Long-Term Survival in Adult Patients With Severe Acute Lung Failure Receiving Veno-Venous Extracorporeal Membrane Oxygenation

Tone Bull Enger, MD, PhD[1]; Alois Philipp, ECCP[2]; Matthias Lubnow, MD, PhD[3]; Marcus Fischer, MD, PhD[3]; Daniele Camboni, MD, PhD[2]; Dirk Lunz, MD[4]; Thomas Bein, MD, PhD[4]; Thomas Müller, MD, PhD[3]

Objectives: To assess long-term survival in adult patients with severe acute lung failure receiving veno-venous extracorporeal membrane oxygenation and explore risk factors for long-term mortality.

Design: Single-center prospective cohort study.

Setting: University Hospital Regensburg, Germany.

Patients: All primary cases supported with veno-venous extracorporeal membrane oxygenation from 2007 to 2016 ($n = 553$).

Interventions: None.

Measurements and Main Results: Patients were followed until January 2017. Long-term survival and predictors of long-term mortality were assessed using Kaplan-Meier survival analyses and Cox proportional hazards modeling, respectively. Two hundred eighty-six patients (52%) died during follow-up (mean follow-up 4.8 yr). Two hundred seventeen patients (39%) died during hospitalization, whereas another 69 patients (12%) died during later follow-up. Among hospital survivors, the 1-month, 3-month, 1-year, and 5-year survival rates were 99%, 95%, 86%, and 76%, respectively. Higher age, immunocompromised status, and higher Sequential Organ Failure Assessment scores were associated with long-term mortality, whereas patients with out-of-center cannulation showed improved long-term survival. Due to nonproportional hazards over time, the analysis was repeated for hospital survivors only ($n = 336$). Only age and immunocompromised state remained significant predictors of late mortality among hospital survivors. Lower Glasgow Outcome Scale at hospital discharge and the University Hospital Regensburg pre–extracorporeal membrane oxygenation score for predicting hospital mortality in veno-venous extracorporeal membrane oxygenation patients before extracorporeal membrane oxygenation initiation were associated with late mortality in hospital survivors ($p < 0.001$).

Conclusions: Whereas acute illness factors may be important in prediction of hospital outcomes in veno-venous extracorporeal membrane oxygenation patients, they do not determine late mortality in hospital survivors. Preexisting morbidity and functional ability at hospital discharge may be important determinants of long-term survival in veno-venous extracorporeal membrane oxygenation patients. (*Crit Care Med* 2017; 45:1718–1725)

Key Words: acute lung injury; extracorporeal membrane oxygenation; long-term survivors; respiratory insufficiency; survival analysis

[1]Department of Laboratory Medicine, Children's and Women's Health, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway.

[2]Department of Cardiothoracic Surgery, University Hospital Regensburg, Regensburg, Germany.

[3]Department of Internal Medicine II, University Hospital Regensburg, Regensburg, Germany.

[4]Department of Anesthesiology, University Hospital Regensburg, Regensburg, Germany.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Dr. Bein is member of the Medical Advisory Board of the Novalung/Xenios Company, Heilbronn, Germany, and received honoraria. Dr. Lunz received travel expenses and lecture honoraria from Maquet Cardiopulmonary AG, Rastatt, Germany, CSL Behring, Hattersheim am Main, Germany, and AstraZeneca, Wedel, Germany, and his institution received research support from Sorin Group, Germany, and Audi AG, Ingolstadt, Germany. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: thomas.mueller@ukr.de

DOI: 10.1097/CCM.0000000000002644

Veno-venous extracorporeal membrane oxygenation (ECMO) can be a life-saving procedure in patients with severe acute lung failure (ALF) refractory to conventional therapy. The randomized controlled trial reporting a survival benefit in adult patients with severe respiratory failure receiving ECMO support compared with conventional care (1) reignited the interest in ECMO for severe ALF. Interest further increased with the recent case series describing benefits of ECMO as a rescue therapy during the H1N1 influenza A pandemic (2–4), as well as technological developments improving the safety and efficacy of ECMO (5).

A recent report on the evolving epidemiology and mortality of the use of ECMO in Germany showed that the application of veno-venous ECMO for respiratory failure has increased

three-fold from 2007 to 2012 (6). In-hospital mortality has slightly decreased with increasing ECMO utilization but remains high (35–62%) (6–8). Several investigations have been performed to explore prognostic factors for veno-venous ECMO patients to further improve patient outcomes (8–10). All of these studies have used hospital mortality as the primary endpoint.

Veno-venous ECMO is a procedure associated with high costs and resource utilization, estimated to double the average cost per patient compared with conventional management (11). Thus, with increasing use of ECMO, knowledge about long-term outcomes are of importance. The hypothesis of this study was that following the initial high mortality rate during and after veno-venous ECMO treatment, patients being discharged from hospital show good long-term survival. As previously observed with hospital outcomes, we hypothesized that patients receiving veno-venous ECMO treatment due to primary lung failure and trauma have better long-term prognosis compared to patients treated with veno-venous ECMO due to secondary ALF. The aim was to explore long-term survival and assess potential risk factors for reduced survival.

