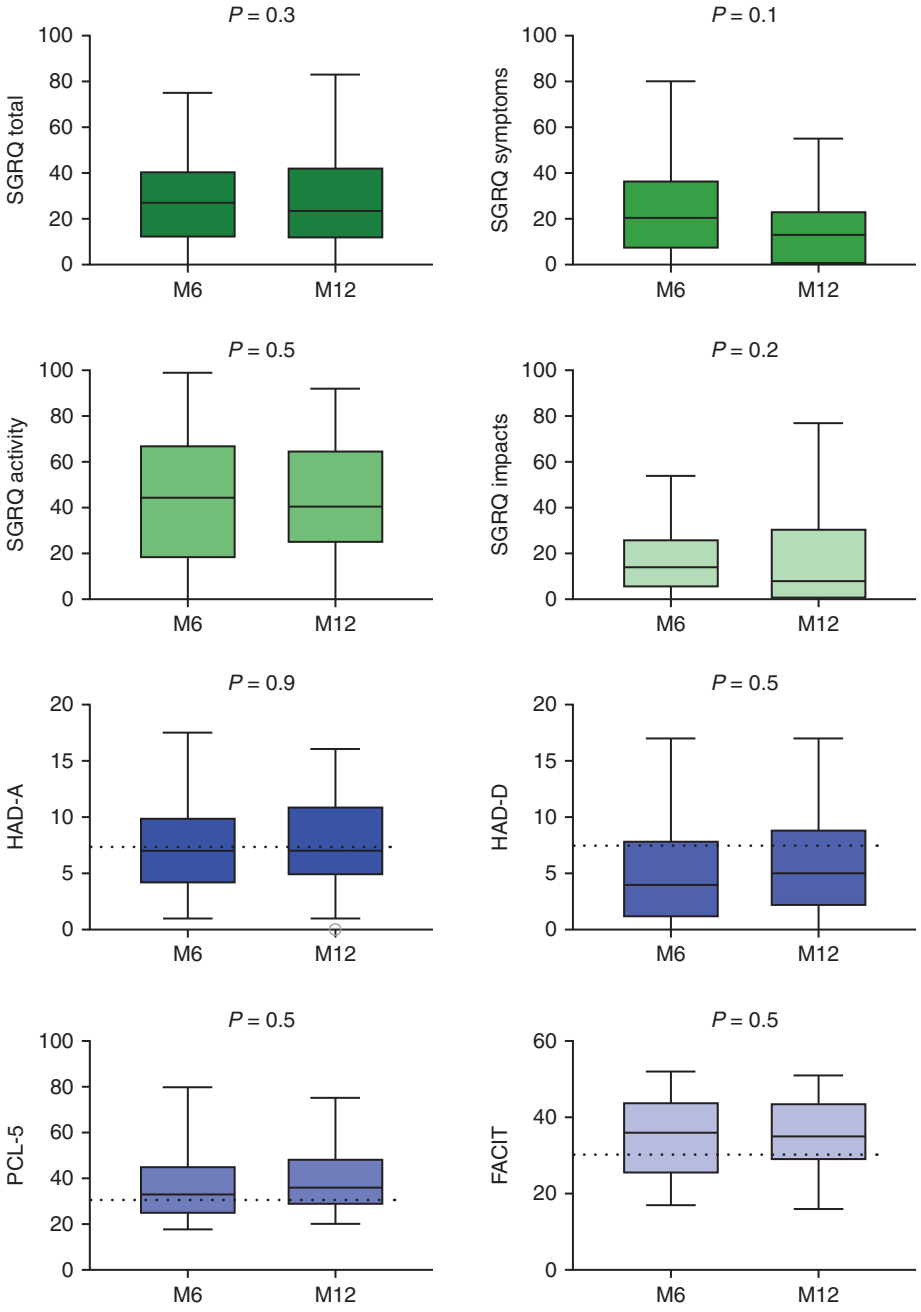


**Figure 1.** Saint George's Respiratory Questionnaire (SGRQ), Hospital Anxiety and Depression Scale–Anxiety (HAD-A), HAD–Depression (HAD-D), Post-traumatic Stress Disorder Checklist for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Post-Traumatic Stress Disorder Checklist for DSM-5 (PCL-5), and Functional Assessment Chronic Illness Therapy-Fatigue (FACIT) assessments at 6 and 12 months in survivors after extracorporeal membrane oxygenation (ECMO) for coronavirus disease (COVID-19) severe acute respiratory distress syndrome. Whisker plots after 6 and 12 months of follow-up after COVID-19–related acute respiratory distress syndrome treated by ECMO are shown. The interior horizontal lines correspond to the median, the lower and upper box limits are the 25th and 75th percentiles, and the T-bars represent the range. The dotted line shows the threshold of clinical significance (for instance, a score ⩾8 for the anxiety and depression subscales, a score ⩾38 for PCL-5, and a score ⩽35 for FACIT). SGRQ was available for 42 and 36 patients at 6 and 12 months. FACIT was available for 46 and 41 patients at 6 and 12 months. HADS and PCL-5 were available for 50 and 43 patients at 6 and 12 months. HADS = Hospital Anxiety and Depression Scale; M6 = 6 months; M12 = 12 months.

overall physical strength, expressed by the MRC, was normal at 6 and 12 months, persistently altered SGRQ domains may reflect fatigability and deconditioning, which may have been underestimated by an almost normal 6-minute-walking test (28, 32). More than half of the survivors reported clinically significant fatigue symptoms. Interestingly, it was not different from other survivors of ARDS without ECMO, of whom two-thirds reported clinically significant fatigue

