ANESTHESIOLOGY

Quality of Life and Lung Function in Survivors of Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome

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ABSTRACT

Background: Survivors of acute respiratory distress syndrome (ARDS) have long-term impairment of pulmonary function and health-related quality of life, but little is known of outcomes of ARDS survivors treated with extracorporeal membrane oxygenation. The aim of this study was to compare long-term outcomes of ARDS patients treated with or without extracorporeal membrane oxygenation.

Methods: A prospective, observational study of adults with ARDS (January 2013 to December 2015) was conducted at a single center. One year after discharge, survivors underwent pulmonary function tests, computed tomography of the chest, and health-related quality-of-life questionnaires.

Results: Eighty-four patients (34 extracorporeal membrane oxygenation, 50 non–extracorporeal membrane oxygenation) were studied; both groups had similar characteristics at baseline, but comorbidity was more common in non–extracorporeal membrane oxygenation (23 of 50 *vs.* 4 of 34, 46% *vs.* 12%, $P < 0.001$), and severity of hypoxemia was greater in extracorporeal membrane oxygenation (median Pao_2/Fio_2 72 [interquartile range, 50 to 103] *vs.* 114 [87 to 133] mm Hg, $P < 0.001$) and respiratory compliance worse. At 1 yr, survival was similar (22/33 *vs.* 28/47, 66% *vs.* 59%; $P = 0.52$), and pulmonary function and computed tomography were almost normal in both groups. Non–extracorporeal membrane oxygenation patients had lower health-related quality-of-life scores and higher rates of posttraumatic stress disorder.

Conclusions: Despite more severe respiratory failure at admission, 1-yr survival of extracorporeal membrane oxygenation patients was not different from that of non–extracorporeal membrane oxygenation patients; each group had almost full recovery of lung function, but non–extracorporeal membrane oxygenation patients had greater impairment of health-related quality of life.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Extracorporeal membrane oxygenation is used in severe acute respiratory distress syndrome; whereas the long-term complications among survivors of acute respiratory distress syndrome treated without extracorporeal membrane oxygenation are well described, the status of extracorporeal membrane oxygenation survivors is poorly understood

What This Article Tells Us That Is New

- In a single-center cohort of acute respiratory distress syndrome survivors, management with (*vs.* without) extracorporeal membrane oxygenation resulted in similar survival at 1 yr, pulmonary function, and computed tomography lung imaging, but less impairment in quality of life

Acute respiratory distress syndrome (ARDS) is an inflammatory condition with diffuse injury to the alveolar-capillary barrier leading to hypoxemic respiratory failure.[1] Mechanical ventilation is a lifesaving maneuver, but an inappropriate ventilatory strategy causes ventilation-induced lung injury.[2] The most severe cases of ARDS require extracorporeal membrane oxygenation to guarantee vital gas exchange and protective ventilation.[3] Mortality of severe ARDS has decreased from more than 60% to around 40%.[4] Nevertheless, ARDS patients remain at high risk for long-term mortality and disability.[5] Several studies have demonstrated that ARDS survivors have long-term impairment of pulmonary function, exercise capacity, and residual radiographic abnormalities.[6–8] Moreover, they present muscle wasting and neurocognitive and psychologic sequelae,[9–12] impairing health-related quality of life.[8]

Little is known on long-term outcomes of ARDS patients treated with extracorporeal membrane oxygenation.[13–16] The aim of the present study was to assess 1-yr outcomes of ARDS patients with regard respiratory function, quantitative pulmonary imaging, and health-related

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quality of life. Specifically, we compared the outcomes of patients supported with extracorporeal membrane oxygenation with those treated with conventional ventilation.

Materials and Methods

The local ethics committee (Comitato Etico Milano Area B, Milan, Italy) approved the protocol (June 31, 2012), and each patient gave written informed consent.

The general intensive care unit of Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico (Milan, Italy) is a tertiary level, 12-bed unit and is a referral center for respiratory failure and extracorporeal membrane oxygenation. Management of ARDS and extracorporeal membrane oxygenation at our Institution is described in detail elsewhere[17–19] and in the online supplement (see Supplemental Digital Content, Additional Methods, http://links.lww.com/ALN/B861).

We conducted a prospective, longitudinal, cohort observation study to compare outcomes of patients treated with extracorporeal membrane oxygenation or conventional treatment. All adult patients with ARDS defined according to Berlin definition criteria[20] admitted to our intensive care unit from January 2013 to December 2015 were evaluated. Exclusion criteria were (1) previous lung transplant, (2) severe chronic disease for which invasive treatment were deemed futile, (3) massive hemorrhage, (4) cardiac arrest, (5) survival in intensive care unit less than 6 h, or (6) recurrent ARDS.