PATIENTS AND METHODS

All adults greater than or equal to 15 years old receiving veno-venous ECMO support due to ALF refractory to conventional therapeutic modalities at University Hospital Regensburg (UKR) between January 1, 2007, and December 31, 2016, were analyzed. Thirteen patients had greater than one ECMO runs; only first entries into the database were included ($n = 553$). As described previously (8), the general indication for veno-venous ECMO was either a Pao_2/Fio_2 ratio of less than 80 mm Hg on a positive end-expiratory pressure (PEEP) of greater than or equal to 16 cm H_2O or a refractory respiratory acidosis ($pH < 7.25$) despite optimization of conservative therapy.

Clinical data regarding pre-, intra-, and post-ECMO characteristics and functions were prospectively registered from the day of hospitalization until discharge. Immunocompromised state included hematologic malignancies, solid tumors, solid organ transplantation, long-term corticosteroid or other immunosuppressive therapy, or HIV infection. Predicted in-hospital mortality with the UKR pre-ECMO score was calculated retrospectively in all patients (8). The score was originally developed based on UKR veno-venous ECMO patients between 2008 and 2013 and remains to be validated in an independent study cohort. Functional ability at hospital discharge was assessed prospectively with the Glasgow Outcome Scale (GOS) (12). It was originally developed to assess outcome after severe brain damage but has also been described for ICU settings (13, 14). It has a score of 5 which indicates good recovery; 4, moderate disability; 3, severe disability; 2, vegetative state; and 1, death.

Vital status per January 2017 and if applicable, date of death were obtained through contact to hospital survivors, relatives, or their general practitioner. Causes of late death were not available. All remaining survivors were successfully contacted in January 2017 via telephone or social medias, and an oral consent was obtained to complete a follow-up interview. The same investigator interviewed all patients, asking the same set of questions, and subsequently categorizing their functional ability according to the Eastern Cooperative Oncology Group (ECOG) Performance Status (0–5) (**eTable 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C787) (15).

The ECMO circuit and settings, as well as patient management, followed an institutional protocol as described previously (16). The study including permission to contact the patients was approved by the local ethical committee at UKR (Ethical board number: 15-101-0051). The requirement for individual patient consent for the analysis and publication data was waived as this study was based on anonymized data from routine care.

Endpoints

The primary endpoint of this study was long-term mortality. To characterize the course of veno-venous ECMO patients in more detail, "in-hospital mortality" will be used to depict short-term mortality, whereas "late mortality" refers to death in hospital survivors during follow-up.

Statistical Analysis

Categorical variables are described as *n* (%); continuous variables as median with interquartile range (IQR, 25th–75th percentile). *p* values of less than 0.05 were considered significant. All statistical analyses were performed with Stata (version 13.1; StataCorp LP, Lakeway Drive, TX) and *R* (version 3.2.2; Foundation for Statistical Computing, Vienna, Austria).

Long-Term Survival

Observed cumulative survival was calculated with time since ECMO weaning as the time variable and death (no/yes) as the event using the Kaplan-Meier estimator. As veno-venous ECMO patients constitute a heterogeneous study group, survival was compared between different diagnostic groups according to the underlying cause for ALF: 1, primary lung failure including bacterial, viral, fungal, or aspiration pneumonia; 2, extrapulmonary sepsis with secondary lung injury; 3, multiple trauma with acute respiratory distress syndrome (ARDS); or 4, other pathologies, including near drowning, chronic lung diseases, such as lung fibrosis, and veno-venous ECMO as a bridge to lung transplantation. Group comparisons were performed with the log-rank test.

Late mortality in veno-venous ECMO patients was compared with the expected mortality in the German population matched on age, sex, and calendar year, using data obtained from the Human Mortality Database (17). Data from the German population were only available throughout 2013. Relative mortality was calculated as the ratio between observed and expected number of deaths (standardized mortality ratio, [SMR]) for hospital survivors weaned off ECMO between 2007 throughout 2013, using 31st of December 2013 as the censoring date.

Predictors of Long-Term Mortality

Predictors of long-term mortality were investigated using Cox proportional hazards (PHs) modelling (**eTable 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/C787). For more details regarding the statistical analysis, see **Supplemental Digital Content 2** (http://links.lww.com/CCM/C788).

RESULTS

Study Population

Patient descriptives are presented in **Table 1**. Whereas patients receiving veno-venous ECMO during the first years presented with higher Sequential Organ Failure Assessment (SOFA) scores, higher lactate, and more invasive ventilation before veno-venous ECMO (higher PEEP, minute ventilation, and tidal volume), management during more recent years has changed toward a more protective ventilation on day 1 of veno-venous ECMO with significantly reduced minute ventilation and ventilator pressures. Commonly used indications for veno-venous ECMO like Pao_2/Fio_2, pH, $Paco_2$, and need for vasopressors did not change on average during the years (**eTable 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/C787).

