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The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome

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Abstract Purpose: This study was designed to identify factors associated with death by 6 months post-intensive care unit (ICU) discharge and to develop a practical mortality risk score for extracorporeal membrane oxygenation (ECMO)-treated acute respiratory distress syndrome (ARDS) patients. We also assessed long-term survivors' health-related quality of life (HRQL), respiratory symptoms, and anxiety, depression and post-traumatic stress disorder (PTSD) frequencies. **Methods:** Data from 140 ECMO-treated ARDS patients admitted to three French ICUs (2008–2012) were analyzed. ICU survivors contacted >6 months post-ICU discharge were assessed for HRQL, psychological and PTSD status. **Results:** Main ARDS etiologies were bacterial (45 %), influenza A[H₁N₁] (26 %) and post-operative (17 %) pneumonias. Six months post-ICU discharge, 84 (60 %) patients were still alive. Based on multivariable logistic regression analysis, the PRESERVE (PREdicting dEath for SEvere ARDS

on VV-ECMO) score (0–14 points) was constructed with eight pre-ECMO parameters, i.e. age, body mass index, immunocompromised status, prone positioning, days of mechanical ventilation, sepsis-related organ failure assessment, plateau pressure and positive end-expiratory pressure. Six-month post-ECMO initiation cumulative probabilities of survival were 97, 79, 54 and 16 % for PRESERVE classes 0–2, 3–4, 5–6 and ≥7 ($p < 0.001$), respectively. HRQL evaluation in 80 % of the 6-month survivors revealed satisfactory mental health but persistent physical and emotional-related difficulties, with anxiety, depression or PTSD symptoms reported, by 34, 25 or 16 %, respectively. **Conclusions:** The PRESERVE score might help ICU physicians select appropriate candidates for ECMO among severe ARDS patients. Future studies should also focus on physical and psychosocial rehabilitation that could lead to improved HRQL in this population.

Keywords Extracorporeal membrane oxygenation · Acute respiratory distress syndrome · Outcome assessment · Long-term quality of life

Introduction

Patients who develop the most severe forms of acute respiratory distress syndrome (ARDS) still have mortality rates exceeding 50 % [1] and survivors have persistently impaired physical, functional and psychological components of health-related quality of life (HRQL), despite optimal supportive care provided during their intensive care unit (ICU) stays [2–6]. In this setting, extracorporeal membrane oxygenation (ECMO) has been proposed as a possible therapeutic option allowing ultraprotective mechanical ventilation (MV) and potentially less ventilator-induced lung damage [7–9]. Indeed, major technological improvements in ECMO machines [7, 8, 10, 11], the conventional ventilation or ECMO for severe adult respiratory failure (CESAR) trial's positive results [9] and recourse to ECMO-rescue therapy for the most severe cases of A(H₁N₁) influenza-induced ARDS that failed on conventional ventilation [12–14] have renewed recent interest in this technique.

Because extended use of ECMO, which requires highly specialized staff and equipment, may increase resource utilization and hospitals costs, early identification of mortality risk factors and detailed analyses of long-term outcomes of survivors are needed. However, to date, studies reporting factors associated with death for severe ARDS adult patients who received ECMO are scarce [15, 16], did not evaluate the impact of pre-ECMO MV settings or rescue maneuvers such as prone positioning [17] and are based on data collected before the development of modern ECMO devices and the widespread adoption of protective MV recommendations based on ARDSnet studies [18]. Additionally, only a few studies based on limited numbers of patients evaluated long-term outcomes in ECMO-treated ARDS survivors [9, 19–21]. Therefore, this study was designed to identify factors associated with death by 6 months post-ICU discharge for ARDS patients treated with the latest generation ECMO systems and to assess long-term survivors' HRQL and psycho-emotional sequelae.

Patients and methods

Study design and objectives

The primary objective of this multicenter retrospective study, which included all consecutive severe ARDS patients who received ECMO in three adult ICUs in French university hospitals between May 2008 and January 2012, was to identify factors associated with death by 6 months following ICU discharge and to derive a practical mortality risk score that might help ICU physicians select appropriate candidates for ECMO. Long-term survivors' HRQL, respiratory symptoms, and anxiety, depression and post-traumatic stress disorder (PTSD) frequencies were also evaluated.