The following patients' data at intensive care unit admission were collected: demographics, major comorbidities, ARDS risk factors, immunocompromised status, severity scores (*i.e.*, Sequential Organ Failure Assessment score and Simplified Acute Physiology Score II of the first 24 h of intensive care unit stay), arterial blood gas analysis, ventilator setting, respiratory system compliance, mean pulmonary artery pressure, and intrapulmonary shunt fraction. For extracorporeal membrane oxygenation patients, transfer from peripheral hospital by mobile extracorporeal membrane oxygenation team and duration of mechanical ventilation before extracorporeal membrane oxygenation connection were recorded.

The following short-term outcomes were assessed: survival at intensive care unit discharge, intensive care unit length of stay, duration of mechanical ventilation and extracorporeal membrane oxygenation, frequency of tracheostomy, prone positioning, and renal replacement therapy, and hospital length of stay and hospital survival.

At 1 yr after discharge from intensive care unit, all patients were contacted by phone and invited to undergo the following follow-up examinations: (1) spirometry (including diffusion capacity of the lung for carbon monoxide), (2) resting arterial blood gas analysis, (3) 6-min walking test, (4) computed tomography of the chest, and (5) evaluation of health-related quality of life with three questionnaires: 36-Item Short Form,[21] St. George's Respiratory Questionnaire,[22] and Impact of Event Scale–Revised Score.[23] All evaluations were performed at our institution during a single-day visit. The questionnaires were administered in person at the beginning of the follow-up day visit by two interviewers (*i.e.*, F.C., E.S., F.B., V.S.) who were blinded to the patients' treatment and had never participated in the care of the patients.[24]

Spirometry and 6-min walking test were performed following international guidelines.[25,26] Computed tomography scan was performed from lung apices to bases and quantitative analysis performed as previously described[27] (see Supplemental Digital Content, Additional Methods, http://links.lww.com/ALN/B861). Moreover, the computed tomography scans were qualitatively assessed for the presence and spatial distribution of six patterns: (1) ground-glass opacifications, (2) consolidations, (3) bullae, (4) interstitial fibrosis, (5) reticular pattern, and (6) bronchiectasis.

Statistical Analysis

Data are reported as median and interquartile range for continuous variables. Categorical variables are expressed as number of patients. No statistical power calculation was performed *a priori*. Sample size was chosen based on available clinical data at our institution. For binary outcome measures, odds ratios and associated 95% likelihood ratio–based CIs were calculated, and comparison between extracorporeal membrane oxygenation and non–extracorporeal membrane oxygenation was performed with the chi-square test or Fisher exact test, as appropriate. The Kruskal–Wallis test was used to compare nonparametric continuous variables between extracorporeal membrane oxygenation and non–extracorporeal membrane oxygenation patients. Kaplan–Meier survival curve analysis was used with log-rank test for comparison of survival time between extracorporeal membrane oxygenation and non–extracorporeal membrane oxygenation patients. Observation were right-censored. All statistical tests were two-tailed, and statistical significance was accepted at $P < 0.05$, while a difference in mortality between 5% and 10% would be of clinical importance. The JMP pro 12.1 (SAS, U.S.A.) was used.

Results

Patient Characteristics

From January 2013 to December 2015, 109 patients with ARDS were admitted to our intensive care unit. Of these, 84 were included in the study. Of the 84 included patients, 34 (40%) received extracorporeal membrane oxygenation whereas 50 (60%) did not (fig. 1).

Patients' characteristics at admission are summarized in table 1. The most common diagnosis was pneumonia (48 patients [58%]). The proportion of patients with one or more comorbidities was higher in non–extracorporeal