The mean time of follow-up was 4.8 years (4.3–5.2 yr). Survival to discharge was 60.8% (336 patients) (**Fig. 1**). Median time to in-hospital mortality following successful weaning from ECMO was 12 days (4–24 d). During follow-up after discharge, another 69 patients (12.5%) passed away after a median survival time of 215 days (88–757 d). A total of 286 patients (51.7%) died during follow-up. In the study cohort between 2007 and 2013, 36 hospital survivors ($n = 207$) died, compared with four expected deaths according to age- and gender-matched data from the German population (SMR 9.4 [95% CI 6.8–13.0]).

TABLE 1. Patient Descriptives

Variables	All	Diagnostic Groups[a]			
		Pulmonary	Extrapulmonary	Trauma	Others
n (%)	553 (100)	318 (57.5)	119 (21.5)	57 (10.3)	59 (10.7)
Age (yr), median (IQR, 25–75th percentile)	52 (38–62)	54 (44–63)	53 (37–64)	30 (22–47)	50 (40–61)
Female, *n* (%)	174 (31.5)	113 (35.5)	32 (26.9)	4 (7.0)	25 (42.4)
Body mass index (kg/m^2), median (IQR, 25–75th percentile)	27.8 (24.4–33.1)	28.4 (24.5–33.8)	27.8 (24.5–33.3)	26.6 (24.7–30.9)	24.8 (23.5–29.3)
Immunocompromised state[b], *n* (%)	102 (18.4)	54 (17.0)	30 (25.2)	0 (0.0)	18 (30.5)
Sequential Organ Failure Assessment score, median (IQR; 25th–75th percentile)	12 (9–15)	12 (9–15)	14 (11–17)	12 (11–15)	9 (7–14)
Pre-ECMO arterial blood gas, median (IQR, 25–75th percentile)					
pH	7.22 (7.14–7.31)	7.23 (7.16–7.32)	7.19 (7.11–7.27)	7.25 (7.16–7.35)	7.23 (7.08–7.33)
$Paco_2$ (mm Hg)	63 (53–75)	63 (53–75)	65 (52–75)	58 (49–70)	55 (62–81)
Lactate (mg/dL)	20 (12–45)	17 (11–32)	30 (15–67)	28 (15–70)	21 (10–42)
Pre-ECMO Pao_2/Fio_2 (mm Hg), median (IQR, 25–75th percentile)	65 (53–83)	66 (54–85)	67 (52–81)	58 (49–78)	70 (55–98)
Cardiopulmonary resuscitation pre-ECMO, *n* (%)	63 (11.4)	38 (11.9)	15 (12.6)	5 (8.8)	5 (8.5)
Out-of-center ECMO, *n* (%)	260 (47.0)	161 (50.6)	53 (44.5)	30 (52.6)	16 (27.1)
Hemofiltration before/during ECMO, *n* (%)	250 (45.2)	139 (43.7)	74 (62.2)	20 (35.1)	17 (28.8)
Duration of ECMO support (d), median (IQR, 25–75th percentile)	8 (5–14)	10 (7–15)	6 (3–9)	6 (4–7)	10 (4–22)
Hospital mortality, *n* (%)	217 (39.2)	112 (35.2)	57 (47.9)	17 (29.8)	31 (52.5)
Late death among hospital survivors, *n* (%)	69 (12.5)	49 (15.4)	14 (11.8)	1 (1.8)	5 (8.5)

ECMO = extracorporeal membrane oxygenation, IQR = interquartile range.

[a]Group 1: primary lung failure, including bacterial, viral, fungal, or aspiration pneumonia; group 2: extrapulmonary sepsis with secondary lung injury; group 3: multiple trauma with acute respiratory distress syndrome; group 4: other pathologies, including near drowning, chronic lung diseases, such as lung fibrosis and veno-venous extracorporeal membrane oxygenation as a bridge to lung transplantation.

[b]Immunocompromised state included hematologic malignancies, solid tumors, solid organ transplantation, high-dose or long-term corticosteroid or other immunosuppressive therapy, or HIV infection.

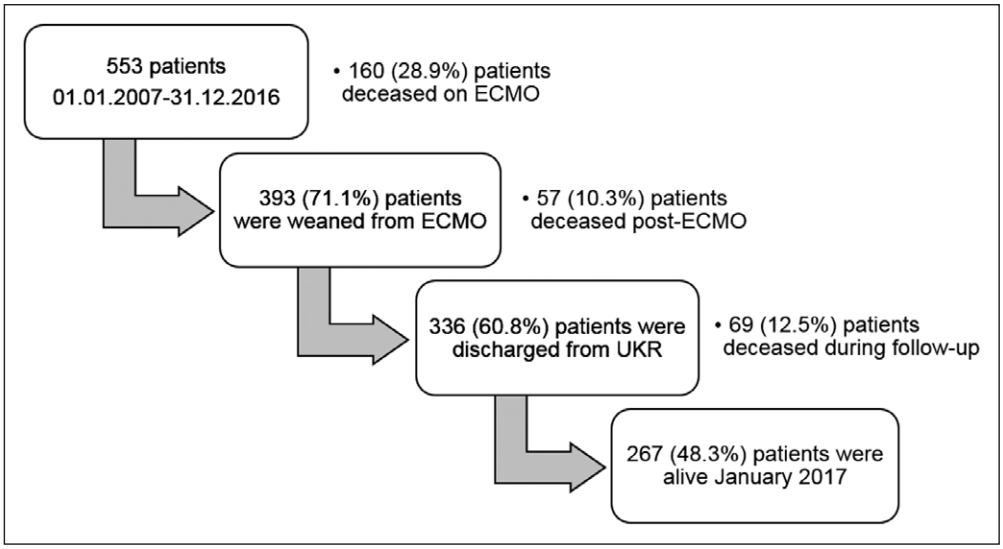

Figure 1. Follow-up of patients supported with veno-venous extracorporeal membrane oxygenation (ECMO) for acute lung failure. UKR = University Hospital Regensburg.