Patients

The decision to initiate ECMO was based on the following: persistent hypoxemia, defined as PaO₂/FiO₂ <80 mmHg with FiO₂ ≥80 % for >6 h, despite optimization of MV (V_t set at 6 mL/kg and trial of positive end-expiratory pressure [PEEP] ≥10 cm H₂O), and despite possible recourse to adjunctive therapies (NO, prone position, HFO ventilation) and/or pH <7.25 (with PaCO₂ ≥60 mmHg) for >6 h resulting from MV settings adjusted to keep plateau pressure (P_{plat}) ≤32 cm H₂O [22]. Exclusion criteria for ECMO were patients with chronic respiratory insufficiency treated with oxygen therapy and/or long-term respiratory assistance, malignancies with fatal prognosis within 5 years, moribund patients or those with irreversible neurological pathologies and decisions to limit therapeutic interventions. In accordance with the ethical standards of our hospital's Institutional Review Board, obtaining informed consent for demographic, physiological and hospital-outcome data analyses was not necessary, because this retrospective observational study did not modify existing diagnostic or therapeutic strategies. Additional information on patients' data and descriptions of ECMO management [23] are detailed in the electronic supplementary material (ESM).

Outcome variables

We recorded ICU events, including cardiac arrest, bleeding, infections [24] and ECMO-related hemolysis, durations of ECMO and MV support, ICU and hospital lengths of stay, and mortality. Patients discharged from the ICU were contacted >6 months later and oral consent was obtained to complete long-term HRQL, pulmonary symptoms and psychological assessment questionnaires. The same investigators (MS, EZ, HR) interviewed all patients, asking the questions in the questionnaire in the same order by telephone.

Long-term HRQL was assessed with the French version of the Medical Outcome Short-Form (SF)-36 [25–27] and our patients' SF-36 scores were compared with age- and sex-matched French control subjects [27]. Pulmonary symptoms were evaluated with the St George's Respiratory Questionnaire (SGRQ) [28]. Anxiety and depression symptoms were assessed with the Hospital Anxiety and Depression (HAD) Scale [29], with respective HAD-A and HAD-D subscale scores ≥8/21 considered clinically significant [29]. PTSD-related symptoms were assessed with the Impact of Event Scale (IES) [30], and patients with a total IES score ≥30/75 points were considered at high risk for PTSD. Lastly, activities of daily living (ADL) were evaluated with the basic ADL and instrumental ADL (IADL) scales [31, 32]. To put questionnaire scores of our ARDS ECMO-treated patients into perspective, we searched the literature for other studies reporting long-term

outcomes of patients who survived ARDS or other severe diseases treated in the ICU. Details on outcome-variable evaluations and on series selected as comparators [3, 4, 9, 19, 20, 25, 33–39] are provided in the ESM.

Statistical analyses

Continuous variables were compared with Student's *t* test or the Mann-Whitney *U* test, as appropriate. For comparisons of patients' mean SF-36 scores with those of their age- and sex-matched control subjects, paired *t* tests or Wilcoxon tests were used. To examine the effects of patients' clinical characteristics associated in the univariable analysis with death by 6 months post-ICU discharge, a logistic regression model was used to test each characteristic. Thereafter, multiple logistic regression using backward stepwise variable elimination (with the variable exit threshold set at $p > 0.05$) was applied. Factors achieving $p \leq 0.20$ in our univariable analysis were entered into the model. Prone positioning was forced in the model because a study recently showed that it was associated with better outcomes in moderate to severe ARDS patients [40]. All potential explanatory variables included in the multivariable analyses were subjected to a correlation matrix for analysis of collinearity. Variables with association among each other were not included in the multivariable model. Then, to derive a simple and practical score to predict survival, i.e. the PRESERVE (PRedicting dEath for SEvere ARDS on VV-ECMO) score, we re-ran the final logistic regression model with continuous variables transformed into categorical variables (by defining best thresholds after analyzing mortality in each quartile of the corresponding variable). PRESERVE subscores for each factor were the β -coefficients of the logistic regression model divided with the smallest coefficient of the model and rounded to the nearest integers. The discriminative performance of the PRESERVE score was evaluated with receiver operating characteristics (ROC) curve and quantified by calculating the area under the curve and 95 % CI. Lastly, Kaplan–Meier survival analysis was used to estimate the probability of survival after ECMO initiation among quartiles of the PRESERVE score. $P < 0.05$ defined statistical significance. Analyses were computed with StatView v5.0 (SAS Institute Inc., Cary, NC, USA) and SPSS 11.0 (SPSS Inc., Chicago, IL, USA) software.

Results

Study population

During the study period, 140 patients (Fig. 1) with refractory ARDS [age 44 (30–56) years, 61 % male]

received ECMO in three French university ICUs (Amiens, $n = 33$; Bordeaux, $n = 23$; Paris, $n = 84$). Patients' characteristics at ICU admission are given in Table 1. Infectious diseases were the leading causes of ARDS: 45 % bacterial and 26 % A(H₁N₁) influenza pneumonias. Before ECMO implantation, median PaO₂/FiO₂ was 53 (43–60). Median time between intubation and ECMO cannulation was 5 (1–11) days. Notably, refractory hypoxemia occurred despite the recourse to prone positioning for almost two-thirds of our patients (Table 2). Venovenous (VV) ECMO was used in 95 % of patients, most frequently with femoral–jugular cannulation ($n = 121$); six patients received Avalon cannulae and six had cannulae inserted in both femoral veins. Venoarterial (VA)-ECMO was used for the seven patients whose ARDS was associated with severe cardiovascular dysfunction [41].