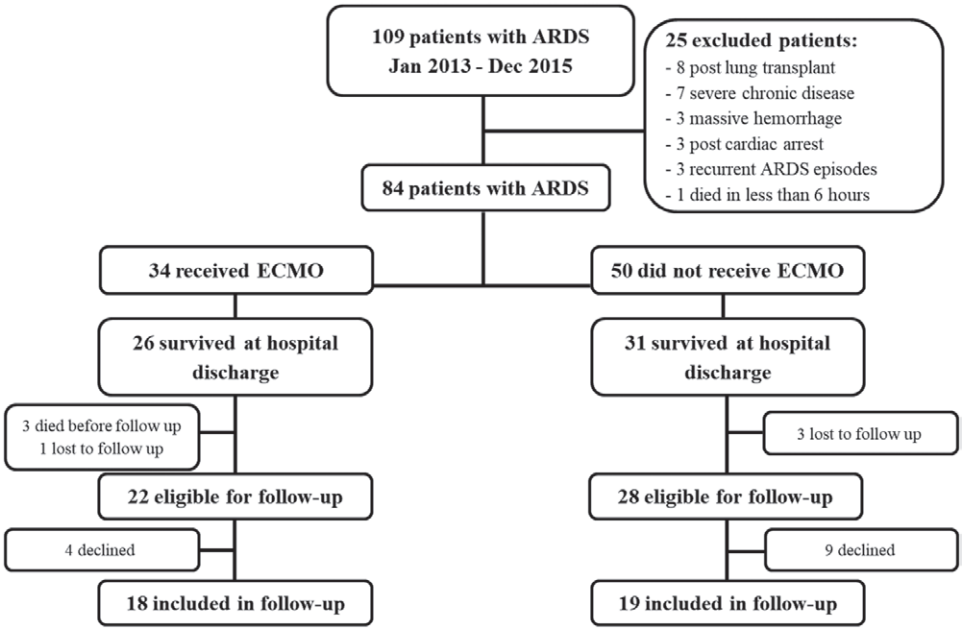

Fig. 1. Patient population flowchart. ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation.

membrane oxygenation subgroup (23 of 50 *vs.* 4 of 34, 46% *vs.* 12%, $P < 0.001$). At admission, extracorporeal membrane oxygenation patients were more hypoxemic (Pao_2/Fio_2 72 [50 to 103] *vs.* 114 [87 to 133] mm Hg; $P < 0.001$) and hypercapnic, had lower arterial pH and respiratory system compliance (27 [19 to 37] *vs.* 31 [26 to 37] ml/cmH_2O; $P = 0.043$), had higher intrapulmonary shunt fraction, and were ventilated with higher positive end-expiratory pressure levels (15 *vs.* 10 cm H_2O; $P = 0.002$).

Intensive Care Unit and Hospital Survival

Overall, 58 (69%) patients were discharged alive from the intensive care unit. At univariate analysis, intensive care unit survival did not differ between extracorporeal membrane oxygenation and non–extracorporeal membrane oxygenation patients (26 of 34 *vs.* 32 of 50, 76% *vs.* 64%; $P = 0.220$; odds ratio, 1.83 [0.70 to 5.07]). Multiorgan failure was the most common cause of death (58%), followed by respiratory failure (17%) and septic shock (17%). It is notable that fatal brain hemorrhage occurred in one extracorporeal membrane oxygenation patient and in one non–extracorporeal membrane oxygenation patient. Table 2 compares clinical endpoints and use of adjunctive measures between the patients' groups. Extracorporeal membrane oxygenation patients had longer median intensive care unit length of stay (24 [15 to 36] days *vs.* 11 [5 to 25] days; $P = 0.017$), higher duration of invasive mechanical ventilation (21 [11 to 35] days *vs.* 8 [5 to 21] days; $P = 0.010$), and higher frequency of use of prone positioning (22 [65%] *vs.* 22 [44%]; $P = 0.049$).

A single extracorporeal membrane oxygenation patient died in step-down unit, after intensive care unit dismissal. Overall, 57 patients (68%) survived to hospital discharge. Hospital survival was not different between extracorporeal membrane oxygenation and non–extracorporeal membrane oxygenation patients (26 of 34 *vs.* 31 of 50, 76% *vs.* 62%; $P = 0.158$; odds ratio 1.99 [0.76 to 5.52]). At intensive care unit discharge, a higher number of extracorporeal membrane oxygenation patients needed supplemental oxygen (7 *vs.* 2, 26% *vs.* 6%; $P = 0.023$; table 3 and Supplemental Digital Content, e-table 1, http://links.lww.com/ALN/B861).

One-year Survival

At 1-yr follow-up, four patients could not be contacted (one extracorporeal membrane oxygenation, three non–extracorporeal membrane oxygenation) and were lost to survival analysis. Three patients (all extracorporeal membrane oxygenation patients) died after hospital discharge because of causes unrelated to ARDS. Thus, at 1-yr follow-up, 50 of 80 patients (62%) were alive. Survival of extracorporeal membrane oxygenation patients was higher but not significantly different from that of non–extracorporeal membrane oxygenation patients (22 of 33 *vs.* 28 of 47; 66% *vs.* 59%, odds ratio 1.35 [0.54 to 3.50], $P = 0.517$). The log-rank test showed no significant difference in survival between groups ($P = 0.412$; fig. 2).

