Long-Term Survival in Adults Treated With Extracorporeal Membrane Oxygenation for Respiratory Failure and Sepsis*

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Objective: The use of extracorporeal membrane oxygenation in adults with respiratory failure and sepsis is steadily increasing, but the knowledge on long-term survival in this group is scarce. The aim of the present study was to investigate the 5-year survival rates and causes of late death in this group of patients.

Design: Single-center retrospective cohort study.

Setting: Karolinska University Hospital, Stockholm, Sweden.

Patients: Adult patients treated with extracorporeal membrane oxygenation for respiratory failure and sepsis between the service being established for adults in 1995 and December 2013.

Interventions: None.

Measurements and Main Results: Survival status was attained from a national Causes of Death registry. Minimal patient background data, along with data on survival and causes of death were collected. Survival rates were calculated using the Kaplan-Meier method. Of 255 subjects, 64% survived to discharge. The median follow-up time in survivors was 4.4 years. There was a high mortality rate within the first months after discharge. In the group of patients who survived the first 90 days after treatment, the 5-year survival rate was 87% and was particularly beneficial in patients treated for infectious diseases (88–100%). Late deaths were seen in most diagnostic groups, but the Kaplan-Meier curves flattened out over time.

Conclusions: Extracorporeal membrane oxygenation treatment in adult patients with respiratory failure and sepsis can be lifesaving in appropriately selected patients. For patients who survive the first months after extracorporeal membrane oxygenation treatment, long-term survival seems good, especially in patients treated for infections. (*Crit Care Med* 2017; 45:164–170)

Key Words: acute respiratory distress syndrome; cause of death; critical care outcomes; extracorporeal circulation; sepsis; survival analysis

The use of extracorporeal membrane oxygenation (ECMO) for neonatal, pediatric, and adult patients with severe respiratory or cardiac failure has become increasingly popular (1–3). To date, more than 73,000 patients have been reported to the International Registry of the Extracorporeal Life Support Organization (ELSO) (4). The number of cases and specialized centers is steadily increasing, aided by the favorable outcomes reported by some centers after the H1N1 pandemic and the potential use of ECMO for new indications such as ECMO in cardiopulmonary resuscitation situations, cardiogenic shock, and as a bridge to lung transplant (5–13). Indications, technology and the use of ECMO and concomitant ICU care are constantly evolving, and there has been a shift in the use of ECMO from primarily a respiratory support in neonates, to a wider set of indications, often in adult patients with respiratory failure that has become one of the fastest growing patient groups worldwide (1–4).

*See also p. 361.

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The local Ethical Committee approved this study (No. 2013/2259-31/4). For this type of study formal consent is not required. On behalf of all authors, the corresponding author states that there is no conflict of interest.

The authors have disclosed that they do not have any potential conflicts of interest.

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The increasing use of ECMO, along with the cost intensity, invasiveness, and potential harmful complications associated with the method creates a great demand on follow-up studies regarding both long-term survival and quality of life (1, 2, 14).

The knowledge on short-term survival has been widely documented, largely thanks to the ELSO registry (4, 15). It is well recognized that in-hospital survival outcomes vary according to diagnoses or indications for ECMO. Few publications have however reported data on long-term survival in the adult group treated for respiratory failure and have mostly had relatively short time horizons or small study groups (16–21). Available data raise the concern of both early and late mortality, as is seen in ECMO-treated children, patients with septic or cardiogenic shock and conventionally treated patients with respiratory failure or sepsis (22–33).

The aim of this study was to systematically investigate the short- and long-term survival and the causes of death in adult patients treated with ECMO at our center for respiratory failure or sepsis.

Our hypothesis was that the long-term survival is good in the vast majority of patients who survive the first critical months after ECMO treatment, and that ECMO as a method causes little or no long-term mortality.

MATERIALS AND METHODS

This study was conducted as a single-center, retrospective cohort study using patient data from the ECMO Center Karolinska, Stockholm, Sweden. The local Ethical Committee approved this study (no. 2013/2259-31/4).

The study population consisted of all adult patients treated for sepsis or respiratory failure at our center between the service being established for adults in 1995 and December 2013. Non-Swedish citizens were excluded.