ECMO support allowed 'ultraprotective' MV settings: Pplat was decreased from 32 (30–35) to 24 (22–26) cm H₂O, tidal volume from 5.9 (5.2–6.7) to 2.8 (2.0–4.4) mL/kg, while PEEP remained stable. Blood gases normalized within 6 h of ECMO initiation (Table 2; Table E1[see ESM]).

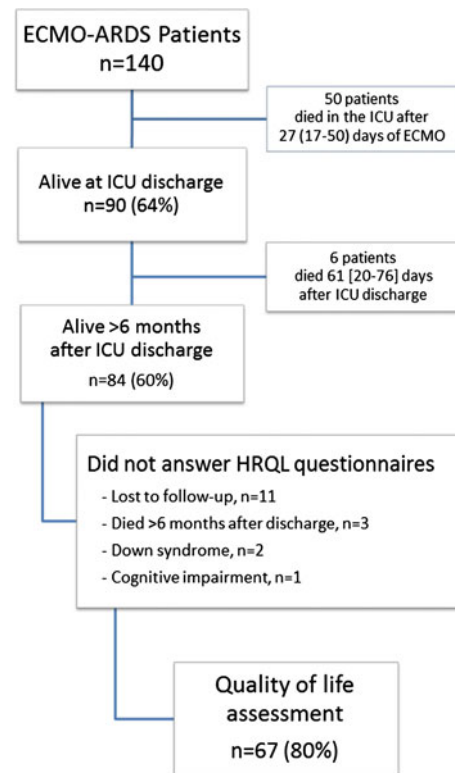


Fig. 1 Study flowchart. Durations are median (interquartile range). ARDS acute respiratory disease syndrome, ECMO extracorporeal membrane oxygenation, HRQL health-related quality of life, ICU intensive care unit

Table 1 Clinical characteristics of ECMO-treated ARDS patients according to survival status 6 months post-ICU discharge

Characteristic	All patients (n = 140)	Status at 6 months post-ICU		p-Value
		Alive (n = 84)	Dead (n = 56)	
Age, years	44 (30–56)	37 (28–47)	53 (44–60)	0.0001
Men	86 (61)	46 (55)	40 (71)	0.04
Body mass index, kg/m ²	27 (24–32)	29 (24–36)	26 (24–31)	0.04
Charlson score	1 (0–2)	1 (0–2)	2 (1–3)	0.0001
McCabe and Jackson score ≥ 2	23 (16)	6 (7)	17 (30)	0.0004
SAPS II	59 (49–71)	57 (47–68)	64 (55–74)	0.04
SOFA score	12 (10–15)	12 (10–15)	13 (11–15)	0.13
Chronic lung disease	21 (15)	11 (13)	10 (18)	0.59
Pregnant or postpartum	7 (5)	7 (8)	0	0.02
Diabetes mellitus	14 (10)	5 (6)	9 (16)	0.05
Renal insufficiency	9 (6)	6 (7)	3 (5)	0.67
Immunocompromised ^a	43 (31)	14 (17)	29 (52)	<0.0001
Hematological malignancies	13 (9)	3 (4)	10 (18)	
Solid tumor	10 (7)	2 (2)	8 (14)	
Solid organ transplantation	8 (6)	4 (5)	4 (7)	
High-dose or long-term CS/IS	8 (6)	3 (4)	5 (9)	
Human immunodeficiency virus	4 (3)	2 (2)	2 (4)	
ARDS etiology				0.01
Peri-/post-operative	24 (17)	13 (15)	11 (20)	
2009 A(H ₁ N ₁) influenza	36 (26)	30 (36)	6 (11)	
Bacterial infection	63 (45)	34 (40)	29 (52)	
Others	17 (12)	7 (8)	10 (18)	

Values are expressed as median (interquartile range) or n (%)

ARDS acute respiratory disease syndrome, CS/IS corticosteroids or immunosuppressants, ECMO extracorporeal membrane oxygenation, ICU intensive care unit, SAPS simplified acute physiology score, SOFA sepsis-related organ failure assessment

^a Immunocompromised status included hematological malignancies, solid tumors, solid-organ transplantation, high-dose or long-term corticosteroid and/or immunosuppressant use, or human immunodeficiency virus infection

Intensive care unit and 6-month outcomes

Complications during ECMO are listed in Table E1 (see ESM). Bleeding events occurred in 46 % of patients. Respectively, 74 and 16 % of patients developed ventilator-associated pneumonia and cannula infection. Renal replacement therapy was required by 56 % of patients and 63 % were tracheostomized. Ninety (64 %) patients survived to ICU discharge. In-ICU deaths were attributed to multiple organ failure for 28, septic shock for 18, hemorrhagic shock for 6, intracranial bleeding for 4 and brain-hypoxia sequelae for 4. Respective median durations of ECMO and MV support were 15 (8–30) and 40 (23–68) days, and median hospital length of stay was 65 (39–111) days.