Long-Term Survival

Estimated 30-day, 90-day, 1-year, and 5-year survival was 62%, 57%, 52%, and 46%, respectively (**Fig. 2*A***). Amongst patients successfully discharged from hospital (n = 336), the survival rates were 99%, 95%, 86%, and 76%, respectively. Long-term mortality was significantly different between different disease categories (log-rank test, p = 0.002) (**Fig. 2*B***), but not when adjusted for age differences (p = 0.10).

Cardiopulmonary resuscitation before ECMO implantation was not associated with altered survival probability (log-rank test, p = 0.27), neither was gender (p = 0.57). Patients with out-of-center ECMO implantation showed better survival (p < 0.001). However, when excluding in-hospital deaths (p = 0.03) and adjusting for age, this difference was no longer significant (adjusted log-rank test, p = 0.38). Patients with higher SOFA scores and patients in need for dialysis before or during ECMO support showed higher long-term mortality (p < 0.001), but this was mainly due to higher in-hospital mortality (adjusted log-rank tests, p = 0.85 and p = 0.44, respectively).

Long-term mortality differed significantly depending on the duration of ECMO support. However, ECMO duration did not influence late mortality among hospital survivors (**eFig. 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/C787). The GOS for patients discharged from hospital varied among 5 (good recovery, n = 278/82.7%), 4 (moderate disability, n = 55/16.4%), and 2 (persistent vegetative, n = 3/0.9%) (**eTable 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/C787). Late mortality increased linearly with decreasing GOS at hospital discharge (**eFig. 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/C787). At the end of follow-up, 185 of all survivors (69%) described full functional ability (ECOG grade 0). Twenty-one percent, 7%, and 3% scored 1, 2, and 3 on the ECOG Performance Score, respectively.

Predictors of Long-Term Mortality

Multivariate analysis showed that advanced age, immunocompromised state, higher pre-ECMO SOFA scores, and longer duration of ECMO support were associated with higher long-term mortality, whereas patients with out-of-center ECMO cannulation showed improved survival (**Table 2**). However, there were non-PHs over time, as shown by fitting piecewise hazard ratios (Table 2). Only age and immunocompromised state remained significant predictors of late mortality.

Following hospital discharge (n = 336), advanced age, immunocompromised state, and lower GOS were associated with higher mortality, whereas there was a trend that trauma patients had higher late survival rates (p = 0.05) (**Table 3**).

Higher UKR pre-ECMO scores were associated with increased long-term mortality (p < 0.001) (**Fig. 2*C***; **eTable 5**, Supplemental Digital Content 1, http://links.lww.com/CCM/C787) and showed good predictive ability (Harrell's concordance statistic 0.76). The UKR pre-ECMO score showed a linear correlation with the risk of long-term mortality, in-hospital mortality, and late mortality (**eFig. 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/C787; time-split analyses: p < 0.001, p < 0.001, and p = 0.01 for 0–6 mo, 6 mo to 2 yr, and > 2 yr, respectively).

A sensitivity analysis including only patients with follow-up greater than or equal to 5 years (n = 212) confirmed the previously described results (data not shown). However, addition of variables made available at hospital discharge did not improve prediction of late mortality in hospital survivors significantly compared with pre-ECMO variables (eTable 5, Supplemental Digital Content 1, http://links.lww.com/CCM/C787; likelihood ratio test, p = 1.00).

DISCUSSION

The present study showed that 1-month, 3-month, 1-year, and 5-year survival following veno-venous ECMO support was 62%, 57%, 52%, and 46%, respectively. Age, immunocompromised state, SOFA score, and out-of-center ECMO cannulation were significantly associated with overall survival rates. Time-split analyses revealed that predictors of early mortality did not sustain as predictors of late mortality. If sepsis or trauma patients survived to hospital discharge, they had good chances of survival, independent of the underlying severity of illness.