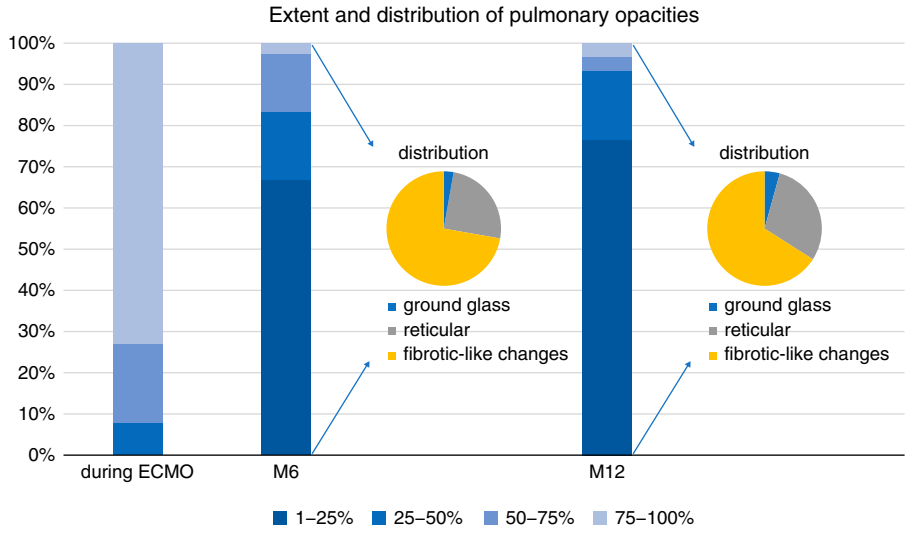


**Figure 2.** Extent and distribution of pulmonary opacities over time. Semiquantitative computed tomography (CT) score was assigned based on the area involved in all lung lobes, as follows: 1, 1–25% involvement; 2, 25–50% involvement; 3, 50–75% involvement; and 4, >75% involvement during ECMO, after 6 and 12 months of follow-up after COVID-19 related ARDS. CT patterns were described as follows: ground-glass, consolidation, and fibrotic-like changes (reticulation, honeycombing, bronchiectasis). ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease; ECMO = extracorporeal membrane oxygenation; M6 = 6 months; M12 = 12 months.

symptoms during the first year after ARDS (38). However, fatigue in our patients was greater than those reported by 56 ICU survivors 1 year after ICU discharge. However, it was mostly surgical admission (64%), with patients with less severe severity scores and shorter ICU length of stay (39). This high rate of significant fatigue symptoms could also be directly attributed to COVID-19 itself, as evidenced by the high rate of this symptom in studies including few ventilated patients (13, 40). Notably, only 19/50 (38%) of our patients had returned to work, compared with 72% of patients without COVID-19 on ECMO in a French multicenter cohort (10). Physical complaints specifically related to ECMO, such as a peripheral neurological deficit, leg paresthesia, or scarring at the puncture points, were very rare. Most complaints referred to unesthetic face scars and hair loss due to prone position or prolonged laying position.