Six patients died 61 (20–76) days after ICU discharge (two had left the hospital before dying). Six months after ICU discharge, 84 (60 %) patients were still alive. The 36 patients with A(H₁N₁)-associated ARDS had the lowest reported mortality to date (17 %). Multivariable analysis (Table E2 [see ESM]; Table 3) retained older age, immunocompromised status, higher simplified acute physiology score (SAPS II) [calculated excluding the age component], higher pre-ECMO Pplat, lower pre-ECMO PEEP, absence of pre-ECMO prone positioning and the number of days on MV before ECMO as factors

independently associated with death by 6 months while higher body mass index (BMI) was associated with lower mortality (see ESM for details). The PRESERVE score developed after transforming continuous into categorical variables (Table E3 [see ESM]) is displayed in Table 4. Cumulative probabilities of survival by 6 months following ECMO initiation were 97, 79, 54 and only 16 % for PRESERVE score classes 0–2 (n = 34), 3–4 (n = 38), 5–6 (n = 26) and ≥ 7 (n = 38), respectively (Fig. 2). ROC curve analysis of the performance of this scoring system (Figure E1) is shown in the ESM. The area under the curve was 0.89 (95 % CI 0.83–0.94).

Interestingly, patients retrieved by our mobile ECMO teams had lower unadjusted mortality than patients who received ECMO inhouse (34 vs. 53 %, p = 0.027, respectively). However, retrieved patients had significantly less comorbidities and suffered A(H1N1) infection more frequently (33 vs. 13 %, p = 0.016). After adjusting for other confounders, this variable was not associated with death at 6 months (Table 3).

Long-term outcomes

Long-term evaluation was conducted a median of 17 (11–28) months after ICU discharge, when three more

Table 2 Ventilation characteristics at the time of ECMO initiation according to survival status

Characteristic	Status at 6 months post-ICU		<i>p</i> -Value	
	All patients (<i>n</i> = 140)	Alive (<i>n</i> = 84)		Dead (<i>n</i> = 56)
Ventilation parameters				
PaO ₂ /FiO ₂	53 (43–60)	53 (42–58)	54 (45–69)	0.15
FiO ₂	100 (100–100)	100 (100–100)	100 (100–100)	0.76
PEEP, cm H ₂ O	10 (8–12)	10 (9–12)	8 (8–10)	0.001
Tidal volume, mL/kg	5.9 (5.2–6.7)	5.9 (5.1–6.6)	5.9 (5.2–6.8)	0.99
Respiratory rate, /min	30 (26–30)	30 (26–30)	30 (25–32)	0.42
Plateau pressure, cm H ₂ O	32 (30–35)	32 (30–35)	34 (31–35)	0.009
Driving pressure, cm H ₂ O	22 (19–27)	21 (18–24)	24 (22–28)	0.0006
Compliance, mL/cm H ₂ O	18 (14–21)	19 (15–21)	16 (12–20)	0.04
Pre-ECMO blood gases				
pH	7.22 (7.15–7.32)	7.23 (7.16–7.32)	7.22 (7.14–7.30)	0.30
PaO ₂ , mmHg	53 (44–58)	52 (42–55)	53 (45–68)	0.11
PaCO ₂ , mmHg	63 (51–77)	60 (50–70)	70 (53–80)	0.02
HCO ₃ ⁻ , mmol/L	27 (23–32)	26 (23–30)	27 (23–34)	0.19
SaO ₂ (%)	80 (74–85)	80 (74–85)	80 (73–88)	0.18
Arterial lactate, mmol/L	2.2 (1.5–3.4)	2.3 (1.8–3.8)	2.1 (1.2–3.1)	0.10
Quadrants with infiltrate, <i>n</i>	4 (4–4)	4 (4–4)	4 (4–4)	1
Rescue therapy				
Any	131 (94)	81 (96)	50 (89)	0.11
Prone positioning	82 (59)	52 (62)	30 (54)	0.32
Nitric oxide	127 (91)	77 (92)	50 (89)	0.63
Almitrine	11 (8)	9 (11)	2 (4)	0.12
HFOV	1 (1)	0	1 (2)	–
Pre-ECMO steroids	35 (25)	14 (17)	21 (38)	0.006
Vasopressors	98 (70)	61 (73)	37 (66)	0.40
Pre-ECMO pneumothorax	5 (4)	2 (2)	3 (5)	0.35
Mobile ECMO team	95 (68)	63 (75)	32 (57)	0.03
Interval (days)				
Hospital–ICU admission	0 (0–1)	0 (0–1)	0.5 (0–3)	0.08
Hospital admission–ECMO	7 (3–14)	5 (2–11)	13 (7–27)	<0.0001
ICU admission–ECMO	6 (2–13)	4 (1–9)	9 (4–17)	<0.0001
MV–ECMO	5 (1–11)	3 (1–9)	7 (3–15)	0.0008