The present hospital survival rate for all veno-venous ECMO patients was 60.8%, which is comparable with international data from the Extracorporeal Life Support Organization

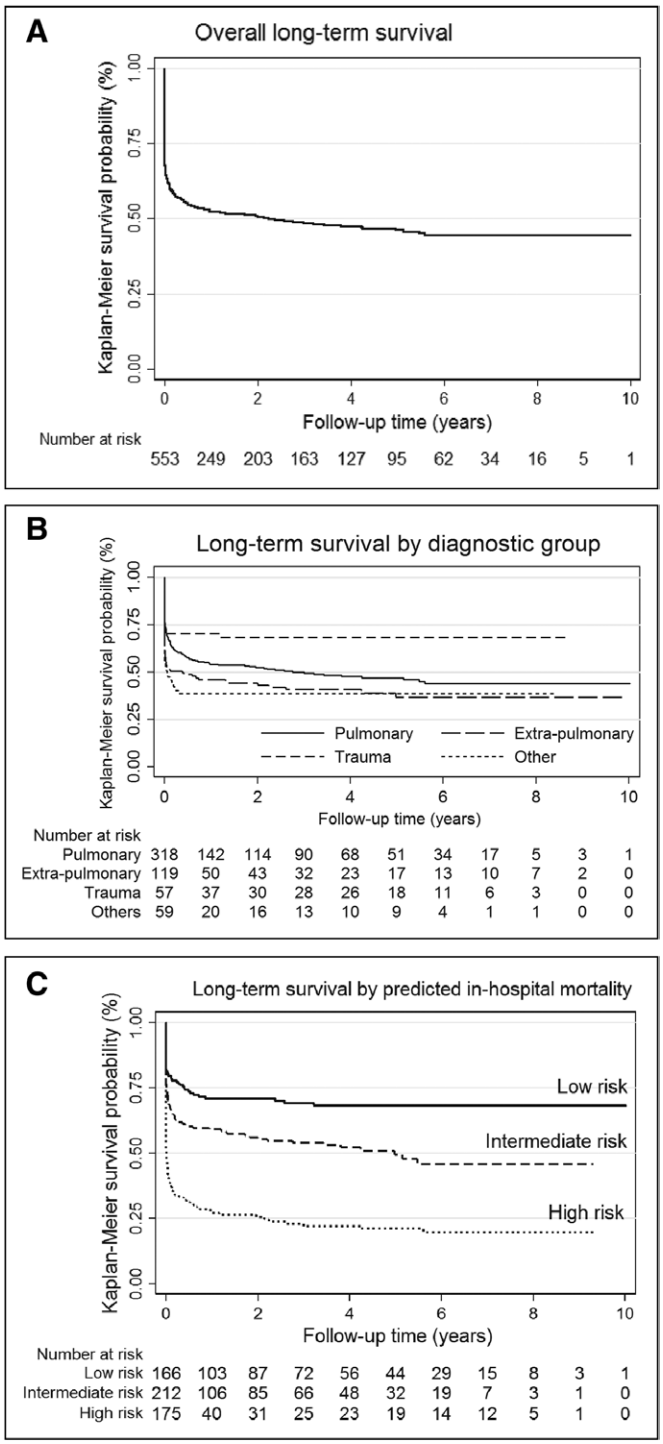

Figure 2. Kaplan-Meier estimated survival during follow-up: (**A**) For all patients ($n = 553$); (**B**) stratified on diagnostic group: pulmonary disease ($n = 318$), extrapulmonary disease ($n = 119$), trauma ($n = 57$), and others ($n = 59$); (**C**) stratified on risk groups based on their calculated predicted mortality probabilities with the University Hospital Regensburg pre–extracorporeal membrane oxygenation score: low risk (score ≤ 25%), intermediate risk (score 26–50%), and high risk (≥ 50%). The effective number at risk (n) for year 0–10 following extracorporeal support are given.

(57%) (18). Presented data on long-term survival are in accordance with data from Karolinska University Hospital, where adults treated with respiratory ECMO between 1995 and 2013 ($n = 255$) showed 3-month, 1-year, and 5-year mortality rates of 54%, 52%, and 47%, respectively (19). The results are also comparable with long-term survival in other ICU patients. Two studies assessed long-term survival in patients with severe sepsis, reporting 5-year survival rates of 43% (age 45–64 yr) (20) and 39% (median age 58; IQR, 45–67) (21), respectively.

Patients admitted to the ICU constitute a heterogeneous group, with a wide range of illness severity and reasons for admission. Hospital survivors following veno-venous ECMO had a nine-fold higher mortality compared with the age- and gender-matched German population. However, a higher relative mortality has also been reported in ICU patients (24–26). Among veno-venous ECMO hospital survivors, 1-month, 3-month, 1-year, and 5-year survival rates were 99%, 95%, 86%, and 76%, respectively. A recent study regarding ICU patients reported a 5-year survival rate of 67.7% following initial hospital discharge ($n = 5{,}215$; median age 60 yr [IQR, 44–72 yr]) (22). Khandelwal et al (23) showed that despite the higher in-hospital mortality seen in ARDS patients on rescue therapies, survivors at hospital discharge had long-term survival similar to other ARDS survivors (23). These comparisons indicate that patients who are discharged from hospital following veno-venous ECMO have a prognosis comparable with other ICU patients.

Previously described predictors of overall mortality were primarily related to short-term mortality. Separate analyses for different periods of the follow-up revealed that pre-ECMO SOFA scores, duration of veno-venous ECMO support, and out-of-center ECMO implantation were not associated with altered late survival in hospital survivors. A higher SOFA score indicates affection of multiple organ systems, whereas either very short or prolonged duration of extracorporeal support may indicate patients with more severe illness. Thus, predictors of in-hospital death may represent markers of the severity of the present illness, but not necessarily predict long-term outcomes. Possible reasons underlying the favorable outcomes in patients with out-of-center ECMO implantation may include a lower threshold for veno-venous ECMO support at local hospitals with less resources and treatment alternatives available in their respective ICU, and thus indicate a different patient population.