Data on survival status, cause of death, and emigration were attained from the Swedish National Cause of Death Register and the population register (Swedish Tax Agency) using the patients' personal identification number, a unique number that follows each Swedish citizen from birth to death. On each death certificate in Sweden, there is one underlying cause of death and an option to specify contributing causes. For subjects who are hospitalized, the death certificate is made by the consultant in charge, and for deaths outside the hospital, the physician in charge (mostly a general practitioner) certifies the death (34). The causes of death were coded according to the *International Classification of Diseases*, 9th Edition or *International Classification of Diseases*, 10th Edition. Emigrated patients were censored at the last known date of survival.

Patient subgroups were defined by modified ELSO criteria for respiratory ECMO diagnoses (15). Patients were categorized by the primary etiological pathology indicating ECMO treatment. Four main groups were created, some with subgroups attached, along with one group called "other pulmonary etiology" (**Table 1**). Two ECMO physicians reviewed all unclear cases based on the patients' charts and met later for discussion, coming to an agreement on the appropriate diagnostic group.

For patients who had more than one support run outcome was attributed to the first instance of mechanical support. Late death in this study was defined as death more than 90 days after decannulation from ECMO, to allow enough time for recovery and for the definition to be consistent with other studies (27).

Statistical Analysis

The influence of age, sex, time on ECMO, P/F ratio, cannulation, and diagnostic group on the patients' survival were evaluated by the Cox's proportional-hazards model and the Kaplan-Meier technique. Statistics were evaluated by Graph Pad InStat 3.10 (Graph Pad Software, San Diego, CA).

Additional information on methods and statistical analyses is provided in **Supplemental Digital Content 1** (http://links.lww.com/CCM/C154).

RESULTS

Cohort Description

Two hundred eighty-eight adult patients were treated with ECMO for respiratory failure or sepsis 1995–2013. Twenty-five patients with unknown personal identification number were excluded; all of whom were non-Swedish citizens. Survival status was traced in all 255 remaining patients. There was one emigrated patient.

One hundred and thirty-four patients (53%) were treated for bacterial pneumonia; in total, 189 patients (74%) were treated for known or highly suspected infectious diseases (nonpulmonary infections and pneumonias except for aspiration pneumonia). The median age at support was 46 years (interquartile range, 33–58; range, 18–76). Twenty-six patients

TABLE 1. Diagnostic Groups and Subgroups by Etiology for Respiratory Failure and Sepsis

Pneumonia		Nonpulmonary Infection	Severe Inflammatory Response		Traumatic Chest/Lung Contusion	Other Pulmonary Etiology
Bacterial	Viral	Aspiration	Post operation/ trauma	Other		

Table showing diagnostic groups according to the etiological pathology indicating ECMO treatment. Patients with confirmed or highly suspected infectious organisms (i.e., sepsis) were classified as pneumonia (bacterial and viral pneumonia) or nonpulmonary infection. Aspiration pneumonia patients, who can suffer from both chemical and infectious pneumonitis, were included as a subgroup to pneumonias. Patients with a systemic inflammation causing respiratory failure were classified as "severe inflammatory response." Traumatic contusions causing immediate respiratory failure were given their own group. Additional information is provided in Supplemental Digital Content 3 (http://links.lww.com/CCM/C156).

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were more than 65 years. The median follow-up time for the survivors was 4.4 years. Background data on the patients are shown in **Table 2**.

Survival and Causes of Death

The estimated survival rates for each diagnostic category are shown in **Table 3**, and the Kaplan–Meier graph is shown in **Figure 1**. Overall, 168 patients (66%) survived ECMO treatment. Five of these patients died before discharge from the Karolinska Hospital. Of the remaining 163 patients, 24 (15%) died within the first 90 days after treatment, resulting in an overall 90-day survival rate of 55%. Five years later, 47% of all ECMO-treated patients were alive. Patients treated for infections (excluding aspiration pneumonia) had the best overall long-term survival rates, ranging from 51% to 57% 3–5 years after treatment.

There were 17 late deaths (i.e., deaths more than 90 d after treatment). Of these, six (35%) occurred within the first year after treatment and 16 (94%) within the first 3 years.