Values are expressed as median (interquartile range) or *n* (%)

ECMO extracorporeal membrane oxygenation, HFOV high-frequency oscillation ventilation, ICU intensive care unit, MV mechanical ventilation, PEEP positive end-expiratory pressure

patients had died. HRQL and psychosocial questionnaires were administered to 67 (80 %) of the 6-month survivors (Fig. 1). Among these 67 patients, 7 were retired, 3 were unemployed and 57 were working full-time before their critical illness. At follow-up, 41/57 (72 %) of the latter had returned to work (35/57 [52 %] to their previous work) and most reported normal functions (Table E1 [see ESM]).

SF-36 assessment of HRQL is reported in Fig. 3. Compared with age- and sex-matched controls, our responding ARDS survivors had significantly lower ($p < 0.001$) SF-36 physical domain scores. Their psychological domain scores were comparable with those of the general population, with the exception of their role-emotional component, which was lower ($p < 0.001$). Their SF-36 physical aggregate scores were also significantly lower ($p < 0.001$), while their mental aggregate scores were comparable. Patients with longer follow-up (>503 days) had significantly improved role-physical

($p = 0.001$) and role-emotional ($p = 0.049$) domain scores (Table E4 [see ESM]). Patients whose ECMO support lasted longer tended to have lower bodily pain domain and aggregate physical scores (Table E5 [see ESM]).

During follow-up questioning, 24 (36 %) patients reported persistent dyspnea. In addition, 20 (30 %) patients were still taking pulmonary medications (long-acting β_2 -agonists for 16 patients, inhaled corticosteroids for 7, home oxygen therapy for 1 and nocturnal MV for 3). The SGRQ scores indicated that patients with longer ECMO support had more pulmonary symptoms (Table E5 [see ESM]).

Twenty-three (34 %), 17 (25 %) and 11 (16 %) of the respondents (Fig. 4), respectively, exhibited significant anxiety and depression symptoms or were at risk for PTSD. HAD and IES scores did not differ significantly for patients with longer versus shorter follow-up or those who had longer ECMO support (Tables E4 and E5 [see ESM]).

Table 3 Factors available at ECMO institution independently associated with death by 6 months post-ICU discharge

Factor	OR (95 % CI)	p-Value
Age	1.08 (1.04–1.12)	<0.001
Body mass index	0.90 (0.84–0.97)	0.004
Immunocompromised ^a	4.33 (1.55–12.12)	0.005
SAPS II ^b	1.04 (1.00–1.08)	0.028
Days of MV	1.07 (1.01–1.14)	0.015
No prone positioning before ECMO	2.93 (1.04–8.25)	0.043
PEEP, cm H ₂ O	0.84 (0.71–0.99)	0.039
Plateau pressure, cm H ₂ O	1.18 (1.05–1.32)	0.006

CI confidence interval, ECMO extracorporeal membrane oxygenation, ICU intensive care unit, MV mechanical ventilation, OR odds ratio, PEEP positive end-expiratory pressure, SAPS II simplified acute physiology score

^a Immunocompromised status included hematological malignancies, solid tumors, solid organ transplantation, high-dose or long-term corticosteroid and/or immunosuppressant use, or human immunodeficiency virus infection

^b Age was not included in SAPS II calculation for multivariable analysis

Table 4 The PRESERVE score calculated with parameters available at the time of decision to initiate ECMO

Parameter	Score
Age (years)	
<45	0
45–55	2
>55	3
Body mass index >30	–2
Immunocompromised	2
SOFA >12 ^a	1
MV >6 days	1
No prone positioning before ECMO	1
PEEP < 10 cm H ₂ O	2
Plateau pressure >30 cm H ₂ O	2
Total score ^c	0–14

ECMO extracorporeal membrane oxygenation, ICU intensive care unit, MV mechanical ventilation, PEEP positive end-expiratory pressure, PRESERVE PRedicting dEath for SEvere ARDS on VV-ECMO, SAPS II simplified acute physiology score, SOFA sepsis-related organ failure assessment

^a Immunocompromised status included hematological malignancies, solid tumors, solid organ transplantation, high-dose or long-term corticosteroid and/or immunosuppressant use, or human immunodeficiency virus infection

^b SOFA score was preferred over SAPS II (excluding the age component) for simpler use of the score at the bedside

^c Higher score indicates higher probability of death by 6 months post-ICU discharge; PRESERVE scores –1 and –2 converted to 0 for simplification