The high burden of ARDS-induced psychological sequelae in our ECMO-rescued patients was still present at 12 months. Notably, we reported a high prevalence of clinical symptoms of anxiety, depression, and post-traumatic stress, which was significantly higher than in patients hospitalized for less severe COVID-19 (41). These results are important, even if expected with such clinical severity and prolonged ICU stay. These psychological sequelae still significantly altered the QoL of our patients in all domains, even if the most severe impairment was observed in mental health and role-emotional domains when compared with patients without COVID-19 on ECMO. It highlights the important role of COVID-19, which may have markedly contributed to persistent mental health impairment. The same findings were reported by Latronico and colleagues after 1 year in patients with COVID-19 on mechanical ventilation who did not receive ECMO (23), despite a lower respiratory severity and shorter ICU and hospital length of stay. Risk factors such as tracheostomy for QoL impairment at 1 year in critically ill patients with COVID-19 have been recently identified (28). Among 13 survivors of COVID-19–associated ARDS supported by ECMO evaluated at 1 year, 50% had returned to work. A high proportion of patients suffered from anxiety (60%), depression (40%), and PTSD (40%), which was similar to our population (42). However, the higher rate of PTSD reported in survivors of COVID-19 ARDS treated by ECMO compared with patients without COVID-19 could also be explained by the ongoing pandemic context (10, 42). Indeed, QoL was assessed at a period when the COVID-19 pandemic was progressing, with frequent travel restrictions, lockdowns, and curfews. During the interviews, our patients were complaining about the constant background noise of the media updating daily the number of deaths due to COVID-19. In addition, some of our ECMO survivors had to handle the death of one or more close relatives during that period. During the first surge in France, family visits to hospitals were forbidden, which could have contributed to this high prevalence of psychological sequelae. Anxiety and post-traumatic stress syndrome in family members (not evaluated in our work) could also have contributed to disrupting family interactions even 1 year later (43, 44).

However, a recent multicenter study reported no difference in the incidence of new disability, psychological function, cognitive function, or health-related QoL in patients with COVID-19 compared with patients without COVID-19 with acute respiratory failure requiring mechanical ventilation (45). Noticeably, these patients were older and had less severe illness than our patients on ECMO.

Our study has several limitations. First, the number of patients studied was limited (only seven French ICUs) compared with other studies reporting long-term follow-up of patients with COVID-19 who did not receive ECMO (12, 13). Second, 18 survivors were lost to follow-up or refused to participate in our study. Multiple interhospital transfers, multiple lockdowns, and travel restrictions have complexified the follow-up of these patients. Patients lost to