TABLE 2. Comparison of Demographics and Baseline Clinical Characteristics by Diagnostic Group

Variable	Total	Pneumonia, Bacterial	Pneumonia, Viral	Pneumonia, Aspiration	Nonpulmonary Infection	Severe Inflammatory Response[a]	Traumatic Chest/ Lung Contusion	Other Respiratory Etiology[b]
N	255[c]	134	31	19	24	23	9	15
Age at treatment (yr)	46 (33–58)	49 (37–59)	44 (29–53)	46 (32–57)	55 (23–66)	34 (24–46)	38 (23–51)	44 (33–63)
Sex, male, *n* (%)	166 (65)	83 (62)	19 (61)	11 (58)	18 (75)	16 (70)	9 (100)	10 (67)
Time on extracorporeal membrane oxygenation ICU[d](d)	8 (4–17)	9 (4–17)	15 (7–34)	5 (3–15)	4 (3–8)	6 (2–19)	7 (4–10)	7 (4–12)
Cannulation, VV,[e] *n* (%)	135 (53)	78 (58)	14 (45)	10 (53)	9 (38)	9 (39)	5 (56)	10 (67)
Cannulation, VA, *n* (%)	70 (27)	29 (22)	10 (32)	5 (26)	12 (50)	6 (26)	3 (33)	5 (33)
Converted to VV,[f] *n* (%)	13 (5)	7 (5)	3 (10)	0 (0)	0 (0)	3 (13)	0 (0)	0 (0)
Converted to VA, *n* (%)	37 (15)	20 (15)	4 (13)	4 (21)	3 (13)	5 (22)	1 (11)	0 (0)
Pa_{O_2}:F_{IO_2} ratio[g] at referral (mmHg)	54 (47–60)	54 (47–60)	51 (44–58)	56 (48–62)	52 (49–56)	52 (38–59)	56 (34–66)	61 (51–67)
Follow-up time in survivors (yr)	4.4 (2.1–9.3)	5.2 (2.2–10.7)	4.2 (1.4–4.4)	5.4 (4.4–6.8)	2.0 (1.3–6.2)	10.4 (1.3–10.6)	10.3 (6.8–12.8)	6.1 (3.6–11.9)
Follow-up time in diseased[h](d)	48 (14–427)	56 (33–544)	*4/502* (*n* = 2)	*21/157/ 334/727* (*n* = 4)	*5/14/15/60* (*n* = 4)	*1/3/15/870* (*n* = 4)	*173/427* (*n* = 2)	12 (11–55)

VA = veno arterial cannulation, VV = veno venous cannulation.

[a]Sixteen developed respiratory failure after surgery or trauma, seven had a variety of causes, e.g., complications following preeclampsia, cytostatics-induced alveolitis, and several unknown causes.

[b]Wegeners granulomatosis/lung bleed (4), tumor lysis syndrome (1), air leak syndrome (3), smoke injury (1), cystic fibrosis (2), pulmonary embolism with cor pulmonale (1), dermatomyositis (1), sickle cell crisis (1).

[c]Four patients had more than one support run; two bacterial pneumonia, one severe inflammatory response, and one other respiratory etiology.

[d]Includes a short observational time after decannulation.

[e]A total of 111 patients were cannulated atrio-femoral, four patients femo-femoral, and eight patients with a double lumen cannula in the internal jugular vein. Cannulation type was missing in 12 patients.

[f]Includes VA to VV (i.e., patients converted from an initial VA cannulation to VV) and VV-VA-VV.

[g]Data missing on 58 patients (23%).

[h]i.e., time to death for the patients who survived to discharge.

Table showing patient characteristics of all included patients. Groups with fewer than five patients are written in italic. A statistical analysis testing covariates' influence on survival is provided in Supplemental Digital Content 1 (http://links.lww.com/CCM/C154). Results are presented as median (interquartile range) or number (percentage).