Discussion

To our knowledge, this is the largest ($n = 140$), comprehensive, multicenter, follow-up study on ECMO-treated severe ARDS patients. Despite very severe disease at ECMO initiation, the 40 % 6-month mortality we observed for this series is lower than the 50 % hospital

mortality rate recently reported in the Oscillation in ARDS (OSCAR) trial (where mean PaO₂/FiO₂ was 113 mmHg at randomization) [42]. It is also lower than those reported in previous series of ECMO-treated ARDS patients [15, 43, 44], and comparable with that of the ECMO arm of the CESAR trial [9], in which initial PaO₂/FiO₂ was higher (76 vs. 53 mmHg). Interestingly, A(H₁N₁)-induced ARDS patients included in this study had the lowest mortality rate (17 %) reported to date [12–14, 45].

The first objective of this study was to identify pre-ECMO outcome predictors to help ICU physicians select, for ECMO support, very severe ARDS patients with reasonable chance of survival. The PRESERVE scoring system we propose herein, which combines eight simple variables easily available at the time of ECMO decision, identified four subgroups of patients with significantly different probabilities of survival (Fig. 3). Age, immunocompromised status, and pre-ECMO Pplat >30 cm H₂O and PEEP <10 cm H₂O (despite optimization of MV settings according to the recommendations based on the ARDSnet studies [18]) had the highest impact on the outcomes of our patients. As opposed to previous studies [15], pre-ECMO PaO₂/FiO₂ was not associated with survival after adjusting for the latter parameters, suggesting that alterations in lung mechanics are more important prognostic factors than severity of hypoxemia. Furthermore, because a recent study indicated major survival improvement with early prone positioning of ARDS patients [40], we forced this parameter into our multivariable model and observed that it was independently associated with lower mortality. Interestingly, prone-positioned patients had significantly higher PEEP and lower Pplat and driving pressures before ECMO (data not shown). While prone placement did not prevent refractory hypoxemia leading to ECMO in nearly two-thirds of our severe ARDS patients (the highest rate in the ECMO series reported to date), it might have protected their lungs from further MV-induced lung injuries and ultimately resulted in better long-term survival. Our study also confirmed that pre-ECMO MV for more than 1 week was associated with lower survival [15, 16]. In severely hypoxemic patients with profound alteration in lung mechanics and not, or only partially, responding to prone placement, ECMO might therefore be discussed very early in the course of the disease. Notably, BMI >30 kg/m² was associated with better outcomes, independently of pre-ECMO Pplat and PEEP. Although it has frequently been reported that obese patients have better ICU outcomes than normal-weight patients [46], this observation might suggest that Pplat might not be a valid surrogate of transpulmonary pressure in obese patients and, therefore, might not necessarily mean more severe respiratory failure, because their chest wall elastance is higher than normal reference values.

HRQL evaluated after a median follow-up of 17 months for 80 % of the 6-month ICU survivors was

Fig. 2 Kaplan–Meier estimates of cumulative probabilities of survival for patients with pre-ECMO PRESERVE score classes 0–3 ($n = 34$), 4–6 ($n = 38$), 7–9 ($n = 31$) and 10–15 ($n = 32$). The p -value was calculated by means of the log-rank test. *ECMO* extracorporeal membrane oxygenation, *PRESERVE* PRedicting dEath for SEvere ARDS on VV-ECMO