Higher age and immunocompromised state were associated with increased mortality throughout follow-up. Using the available data, we could not find indices during acute illness that would help to predict late death following veno-venous ECMO. Similar findings have also been described in ARDS patients without ECMO support (22, 27, 28). In a 1-year follow-up study, Wang et al (27) showed that long-term outcomes in ARDS were more related to age and premorbid illnesses than the critical illness per se. Premorbid illnesses included HIV and malignancies, considered as an immunocompromised state in the present study. Importantly, neither resuscitation before ECMO, renal failure before and during ECMO, nor long duration of ECMO impacted long-term survival when patients survived to hospital discharge. These findings may have important implications for physicians caring for veno-venous ECMO patients, as the critical illness may not automatically incur an additional risk of mortality later in life.

TABLE 2. Multivariate Survival Analysis Showing Predictors of Long-Term Mortality in All Patients Supported With Extracorporeal Membrane Oxygenation for Acute Lung Failure (*n* = 553)

Variables	Hazard Ratios for Complete Follow-up	Hazard Ratios for Specified Time Periods		
		0–0.5 Yr	0.5–2 Yr	> 2 Yr
Age (yr)	1.02 (1.01–1.03)[a]	1.02 (1.01–1.03)[a]	1.03 (1.00–1.07)	1.05 (1.01–1.09)[b]
Immunocompromised state[c]	1.51 (1.14–1.99)[b]	1.36 (1.01–1.84)[b]	4.67 (1.64–13.32)[c]	2.25 (0.68–7.43)
Pre-ECMO hemoglobin (g/dl)	0.92 (0.87–0.97)[c]	0.92 (0.87–0.98)[b]	0.87 (0.70–1.08)	0.78 (0.61–1.01)
Sequential Organ Failure Assessment score	1.08 (1.04–1.11)[a]	1.08 (1.04–1.12)[a]	1.08 (0.94–1.23)	1.01 (0.88–1.16)
Diagnostic group[d]				
Pulmonary	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Extrapulmonary	1.00 (0.74–1.35)	1.05 (0.76–1.45)	0.63 (0.19–2.08)	0.68 (0.21–2.22)
Trauma	0.82 (0.48–1.40)	0.98 (0.56–1.71)	0.45 (0.05–4.29)	–
Other	1.27 (0.87–1.87)	1.49 (1.01–2.21)[b]	–	–
Out-of-center ECMO implantation	0.73 (0.55–0.95)[b]	0.71 (0.53–0.96)[b]	1.74 (0.58–5.26)	0.63 (0.20–2.03)
Duration of ECMO support (d)				
1–2	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
3–7	0.55 (0.36–0.82)[c]	0.53 (0.34–0.81)[a]	0.45 (0.05–3.95)	0.61 (0.07–5.79)
7–14	0.49 (0.32–0.75)[a]	0.54 (0.35–0.83)[a]	0.19 (0.02–1.97)	0.23 (0.02–2.53)
> 14	0.71 (0.46–1.09)	0.78 (0.50–1.21)	0.35 (0.03–3.78)	0.19 (0.01–2.42)

ECMO = extracorporeal membrane oxygenation.

[a]$p < 0.001$.

[b]$p < 0.05$.

[c]$p < 0.01$.

[e]Immunocompromised state included hematologic malignancies, solid tumors, solid organ transplantation, high-dose or long-term corticosteroid or other immunosuppressive therapy, or HIV infection.

[d]Group 1: primary lung failure, including bacterial, viral, fungal, or aspiration pneumonia; group 2: extrapulmonary sepsis with secondary lung injury; group 3: multiple trauma with acute respiratory distress syndrome; group 4: other pathologies, including near drowning, chronic lung diseases, such as lung fibrosis and veno-venous extracorporeal membrane oxygenation as a bridge to lung transplantation.

Hazard ratios (95% CIs) are given for patients with complete data during the total follow-up period, as well as piecewise for the first 6 mo ($n = 552$), 6 mo to 2 yr ($n = 288$), and > 2 yr ($n = 203$) of follow-up.

"–" indicates too few observations.

Interestingly, we found that the UKR pre-ECMO mortality score developed to predict in-hospital mortality predicted long-term mortality. This finding must be interpreted with caution, as most deaths occur early and will fit with the original purpose of the score. Nevertheless, its independent association with late mortality, shown with the time-split analyses and repeated analysis of hospital survivors, strengthens the reliability of the score as a predictor of long-term mortality.

The separate analysis of hospital survivors showed that lower GOS at discharge was associated with lower survival. GOS at hospital discharge may be a simple and practical tool to identify high-risk patients for late mortality. As the acute illness seems to be of less prognostic importance for later outcomes, a thorough evaluation of functional ability at hospital discharge may provide both patients and caretakers with important prognostic information. However, addition of variables available at hospital discharge did not significantly enhance clinical prediction of late mortality compared with pre-ECMO variables. More detailed scoring systems such as the Barthel index (29) or Karnovsky Performance Scale Index (30) may discriminate between different risk levels more accurately. These were not available in the present study, and thus more investigation into this field is warranted.