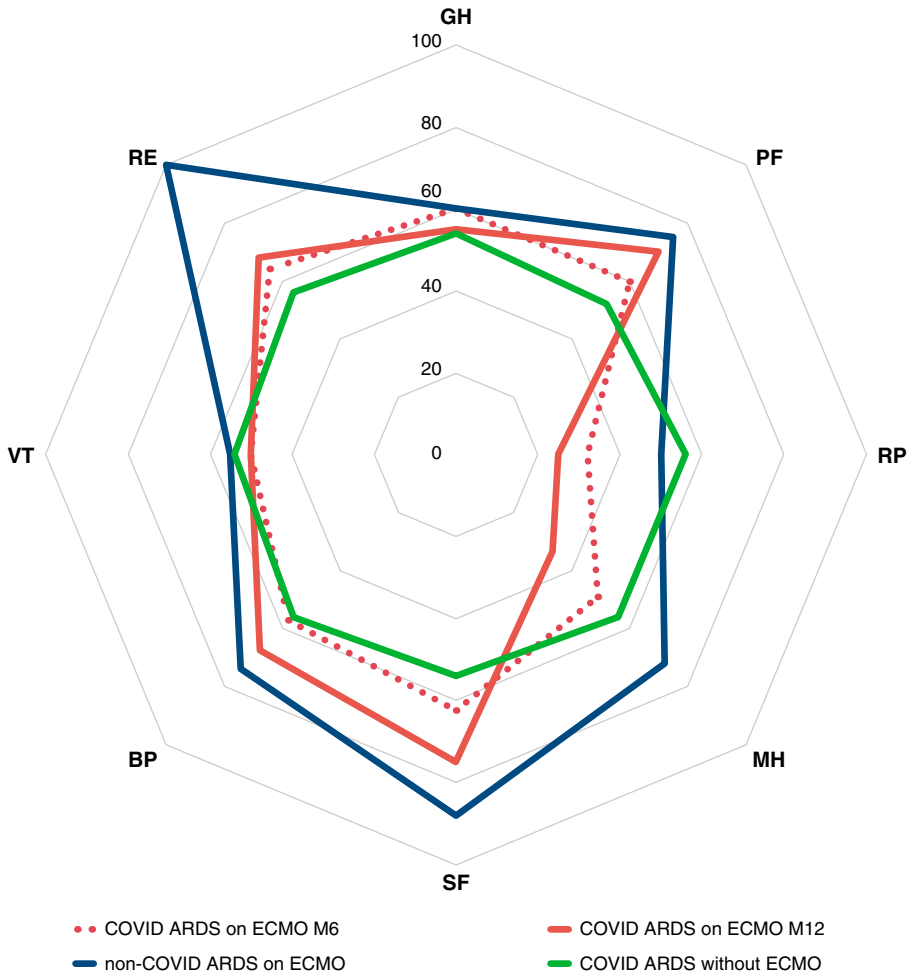


**Figure 3.** Comparison of 36-Item Short-Form Health Survey questionnaire scores of 62 survivors of coronavirus disease (COVID-19) acute respiratory distress syndrome (ARDS) treated by extracorporeal membrane oxygenation (ECMO) at 6 and 12 months with 67 patients with non-COVID ARDS treated by ECMO (8), and 51 conventionally treated survivors of COVID-19 ARDS at 1 year of follow-up (23). Higher scores denote a better health-related quality of life. BP = body pain; GH = general health; M6 = 6 months; M12 = 12 months; MH = mental health; PF = physical functioning; RE = role emotional; RP = role physical; SF = social functioning; VT = vitality.

follow-up were older and had a shorter hospital length of stay. Third, pulmonary assessment (CT, 6-minute-walk test) was missing for some patients because of multiple lockdowns and the unavailability of overbooked tests. Fourth, no initial (i.e., pre-COVID) QoL assessment was available in our patients, who were middle-aged and mostly in good health before the pandemic. Comparisons of QoL indicators before and after the ICU stay are therefore impossible. Fifth, we did not conduct a specific cognitive assessment, although more than half of ARDS survivors have a cognitive disability (46). Last, because an increase in mortality in patients with COVID-19 patients on ECMO has been recently reported during the second surge of the pandemic (i.e., after September 2020) (47, 48), the long-term outcomes of patients supported by ECMO for ARDS due to other variants of SARS-CoV-2 may be different. Their long-term mental and physical health should also be compared with patients without COVID-19 receiving ECMO to confirm our findings.

## Conclusions

Despite the partial recovery of lung function tests at 2 year, the physical and psychological function of patients supported by ECMO for severe ARDS during the first surge of the pandemic is still impaired, with consequences on their QoL. Noticeably, almost 50% of them reported persistent long-term psychological and emotional sequelae, only 40% had returned to work, and only one-third had recovered a normal sex drive. Based on the comparison with long-term follow-up of patients without COVID-19 receiving ECMO, poor mental and physical health may be more related to COVID-19 than to ECMO in itself, although this needs confirmation. A personalized, multidisciplinary, and prolonged follow-up after hospital discharge of future patients with COVID-19 and their families is needed to further improve their outcomes. Future trials should also evaluate the long-term outcomes of patients who needed ECMO at later phases of the pandemic, when potentially more severe SARS-CoV-2 variants were responsible for severe ARDS. ■

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

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