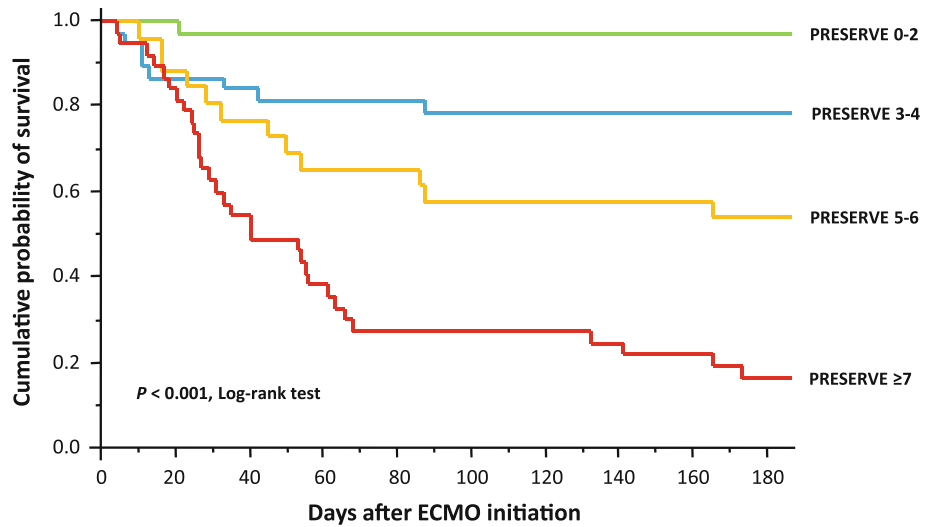
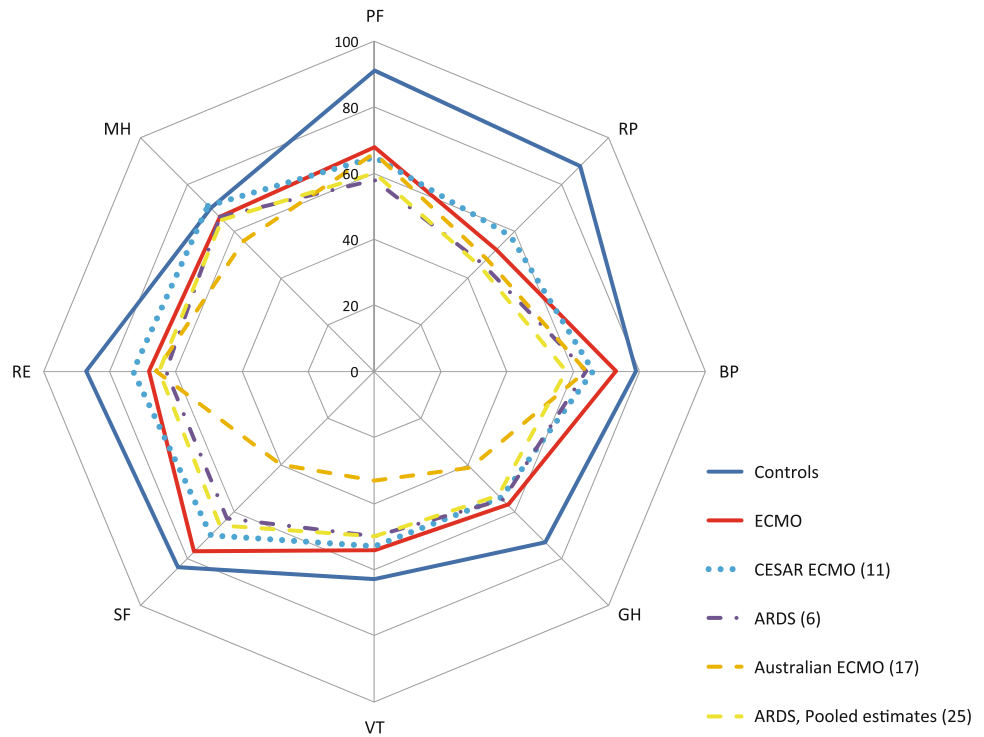


Fig. 3 Comparison of median SF-36 scores of 67 of our ARDS survivors treated by ECMO after a median follow-up of 17 months after intensive care unit discharge and their 67 age- and sex-matched control subjects [27], and 80 conventionally treated ARDS survivors at 1-year of follow-up [4], 57 ECMO-arm ARDS patients included in the conventional ventilation or ECMO for severe adult respiratory failure (CESAR) trial [9], 15 ECMO-treated Australian patients with refractory hypoxemia [19] and a pooled estimated score of five follow-up studies on ARDS survivors [33]. Higher scores denote better health-related quality of life. *ARDS* acute respiratory distress syndrome, *BP* body pain, *ECMO* extracorporeal membrane oxygenation, *GH* general health, *MH* mental health, *PF* physical functioning, *RE* role-emotional, *RP* role-physical, *SF* social functioning, *SF-36* Short Form-36, *VT* vitality



still impaired compared with that of sex- and age-matched controls, especially concerning SF-36 physical health and vitality domains, while social functioning and mental health were considered satisfactory. Although differences in case-mixes make comparisons between series difficult, we observed that our patients' SF-36 scores were better (Fig. 3) than those of eighty 1-year ARDS survivors evaluated by Herridge et al. [4], or a pooled estimated SF-36 score based on five ARDS-survivor cohorts [33]. In agreement with Herridge et al. [4, 5], we also found that

physical and emotional domains improved with longer follow-up. Data on long-term HRQL of ECMO-treated ARDS patients are scarce. Although the 57 ECMO-arm survivors included in the CESAR trial [9] and 15 ECMO-treated A(H₁N₁)-induced ARDS patients from the French réseaux européen de recherche en ventilation artificielle (REVA) cohort [21] had SF-36 scores comparable with those of our patients (Fig. 3), a recent study on 15 Australian ARDS survivors [19] reported lower social function, vitality and general health-domain scores.