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TABLE 3. Survival Estimates by Diagnostic Group, Age, and Cannulation

Variable	*n*	Survives Treatment	Survives to Discharge	Survives 90 d	1-yr Survival[a]	5-yr Survival[a]	1-yr Conditional[b] Survival (%)	5-yr Conditional[b] Survival (%)
Total	255	168 (66%)	163 (64%)	139 (55%)	52% NAR 125	47% NAR 53	96	87
Pneumonia, bacterial	134	92 (69%)	89 (66%)	78 (58%)	56% NAR 70	51% NAR 36	96	88
Pneumonia, viral	31	20 (65%)	20 (65%)	19 (61%)	61% NAR 19	57% (3 yr)[c]	100	3 yr: 93§
Pneumonia, aspiration	19	12 (63%)	12 (63%)	11 (58%)	47% NAR 9	41% NAR 5	82	72
Nonpulmonary infection	24	17 (71%)	17 (71%)	13 (54%)	54% NAR 11	*54% NAR 4*	100	100
Severe inflammatory response	23	10 (43%)	9 (39%)	6 (26%)	26% NAR 5	*20% NAR 3*	100	75
Traumatic chest/lung contusion	9	6 (67%)	5 (56%)	5 (56%)	*44% NAR 4*	*33% NAR 2*	80	60
Other respiratory etiology	15	11 (73%)	11 (73%)	7 (47%)	47% NAR 7	*40% NAR 3*	100	86
Survival based on cannulation and age								
Age ≥ 65 yr	26	17 (65%)	17 (65%)	14 (54%)	54% NAR 13	*54% NAR 2*	100	100
VV-ECMO	135	103 (76%)	99 (73%)	84 (62%)	60% NAR 76	56% NAR 39	96	90
VA-ECMO	70	46 (66%)	45 (64%)	38 (54%)	51% NAR 34	44% NAR 10	97	84
Converted to VV[d]	13	10 (77%)	10 (77%)	9 (69%)	69% NAR 8	41% (3 yr)[e]	100	60
Converted to VA	37	9 (24%)	9 (24%)	8 (22%)	19% NAR 7	*19% NAR 4*	88	88

NAR = number at risk, VA = veno arterial cannulation, VV = veno venous cannulation.

[a]Survival calculated by means of the Kaplan-Meier method.

[b]Survival for patients that were alive 90 days after treatment.

[c]Follow-up time was 4.6 years, in median 3.6 years. Number at risk (NAR) (3 yr) = 12.

[d]Includes veno arterial cannulation (VA)-veno venous cannulation (VV) (i.e., patients converted from an initial VA cannulation to VV) and VV-VA-VV.

[e] Follow-up time was 4.5 years, in median 2.3 years. NAR (3 yr) = 3.

Table showing survival estimates based on diagnostic group, old age and cannulation. Groups with fewer than five patients are written in italic. A statistical analysis is provided in Supplemental Digital Content 1 (http://links.lww.com/CCM/C154). Results are presented as number (percentage).

Conditional survival rates (i.e., survival in patients who survived to 90 d after treatment) are shown in Table 3.

In a multivariable Cox model for long-term survival (Supplemental Digital Content 1, http://links.lww.com/CCM/C154), diagnostic group, age, sex, P/F ratio, and cannulation were not significantly linked to risk of late death. Age and cannulation were linked to overall survival.

Three patients (two belonging to the bacterial pneumonia group and one treated for aspiration pneumonia) died from intoxications, of whom two had a known intoxication history. One patient treated for trauma never recovered and died six months after ECMO treatment. Three patients died from their ECMO-treated main disease (two with cystic fibrosis and one with a never fully diagnosed interstitial lung disease), and six patients died from common societal causes (one metastatic cancer, one ischemic heart disease, one stroke, one pancreatitis, and two sepsis, of whom one acquired influenza with a complicating pneumonia). One patient died from acute kidney failure and one from an unspecified immune disease. Two causes of death were unknown. Additional information on timing and causes of death are provided in **Supplemental Digital Content 2** (http://links.lww.com/CCM/C155).