The characteristics at admission associated with a higher intensive care unit mortality were older age, lower weight, immunocompromised status, use of renal replacement therapy during intensive care unit stay, and higher Simplified

Table 1. Baseline Patients' Characteristics at Intensive Care Unit Admission (n = 84)

	ECMO (n = 34)	Non-ECMO (n = 50)	Overall (n = 84)	*P*	Odds Ratio (95% CI)
Gender (male)	24 (70%)	31 (62%)	55 (65%)	0.414	1.47 (0.58–3.80)
Age, yr	54 (41–63)	54 (45–70)	54 (43–67)	0.587	0.99 (0.96–1.02)
Weight, kg	73 (64–78)	72 (60–80)	72 (62–76)	0.857	0.99 (0.96–1.03)
Year					
2013	14 (41%)	19 (38%)	33 (39%)	0.770	1.14 (0.46–2.78)
2014	9 (26%)	15 (30%)	24 (29%)	0.724	0.84 (0.30–2.19)
2015	11 (32%)	16 (32%)	27 (32%)	0.972	1.01 (0.39–2.57)
Comorbidities					
COPD	1 (3%)	8 (16%)	9 (11%)	0.077	0.16 (0.01–0.93)
Diabetes mellitus	3 (9%)	5 (10%)	8 (10%)	1	0.87 (0.16–3.81)
Heart failure*	1 (3%)	1 (2%)	1 (2%)	1	1.48 (0.05–38.0)
Chronic renal failure	1 (3%)	6 (12%)	7 (8%)	0.233	0.22 (0.01–1.38)
Chronic liver failure†	1 (3%)	6 (12%)	7 (8%)	0.233	0.22 (0.01–1.38)
1 or >1 comorbidities	4 (12%)	23 (46%)	27 (32%)	**0.001**	**0.15 (0.04–0.46)**
ARDS risk factors					
Pneumonia	23 (67%)	26 (52%)	48 (58%)	0.1508	1.93 (0.78–4.9)
Septic shock	4 (9%)	10 (20%)	13 (15%)	0.152	0.39 (0.08–1.39)
Pulmonary vasculitis	3 (9%)	3 (6%)	6 (7%)	0.625	1.51 (0.26–8.65)
Gastric aspiration	2 (6%)	3 (6%)	5 (6%)	0.982	0.97 (0.12–6.22)
Blood transfusion	0 (0%)	3 (6%)	3 (4%)	0.074	—
Pancreatitis	0 (0%)	1 (2%)	1 (1%)	0.306	—
Pulmonary contusion	0 (0%)	1 (2%)	1 (%)	0.795	—
None	1 (6%)	2 (4%)	3 (4%)	0.692	1.50 (0.17–13.0)
Transferred from peripheral hospital	26 (76%)	20 (43%)	46 (55%)	**0.001**	**4.87 (1.90–13.5)**
Transferred on ECMO support	21 (62%)	n/a	21 (25%)	—	—
Infection at admission	28 (87%)	36 (85%)	64 (86%)	0.823	1.16 (0.30–4.93)
H1N1 positive	9 (32%)	4 (11%)	13 (20%)	**0.039**	**3.79 (1.07–15.5)**
Immunocompromise	6 (17%)	15 (30%)	21 (25%)	0.192	1.99 (0.71–6.22)
Pao_2/Fio_2, mm Hg, <100	25 (74%)	22 (44%)	47 (56%)	**0.006**	**3.53 (1.41–9.45)**
Pao_2/Fio_2, mm Hg	72 (50–103)	114 (87–133)	95 (69–127)	**0.001**	**0.97 (0.95–0.98)**
Minute ventilation, l/min‡	2.4 (1.8–3.2)	9.1 (7.7–11)	—	—	—
Tidal volume, ml‡	244 (181–330)	465 (382–556)	—	—	—
SAPS II	38 (31–49)	43 (31–54)	40 (31–50)	0.655	0.99 (0.96–1.02)
SOFA score	9 (6–12)	8 (5–11)	8 (6–12)	0.319	1.03 (0.93–1.15)
Blood gas analysis					
pH	7.25 (7.18–7.40)	7.34 (7.28–7.39)	7.32 (7.25–7.39)	**0.003**	**0.03 (0.00–0.33)**
$PaCO_2$ (mmHg)	53 (37–66)	41 (36–46)	43 (37–54)	**0.001**	**1.06 (1.02–1.11)**
Pao_2 (mmHg)	62 (50–83)	77 (69–97)	75 (60–91)	**0.001**	**0.96 (0.94–0.98)**
Fio_2, %	100 (80–100)	80 (60–90)	90 (70–100)	**0.001**	**1.04 (1.02–1.07)**
Compliance, ml/cm H_2O	27 (19–37)	31 (26–37)	29 (24–37)	**0.043**	**0.95 (0.90–0.99)**
Driving force, cm H_2O	12 (10–20)	15 (13–18)	15 (11–18)	0.335	0.95 (0.85–1.05)
PEEP, cm H_2O	15 (10–18)	10 (10–15)	12 (10–15)	**0.002**	**1.20 (1.06–1.38)**
Intrapulmonary shunt, %	47 (39–58)	30 (22–35)	35 (25–44)	**0.001**	**1.16 (1.09–1.26)**
Mean pulmonary artery pressure, mm Hg	31 (25–40)	31 (29–37)	31 (28–38)	0.622	0.98 (0.91–1.06)