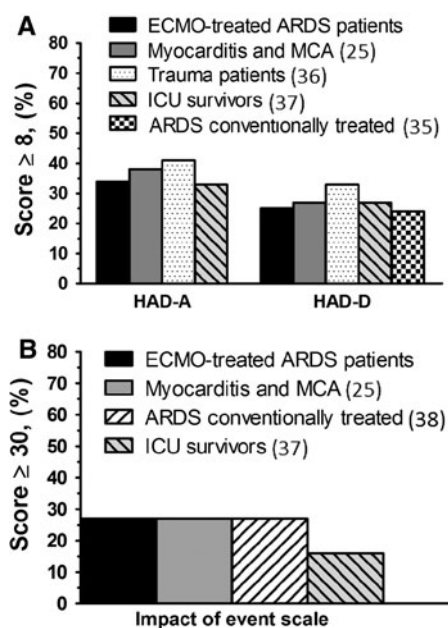


Fig. 4 a Mean percentages of our ARDS survivors treated by ECMO (evaluated after a median follow-up of 17 months after ICU discharge) with clinically significant anxiety and/or depression (HAD-A/D subscale scores $\geq 8/21$) compared with those of 156 conventionally treated ARDS patients [35], 26 myocarditis survivors treated by MCA [25], 153 trauma patients [36] and 194 ICU survivors [37]. **b** Mean percentages of our ECMO-treated ARDS survivors at risk of post-traumatic stress disorder compared with those of 80 conventionally treated ARDS patients [38], 26 myocarditis survivors [25] and 194 ICU survivors [37]. ARDS acute respiratory distress syndrome, ECMO extracorporeal membrane oxygenation, HAD Hospital Anxiety and Depression, ICU intensive care unit, MCA mechanical circulatory assistance

Notably, less than half of those Australian patients had returned to work, compared with 72 % of our patients.

Regular episodes of dyspnea were reported herein by 36 % of the respondents, and SGRQ scores revealed a perception of physical limitations comparable with that reported in previous ARDS series with different case-mixes [3, 6, 9, 20, 34, 39] (Fig. E2 [see ESM]). ARDS survivors frequently complain of subjective symptoms such as ‘shortness of breath’ even during light exercise, despite minor residual abnormalities on pulmonary computed tomography scan [21, 47]. ICU-acquired diaphragmatic dysfunction and respiratory muscle weakness may therefore contribute to the persistence of these symptoms despite improvement in pulmonary function. Future studies should now focus on the pathophysiology of musculoskeletal sequelae of critical illnesses, and establishment of customized, patient-centered, rehabilitation programs that might help improve long-term outcomes.

The burden of ARDS-induced psychological sequelae in our ECMO-treated patients was still perceptible

17 months post-ICU discharge. Notably, 34 and 25 % reported symptoms of severe anxiety and/or depression, and 15 % were at risk of PTSD. Although they were more severely ill during the acute disease phase, their probabilities of anxiety, depression and/or PTSD were similar to those reported in other post-ICU studies [25, 35–37, 48, 49] (Fig. 3a, b). Identification of anxious and/or depressive patients and those at risk of developing PTSD might allow prescription of specific medications and cognitive and/or behavioral strategies to control their emotional and psychological distress.

Our study’s strengths are the large number of patients included, detailed characterization of the population considered, and its multicenter and longitudinal design, with high rates of follow-up 17 months after ICU discharge. However, our study also has limitations. First, since it was not possible to measure HRQL before disease onset, the lower HRQL observed could be attributable to pre-existing health conditions and not directly related to severe ARDS and/or ECMO. Second, the self-assessed, persistently impaired physical health and vitality might not be specific to ARDS but may represent sequelae of any severe disease requiring prolonged ICU stay, including critical illness, muscle-wasting and weakness. Third, Papazian et al. [50] demonstrated that 48 h of intravenous cisatracurium besylate significantly improved outcomes of ARDS patients. However, prescription of neuromuscular blocking agents was not recorded in our database and therefore this variable was not tested into our multivariable models. Lastly, the PRESERVE score should now be tested in other populations of severe ARDS patients receiving ECMO since its performance might be overestimated if only based on the analysis of our cohort of patients.

In conclusion, long-term survival of this multicenter cohort of 140 ECMO-treated patients with refractory ARDS reached 60 %. HRQL evaluation in 80 % of the 6-month survivors revealed persistent physical and emotional-related difficulties, with anxiety, depression or PTSD symptoms reported by 34, 25 or 16 %, respectively. The PRESERVE score we developed might help ICU physicians select appropriate candidates for ECMO among severe ARDS patients. However, before widespread utilization, this scoring system should now be tested in other groups of ECMO-treated severe ARDS patients with different case-mixes. Ongoing randomized studies might also help better define indications of ECMO for severe ARDS patients [22].

Conflicts of interest Professor Combes is the primary investigator of the ECMO to rescue lung injury in severe ARDS (EOLIA) trial, NCT01470703, a randomized trial of VV-ECMO supported in part by MAQUET. He has received honoraria for lectures by MAQUET. All other authors have no conflicts of interest to declare.

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