In the present study cohort, 69% of veno-venous ECMO survivors had gained their full function in daily life (ECOG = 0) at the end of follow-up, another 21% had only a slight impairment (ECOG = 1). Previous studies in veno-venous ECMO patients (n = 8–67) have assessed long-term outcomes with regards to respiratory function, psychologic impairment, and quality of life, up to 2 years post ECMO (10, 31–33). They have indicated that veno-venous ECMO treatment is associated with significant physical and psychologic impairment. Patients treated with veno-arterial ECMO due to cardiogenic shock have shown impaired health-related quality of life compared with

TABLE 3. Multivariate Survival Analysis Showing Predictors of Late Mortality in Patients Discharged From Hospital (*n* = 336)

Variables	Hazard Ratio	95% CI	*p*
Age (yr)	1.04	1.02–1.06	< 0.001
Immunocompromised state[a]	1.95	1.04–3.67	0.04
Pre–extracorporeal membrane oxygenation hemoglobin (g/dL)	0.92	0.82–1.03	0.13
Diagnostic group[b]			
Pulmonary	1.00 (reference)		
Extrapulmonary	0.73	0.39–1.34	0.31
Trauma	0.14	0.02–1.03	0.05
Other	1.18	0.45–3.05	0.74
Length of hospital stay (d)	1.01	0.99–1.01	0.61
Glasgow Outcome Score			
5:Good recovery	1.00 (reference)		
4:Moderate disability	2.38	1.36–4.15	0.002
3:Severe disability	–		
2:Vegetative	21.64	6.30–74.31	< 0.001

[a]Immunocompromised state included hematologic malignancies, solid tumors, solid organ transplantation, high-dose or long-term corticosteroid or other immunosuppressive therapy, or HIV infection.

[b]Group 1: primary lung failure, including bacterial, viral, fungal, or aspiration pneumonia; group 2: extrapulmonary sepsis with secondary lung injury; group 3: multiple trauma with acute respiratory distress syndrome; group 4: other pathologies, including near drowning, chronic lung diseases, such as lung fibrosis and veno-venous extracorporeal membrane oxygenation as a bridge to lung transplantation.

"–" indicates no observations.

sex- and age-matched controls (34). However, they compared favorably with other patients with chronic or other life-threatening conditions (New York Heart Association Functional class III, dialysis-dependent chronic renal failure, and ARDS) (34). These outcomes may therefore be at least partially attributable to the patient's ICU length of stay and underlying disease.

There are some limitations that should be addressed. This is a single-center study. Due to the lack of robust data on pre-ICU morbidity, we were not able to assess the effect of preexisting chronic diseases on long-term survival. The present study was not designed to provide a detailed evaluation of health-related quality of life following ECMO support but asserted its main research focus on survival trends and predictors of increased mortality. Strengths include the large number of veno-venous ECMO-treated patients in a specialized ECMO center, the close follow-up of each individual over a long time range, and the broad range of variables registered prospectively into the database.

CONCLUSIONS

The present study showed that 1-month, 3-month, 1-year, and 5-year survival for hospital survivors following veno-venous ECMO support was 99%, 95%, 86%, and 76%, respectively. Age, immunocompromised state, SOFA score, and out-of-center ECMO implantation were significantly associated with overall survival rates; need of resuscitation before ECMO was not. Only age and immunocompromised state remained predictors of late mortality when surviving to hospital discharge. Ninety percent of veno-venous ECMO survivors regained their full or almost full function in daily life at the end of follow-up. This report should serve to be an inspiration and motivation for patients, relatives, and clinicians, showing that early intensive therapy integrating ECMO when needed can result in good long-term outcomes.

REFERENCES

1. Peek GJ, Mugford M, Tiruvoipati R, et al; CESAR trial collaboration: Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicentre randomised controlled trial. *Lancet* 2009; 374:1351–1363
2. Davies A, Jones D, Bailey M, et al; Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators: Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA* 2009; 302:1888–1895
3. Patroniti N, Zangrillo A, Pappalardo F, et al: The Italian ECMO network experience during the 2009 influenza A(H1N1) pandemic: Preparation for severe respiratory emergency outbreaks. *Intensive Care Med* 2011; 37:1447–1457
4. Pham T, Combes A, Rozé H, et al; REVA Research Network: Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: A cohort study and propensity-matched analysis. *Am J Respir Crit Care Med* 2013; 187:276–285
5. Combes A, Bacchetta M, Brodie D, et al: Extracorporeal membrane oxygenation for respiratory failure in adults. *Curr Opin Crit Care* 2012; 18:99–104