Data are presented as absolute frequency (% of the included patients) or as median and interquartile range. Odds ratio of continuous variables are odds ratio per unit increase in variable. Statistically significant results are highlighted in bold. ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; n/a, not applicable; PEEP, positive end expiratory pressure; SAPS II, simplified acute physiology score; SOFA, sequential organ-failure assessment. *NYHA classes III–IV. †Child-Pugh Class C–D. ‡After ECMO institution.

Acute Physiology Score II and Sequential Organ Failure Assessment scores (Supplemental Digital Content, e-table 2, http://links.lww.com/ALN/B861).

Respiratory Function and Health-related Quality of Life at 1-yr Follow-up

Of the 50 patients alive at 1 yr, 13 (four extracorporeal membrane oxygenation, nine non–extracorporeal membrane oxygenation) refused our invitation to undergo the planned follow-up visit. All reported as cause of refusal an excessive distance to the hospital. Hence, 37 patients (18 extracorporeal membrane oxygenation, 19 non–extracorporeal membrane oxygenation) underwent follow-up assessments: among them, extracorporeal membrane oxygenation patients showed longer intensive care unit length of stay, longer invasive mechanical ventilation, and higher frequency of use of pronation (see SupplementalDigital Content, e-table 3, http://links.lww.com/ALN/B861).

Table 2. Clinical Outcomes and Use of Adjunctive Therapy

	ECMO (n = 34)	Non-ECMO (n = 50)	Overall (n = 84)	*P*	Odds Ratio
Length of ICU stay, days	24 (15–36)	11 (5–25)	17 (7–31)	**0.017**	—
Length of Hospital stay, days	33 (19–48)	23 (12–45)	29 (13–47)	0.260	—
Duration of ECMO, days	9 (6–13)	—	—	—	—
IMV before ECMO, days	1 (0–3)	—	—	—	—
IMV, days	21 (11–35)	8 (5–21)	16 (5–28)	**0.010**	—
Tracheostomy	22 (65%)	25 (50%)	47 (56%)	0.134	0.54 (0.22–1.33)
Prone position	22 (65%)	22 (44%)	44 (52%)	**0.049**	**0.43 (0.17–1.05)**
RRT	14 (41%)	19 (38%)	33 (39%)	0.473	0.87 (0.36–2.13)

Data are presented as absolute frequency (% of the included patients) or as median and interquartile range. Statistically significant results are highlighted in bold. ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IMV, invasive mechanical ventilation; RRT, renal replacement therapy.

Follow-up data are shown in table 3. Arterial blood gas values and walking test were normal, with no differences between treatment groups, and no patient needed supplemental oxygen. Spirometric values were at the lower normal range, whereas diffusion capacity of the lung for carbon monoxide showed a mild compromise, similar in the two groups.

Quality-of-life questionnaires demonstrated non–extracorporeal membrane oxygenation patients to have more severe impairment of health-related quality of life. Indeed, non–extracorporeal membrane oxygenation patients had 36-Item Short Form compromised in all domains (with general health significantly reduced as compared with extracorporeal membrane oxygenation patients), St. George's Respiratory Questionnaire activity and impact domains significantly more impaired than extracorporeal membrane oxygenation patients, and Impact of Event Scale–Revised Score scores higher than extracorporeal membrane oxygenation patients. Of note, among the overall population, one quarter of the patients had symptoms compatible with posttraumatic stress disorder (*i.e.*, Impact of Event Scale–Revised Score greater than 37).