DISCUSSION

In this retrospective cohort, survival and causes of death in 255 patients treated with ECMO for respiratory failure and

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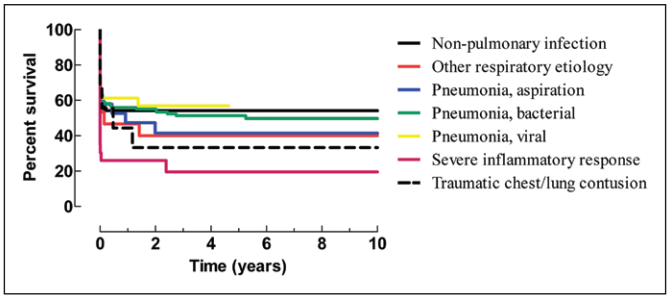

Figure 1. Kaplan-Meier graph to show survival estimates in years for all ECMO-treated patients ($n = 255$) based on diagnostic group. The initial descending part represents deaths during treatment. Numbers at risk after 1 and 5 years are shown in Table 3. Statistical analyses were used for the comparison of the survival curves, with $p = 0.15$, i.e., not statistically significant (additional information about statistical analyses can be found in, **Table E2**, Supplemental Digital Content 1, http://links.lww.com/CCM/C154).

sepsis at our center were investigated. There was no loss to follow-up, and a median follow-up time for survivors of 4.4 years. Modified ELSO diagnose group criteria were used, with the aim to create a more homogenous presentation of patients.

The present findings suggest that both short- and long-term survival after ECMO treatment can be good in appropriately selected patients, but that the prognosis varies greatly depending on diagnostic group. Seventeen percent of the patients who survived ECMO treatment died within 90 days. For the patients who were alive 90 days after ECMO treatment, the survival prognosis seems favorable, especially in patients treated for infections. The causes of death suggest that the patients died mainly from common societal causes such as cancer, heart disease, and intoxication or that they never fully recovered or died from their ECMO-treated main disease. Almost all groups had late deaths, but the flattening of the Kaplan-Meier curves gives no indication of ECMO caused long-term mortality.

When discussing ECMO survival, the terms "survival of treatment" and "survival to discharge" are often used. According to the ELSO registry, the survival to discharge in the adult respiratory group is on average 58%, i.e., in line with this study's presented 64% (4). Our data do however suggest that there is a high risk of death within the first 3 months after treatment. Many of these deaths are probably expected, given the level of respiratory distress and risk of death when admitted for ECMO treatment. Survival to at least 3 months after ECMO treatment would probably be a better measure of short-term survival, and this also raises the question of whether a closer ECMO follow-up program should be implemented. More studies are, however, needed before such conclusions can be made.

Little is known regarding long-term survival after ECMO treatment in the adult respiratory group. To our knowledge, the studies that do exist often cover only one or a few diagnostic groups have short time horizons or few patients studied. The lack of national registries and few centers with long enough ECMO experience and high number of cases is likely to contribute to this. In addition, survival comparison between studies and centers is difficult, given the differences in the general mix of patients, annual patient volume, the number of patients accepted for ECMO as a "last resort" salvage therapy, and other different local practices.

Iguchi et al (27) in 2013 presented long-term survival rates and causes of late death among ECMO-treated children. Similar to the present results, there was a high mortality rate within the first months after treatment, and they argued for the 90-day cut-off to define late death. Five-year survival rates, conditional on the patient being alive 90 days after treatment, varied greatly but could be as high as 90–98% in some groups.

The CESAR study presented 6-month survival rates in 180 acute respiratory distress syndrome (ARDS) patients. In the ECMO arm group, there was a high initial mortality, especially during the first 50 days after treatment, and an overall 63% 6-month survival, in contrast to our 54% 3-month survival. In the conventionally treated group, mortality was highest during the first month after treatment (17). This pattern was supported by a recent publication comparing Acute Physiology and Chronic Health Evaluation II score- and age-matched ARDS patients treated with either ECMO or conventional methods (21).

Hsu et al (18) in 2015 presented data on both cardiac and respiratory ECMO. The survival to discharge was low (33%), and in the respiratory group, a high mortality was seen the first 5 years after treatment at a seemingly persistent rate. Patients aged 55 years or older had steeply descending survival curves 5–10 years after treatment. This study has raised the question of the lack of appropriate selection of patients.

Several studies have presented long-term survival rates in adults after ECMO for cardiac indications and septic shock, with a high variation in outcomes (22, 23, 26). In a review from 2010, Winters et al (33) argued that conventionally treated sepsis patients have ongoing mortality up to 2 years and beyond, and that the use of 28-day mortality as an end point for clinical studies may lead to inaccurate inferences.