6. Karagiannidis C, Brodie D, Strassmann S, et al: Extracorporeal membrane oxygenation: Evolving epidemiology and mortality. *Intensive Care Med* 2016; 42:889–896
7. Rozencwajg S, Pilcher D, Combes A, et al: Outcomes and survival prediction models for severe adult acute respiratory distress syndrome treated with extracorporeal membrane oxygenation. *Crit Care* 2016; 20:392
8. Enger T, Philipp A, Videm V, et al: Prediction of mortality in adult patients with severe acute lung failure receiving veno-venous extracorporeal membrane oxygenation: A prospective observational study. *Crit Care* 2014; 18:R67
9. Pappalardo F, Pieri M, Greco T, et al; Italian ECMOnet: Predicting mortality risk in patients undergoing venovenous ECMO for ARDS due to influenza A (H1N1) pneumonia: The ECMOnet score. *Intensive Care Med* 2013; 39:275–281
10. Schmidt M, Zogheib E, Rozé H, et al: The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *Intensive Care Med* 2013; 39:1704–1713
11. Peek GJ, Elbourne D, Mugford M, et al: Randomised controlled trial and parallel economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR). *Health Technol Assess* 2010; 14:1–46
12. Jennett B, Bond M: Assessment of outcome after severe brain damage. *Lancet* 1975; 1:480–484
13. Christakou AP PI, Sidiras G, Nanas S. Functional Assessment Scales in a general intensive care unit. *A review. Hospital Chron* 2013; 8:164–170
14. Fernandez RR, Cruz JJ, Mata GV: Validation of a quality of life questionnaire for critically ill patients. *Intensive Care Med* 1996; 22:1034–1042
15. Oken MM, Creech RH, Tormey DC, et al: Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; 5:649–655
16. Müller T, Philipp A, Luchner A, et al: A new miniaturized system for extracorporeal membrane oxygenation in adult respiratory failure. *Crit Care* 2009; 13:R205
17. Human Mortality Database: University of California, Berkeley (USA), and Max Planck Institute for Demographic Research (Germany). 2016. Available at: http://www.mortality.org or http://www.human-mortality.de. Accessed December 6, 2016
18. ECLS Registry Report (January 2017) International Summary: ECMO Registry of the Extracorporeal Life Support Organization (ELSO). 2017. Available at: https://www.elso.org/Registry/Statistics/InternationalSummary.aspx. Accessed January 31, 2017
19. von Bahr V, Hultman J, Eksborg S, et al: Long-term survival in adults treated with extracorporeal membrane oxygenation for respiratory failure and sepsis. *Crit Care Med* 2017; 45:164–170
20. Weycker D, Akhras KS, Edelsberg J, et al: Long-term mortality and medical care charges in patients with severe sepsis. *Crit Care Med* 2003; 31:2316–2323
21. Cuthbertson BH, Roughton S, Jenkinson D, et al: Quality of life in the five years after intensive care: A cohort study. *Crit Care* 2010; 14:R6
22. Lone NI, Gillies MA, Haddow C, et al: Five-year mortality and hospital costs associated with surviving intensive care. *Am J Respir Crit Care Med* 2016; 194:198–208
23. Khandelwal N, Hough CL, Bansal A, et al: Long-term survival in patients with severe acute respiratory distress syndrome and rescue therapies for refractory hypoxemia. *Crit Care Med* 2014; 42:1610–1618
24. Niskanen M, Kari A, Halonen P: Five-year survival after intensive care–comparison of 12,180 patients with the general population. Finnish ICU Study Group. *Crit Care Med* 1996; 24:1962–1967
25. Wright JC, Plenderleith L, Ridley SA: Long-term survival following intensive care: Subgroup analysis and comparison with the general population. *Anaesthesia* 2003; 58:637–642
26. Williams TA, Dobb GJ, Finn JC, et al: Determinants of long-term survival after intensive care. *Crit Care Med* 2008; 36:1523–1530
27. Wang CY, Calfee CS, Paul DW, et al: One-year mortality and predictors of death among hospital survivors of acute respiratory distress syndrome. *Intensive Care Med* 2014; 40:388–396
28. Davidson TA, Rubenfeld GD, Caldwell ES, et al: The effect of acute respiratory distress syndrome on long-term survival. *Am J Respir Crit Care Med* 1999; 160:1838–1842
29. Mahoney FI, Barthel DW: Functional evaluation: The Barthel index. *Md State Med J* 1965; 14:61–65
30. Schag CC, Heinrich RL, Ganz PA: Karnofsky performance status revisited: Reliability, validity, and guidelines. *J Clin Oncol* 1984; 2:187–193
31. Hodgson CL, Hayes K, Everard T, et al: Long-term quality of life in patients with acute respiratory distress syndrome requiring extracorporeal membrane oxygenation for refractory hypoxaemia. *Crit Care* 2012; 16:R202
32. Li XY, Sun B, Wang CT, et al: A follow-up study on acute respiratory distress syndrome survivors after extracorporeal membrane oxygenation by pulmonary high-resolution CT. *Arch Iran Med* 2015; 18:6–11
33. Lindén VB, Lidegran MK, Frisén G, et al: ECMO in ARDS: A long-term follow-up study regarding pulmonary morphology and function and health-related quality of life. *Acta Anaesthesiol Scand* 2009; 53:489–495
34. Combes A, Leprince P, Luyt CE, et al: Outcomes and long-term quality-of-life of patients supported by extracorporeal membrane oxygenation for refractory cardiogenic shock. *Crit Care Med* 2008; 36:1404–1411