Quantitative computed tomography scan analyses showed that lung weight, volume, and frequency distribution were in the normal range (see Supplemental Digital Content, e-fig. 1, http://links.lww.com/ALN/B861); non–extracorporeal membrane oxygenation patients had higher ratio of overinflation (8% [4 to 13] *vs.* 4% [1 to 8], $P = 0.045$). Qualitative lung analysis detected mild signs of interstitial fibrosis in 50% of the patients, with no difference between extracorporeal membrane oxygenation and non–extracorporeal membrane oxygenation patients. Ground-glass opacifications (distributed mainly in the nondependent areas) were more frequent in extracorporeal membrane oxygenation patients (40% *vs.* 5%, $P = 0.013$).

We did not observe any missing data, except for a single computed tomography scan that could not have undergone quantitative analysis because of data corruption. Overall, study data have never been reported in any public form (*i.e.*, publication or congress), but only in divisional meetings. All the analyses are primary analysis. All data collection was preplanned, and no data have been removed from the analysis or unreported.

Discussion

In this prospective study we compared long-term outcomes from ARDS in patients treated with extracorporeal membrane oxygenation and patients not supported with extracorporeal membrane oxygenation. Despite higher severity of respiratory failure at admission, 1-yr survival of extracorporeal membrane oxygenation patients was not different from that of patients treated with conventional mechanical ventilation (*i.e.*, 65% *vs.* 56%). Overall, most of our patients had almost full recovery of respiratory function and lung morphology. Non–extracorporeal membrane oxygenation patients had a greater impairment of health-related quality of life.

In the last decade, extracorporeal membrane oxygenation use has increased, either for refractory hypoxemia[28] or to allow protective ventilation in ARDS patients.[29] Several authors have described long-term sequelae on respiratory, cognitive, and neuropsychologic function in ARDS survivors.[5,8] However, few studies have included patients treated with extracorporeal membrane oxygenation.[13–16] On the one hand, we might expect worse outcomes in extracorporeal membrane oxygenation patients, because of higher illness severity or because of extracorporeal membrane oxygenation–related complications. On the other hand, we can speculate that extracorporeal membrane oxygenation, by facilitating protective ventilation, may mitigate ventilation-induced lung injury–associated long-term sequelae.

Patients in the two groups were comparable with respect to cause of ARDS and nonrespiratory severity scores at admission. Non–extracorporeal membrane oxygenation patients had a higher number of comorbidities, whereas extracorporeal membrane oxygenation patients had a more severe respiratory compromise (*i.e.*, worse gas exchanges and respiratory mechanics, higher intrapulmonary shunt fraction, positive end-expiratory pressure levels,

Table 3. Patient Characteristics at 1-yr Follow-up

	ECMO (n = 18)	Non-ECMO (n = 19)	Overall (n = 37)	*P*
Body weight, kg	74 (62–90)	76 (65–89)	74 (63–89)	0.837
Spirometry				
FVC, %	94 (75–111)	96 (84–112)	96 (79–111)	0.569
FEV_1, %	90 (78–106)	93 (73–105)	94 (75–108)	0.890
FEV_1/FVC, %	103 (95–111)	100 (93–105)	101 (94–108)	0.116
TLC, %	91 (77–105)	100 (80–114)	96 (78–109)	0.188
RV, %	76 (67–108)	97 (88–130)	93 (73–117)	0.154
DLCO, %	63 (55–74)	71 (59–92)	64 (57–81)	0.564
Walking test, mt				
DLCO/VA, %	95 (68–108)	83 (73–98)	86 (72–102)	0.447
Blood gas analysis				
pH	7.42 (7.39–7.43)	7.43 (7.41–7.46)	7.43 (7.39–7.44)	0.150
Pao_2, mm Hg	84 (76–91)	87 (83–98)	86 (78–95)	0.259
$Paco_2$, mm Hg	40 (37–43)	38 (34–40)	39 (35–42)	0.139
Quantitative CT scan analysis				
Air volume, ml	3193 (2711–4860)	3925 (3415–4742)	3769 (2805–4770)	0.563
Gas/tissue, %	78 (76–81)	81 (77–83)	81 (77–82)	0.240
Weight, g	1003 (767–1056)	871 (756–1089)	900 (757–1058)	0.934
Overinflated, %	4 (1–8)	8 (4–13)	6 (1–10)	0.045
Normal, %	73 (64–78)	66 (60–77)	70 (63–76)	0.248
Poorly inflated, %	17 (15–19)	16 (10–19)	17 (15–19)	0.531
Not inflated, %	5 (2–9)	4 (2–10)	5 (2–10)	0.704
Qualitative CT scan analysis				
Ground-glass opacification	6 (40)	1 (5)	7 (21)	0.013
Consolidation	4 (25)	2 (11)	6 (18)	0.286
Bullae	1 (6)	5 (28)	6 (18)	0.086
Interstitial fibrosis	7 (43)	10 (56)	17 (50)	0.491
Reticular pattern	6 (37)	4 (22)	10 (29)	0.328
Bronchiectasis	7 (44)	3 (17)	10 (29)	0.081
SF-36 score				
Physical function	95 (75–100)	75 (40–95)	87 (55–95)	0.097
Role physical	75 (25–100)	50 (0–100)	62 (0–100)	0.656
Bodily pain	100 (58–100)	68 (45–100)	78 (52–100)	0.140
General health	80 (45–85)	55 (25–70)	60 (44–81)	0.025
Vitality	70 (58–85)	60 (35–75)	65 (47–80)	0.217
Social functioning	88 (63–100)	75 (50–100)	80 (60–100)	0.245
Role emotional	100 (67–100)	67 (33 -100)	100 (33–100)	0.426
Mental health	75 (56–88)	70 (46–84)	72 (52–86)	0.140
SGRQ score				
Symptoms	17.8 (11.0–27.5)	32.5 (2.7–41.4)	24.8 (5.1–40.3)	0.143
Activity	13.7 (6.1–35.5)	54.0 (5.8–67.0)	26.8 (6.1–65.6)	0.027
Impacts	8.3 (0.0–10.1)	21.8 (0.0–44.0)	8.9 (0.0–32.4)	0.029
Total	10.5 (5.3–20.8)	33.9 (3.4–54.5)	15.9 (4.4–41.8)	0.004
IES-R score				
Total	9.0 (4.0–26)	19.0 (4.0–54.0)	16.0 (4.0–36.5)	0.029