In our cohort, patients treated with ECMO for infections (with the exception for aspiration pneumonia) seem to have a good survival both in the short term and long term. This probably represents the reversibility of the disease process, i.e., if the patient is given adequate treatment and survives the acute phase, the long-term prognosis is good. The aspiration pneumonia patients constitute quite a heterogeneous group, often with multiple organ failure, where some patients were treated for drowning and others for complex aspiration after esophageal rupture or trauma. Of the patients with viral pneumonia, 11 were treated for H1N1 influenza during the 2009 pandemic (6). In the bacterial pneumonia group, nine late deaths were seen, most of which were due to common societal causes. Lung disease constituted three of these, two being the ECMO-treated main disease (cystic and interstitial fibrosis, respectively), and one developed pneumonia-associated ARDS from the seasonal influenza approximately 3 years after ECMO treatment. Other researchers have shown that patients who have suffered from severe ARDS and often ventilator-induced lung injury will have persistent lung pathology many years after treatment

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(35), and therefore these patients may have a susceptibility to new pulmonary infections.

Intuitively, trauma patients who survive should have a good long-term survival if otherwise healthy. According to the present study's results, trauma patients had many early and two late deaths, one due to lack of recovery after six months and one due to unknown cause more than 1 year after treatment. The few patients at risk caused steep falls in the Kaplan-Meier curve, which may have given this group a falsely dismal survival picture.

The group severe inflammatory response (which is similar to noninfectious ARDS) stands out regarding both short- and long-term mortality. After closer inspection, the majority of these patients had developed ARDS as part of multiple organ failure for unknown reasons after trauma or surgery, and ECMO was frequently used as a salvage therapy.

Several patients aged 65 years or older have been treated at the ECMO Center Karolinska. The results suggest, unlike the results by Hsu et al (18), that survival can indeed be good in this group, both in the short term and long term if appropriately selected.

For patients converted to veno arterial ECMO, the survival to discharge was very poor. This need for conversion in many cases probably represents a complicating circulatory failure and deterioration despite veno venous ECMO support. This calls for additional research and is discussed further in **Supplemental Digital Content 3** (http://links.lww.com/CCM/C156) (36).

All patients were treated at the ECMO Center Karolinska in Stockholm, Sweden, which is a high-volume center involved in ECMO treatment since 1987. The wide spectrum of patients treated with ECMO makes grouping of patients difficult. Therefore, modified ELSO subgroups were created (Supplemental Digital Content 3, http://links.lww.com/CCM/C156).

A major limitation with this study is that very little data on patient characteristics could be presented, especially factors that are known to affect survival such as the level of multiple organ failure, time on mechanical ventilation before ECMO, and comorbidities (20, 37). The available database and patient charts, especially from the early years of our service, contain little such data. However, ELSO-accepted criteria for ECMO have generally been used as these have changed somewhat over time (16, 38) (Supplemental Digital Content 3, http://links.lww.com/CCM/C156), and ECMO was sometimes used as a salvage therapy.

It is important to remember that ECMO treatment is a constantly evolving field, and the reported survival data should therefore mainly work as a historic reference. Another limitation with this study is that the results capture survival outcomes only. Published evidence suggests a proportion of both conventionally treated and ECMO-treated ARDS patients, and ECMO-treated children have long-term deficits in these areas (19, 29–31, 35, 39, 40). Also, few patients in each group are followed up over time, causing few patients at risk in most groups after 5 years. The listed cause of death is a rough measure because it is based on a physician's best judgement and seldom on autopsy reports. Finally, the quality limitations of retrospective data must be kept in mind.

The strength with the present study is the number of ECMO-treated patients in total and the relatively long time range of follow-up, especially in the bacterial pneumonia group (to a maximum of 16.8 yr, with no additional late deaths). Survival status could be traced in all included patients, with no patients lost to follow-up.

CONCLUSIONS

Outcome after ECMO treatment is highly variable. It is suggested that survival to discharge is a poor estimate of survival because many deaths occur in the first 90 days after weaning from ECMO. For the patients who survive the initial critical time after ECMO treatment, survival in the coming years seems good, especially if treated for an infectious disease. No indications of long-term mortality caused by ECMO treatment were found. Future studies are needed to validate our results and in particular to investigate how the ECMO survivors perform in terms of pulmonary function, cognitive function and quality of life.

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