Data are presented as absolute frequency (% of the included patients) or as median and interquartile range. Spirometry parameters are shown as % of the predicted by weight and age. CT, computed tomography; DLCO, diffusion capacity of carbon monoxide; DLCO/VA, diffusion capacity of carbon monoxide corrected for ventilation; ECMO, extracorporeal membrane oxygenation; FCV, forced vital capacity; FEV_1, forced expiratory flow in the first second of expiration; ICU, intensive care unit; IES-R, Impact of Event Scale–Revised Score; RV, residual volume; SF-36, 36-Items Short Form; SGRQ, St. George's Respiratory Questionnaire; TLC, total lung capacity.

and use of prone positioning). Duration of intensive care unit stay and of mechanical ventilation were more than double in extracorporeal membrane oxygenation patients. Despite this, extracorporeal membrane oxygenation and non–extracorporeal membrane oxygenation patients had similar survival rates.

Factors significantly associated with the risk of death were independent from the severity of respiratory disease, and the main cause of mortality was multi-organ failure.

At 1 yr after intensive care unit discharge, only three patients (all in the extracorporeal membrane oxygenation group) died of causes not related to ARDS. One-year survival rates were very similar to those recently reported[28]: 65% and 56% in extracorporeal membrane oxygenation and non–extracorporeal membrane oxygenation patients, respectively. Survivors in both groups did not develop major respiratory sequelae, and respiratory function tests did not show clinically meaningful alterations. As previously described,[7,16,30] we observed a slight impairment

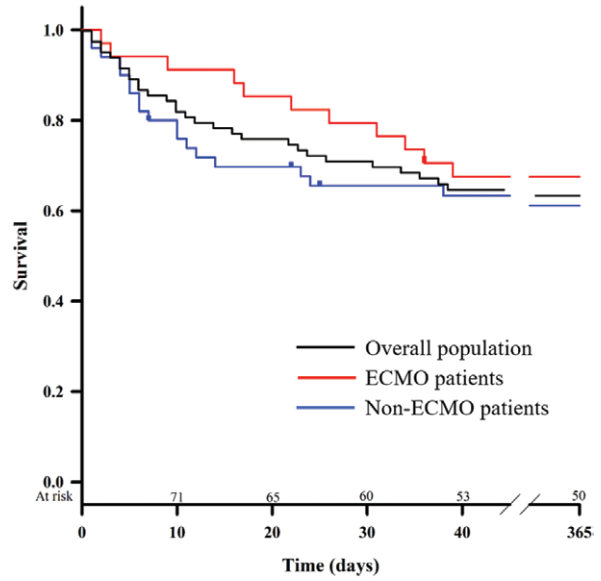

Fig. 2. Probability of survival. Kaplan–Meier estimates of the unadjusted cumulative probability of survival. *Black line* represent the overall population, *red line* the ECMO subgroup, and *blue line* the non-ECMO patients. ECMO, extracorporeal membrane oxygenation.

of diffusion capacity of the lung for carbon monoxide in both groups. Quantitative analysis of computed tomography scans was in the normal range. Non–extracorporeal membrane oxygenation patients had higher ratio of overinflated parenchyma, confirming our previous findings.[31] As previously observed,[13] qualitative analysis of computed tomography scans showed mild, diffuse signs of interstitial fibrosis in most of our patients. Ground-glass opacities were more frequent in extracorporeal membrane oxygenation patients, but they were limited to the nondependent lung regions, sparing extensive areas of the remaining parenchyma. Taken together, these findings confirm the previous evidence of a return to near-normal physiology after ARDS,[8] without major differences between extracorporeal membrane oxygenation and non–extracorporeal membrane oxygenation patients.[32]

An important and new finding of our study is that quality of life of non–extracorporeal membrane oxygenation patients was significantly more compromised. At the 36-Item Short Form, non–extracorporeal membrane oxygenation patients had a median reduction of more than five points in all domains, indicative of a clinically relevant impairment of quality of life; the difference was particularly marked (more than 30 points) in the emotional domain. Similarly, non–extracorporeal membrane oxygenation patients had a significant reduction in activity and impact (*i.e.*, social functioning and psychologic disturbances) St. George's Respiratory Questionnaire domains, rather than in the symptom domain (*i.e.*, respiratory symptoms). Moreover, Impact of Event Scale–Revised Score demonstrated a higher risk for posttraumatic stress disorder in non–extracorporeal membrane oxygenation patients. In other words, whereas respiratory function tests and lung imaging showed an almost complete functional recovery in both groups, non–extracorporeal membrane oxygenation patients reported more fatigue, weakness, limitation in daily activities, and hardship in return to previous life as for posttraumatic stress disorder.

Several studies have shown that long-term functional limitation in ARDS survivors is not related to the degree of pulmonary dysfunction at admission, but rather to the consequences of the invasiveness of intensive care unit treatments and of critical illness *per se*: critical illness polyneuropathy/myopathy,[9] neurocognitive impairment,[10] and psychologic distress[12] (*e.g.*, posttraumatic stress disorder, depression, anxiety).

Contrary to most of the previous studies[13–16] we did not observe a reduction in functional capacity of extracorporeal membrane oxygenation patients as compared with non–extracorporeal membrane oxygenation patients. Moreover, similar to findings from two previous studies, extracorporeal membrane oxygenation survivors presented a significantly lower psychologic morbidity (*i.e.*, depression and anxiety).[28,33]

The reasons for this positive effect of extracorporeal membrane oxygenation on health-related quality of life are not clear. One can hypothesize that extracorporeal membrane oxygenation, by allowing ultra-protective ventilation, may reduce the risk of polyneuropathy or myopathy associated with mechanical ventilation. Still, in our population, extracorporeal membrane oxygenation patients had longer duration of mechanical ventilation. Moreover, better health-related quality of life at follow-up for extracorporeal membrane oxygenation patients may be attributable to particular care that these patients receive from medical and paramedical, psychologic support, and resource teams compared with standard treatment (*i.e.*, nutrition, wound care, physical therapy). On the other hand, given the observational (noninterventional) nature of our study, patient-selection bias may have occurred, as shown by the reduced number of comorbidities in extracorporeal membrane oxygenation patients.

Our study has several limitations. First, it is a single-center study conducted in a highly specialized unit: thus, our results may not be generalizable to the population of patients treated in less experienced centers. Second, the number of patients was relatively small, and the study was not powered to detect significant differences in survival. Third, it is an observational study: no standardized treatment regimens were applied during the study period, and patients were not randomly assigned to extracorporeal membrane oxygenation support or conventional treatment. Fourth, a significant number of patients were lost to follow-up (four extracorporeal membrane oxygenation, nine non–extracorporeal membrane oxygenation). Nevertheless, these patients were alive, and their refusal to participate was mainly attributable to the distance to our center rather than to health issues.

In conclusion, in a cohort of ARDS patients, subjects treated with extracorporeal membrane oxygenation had higher respiratory compromise at admission. Nonetheless, extracorporeal membrane oxygenation and non–extracorporeal membrane oxygenation cohorts had similar survival. Although overall respiratory function and lung morphology almost fully recovered in both patient groups, non–extracorporeal membrane oxygenation patients reported a greater impairment of health-related quality of life. These findings need to be confirmed prospectively in larger patient populations. Assessment of long-term outcomes from ARDS in specialized post–intensive care unit clinics may be important to improve the patients' health-related quality of life by means of dedicated rehabilitation programs.

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Competing Interests

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