ORIGINAL ARTICLE

Predicting Survival after Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Failure

The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) Score

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Abstract

Rationale: Increasing use of extracorporeal membrane oxygenation (ECMO) for acute respiratory failure may increase resource requirements and hospital costs. Better prediction of survival in these patients may improve resource use, allow risk-adjusted comparison of center-specific outcomes, and help clinicians to target patients most likely to benefit from ECMO.

Objectives: To create a model for predicting hospital survival at initiation of ECMO for respiratory failure.

Methods: Adult patients with severe acute respiratory failure treated by ECMO from 2000 to 2012 were extracted from the Extracorporeal Life Support Organization (ELSO) international registry. Multivariable logistic regression was used to create the Respiratory ECMO Survival Prediction (RESP) score using bootstrapping methodology with internal and external validation.

Measurements and Main Results: Of the 2,355 patients included in the study, 1,338 patients (57%) were discharged alive from hospital. The RESP score was developed using pre-ECMO variables independently associated with hospital survival on logistic regression, which included age, immunocompromised status, duration of mechanical ventilation before ECMO, diagnosis, central nervous system dysfunction, acute associated nonpulmonary infection, neuromuscular blockade agents or nitric oxide use, bicarbonate infusion, cardiac arrest, Pa_{CO_2}, and peak inspiratory pressure. The receiver operating characteristics curve analysis of the RESP score was $c = 0.74$ (95% confidence interval, 0.72–0.76). External validation, performed on 140 patients, exhibited excellent discrimination ($c = 0.92$; 95% confidence interval, 0.89–0.97).

Conclusions: The RESP score is a relevant and validated tool to predict survival for patients receiving ECMO for respiratory failure.

Keywords: predictive score model; extracorporeal membrane oxygenation; acute respiratory distress syndrome; outcome; adult

Extracorporeal membrane oxygenation (ECMO) has been proposed as a possible therapeutic option for patients with severe acute respiratory distress syndrome (ARDS) who have refractory hypoxemia or excessively high inspiratory airway pressures and are unable to tolerate volume- and pressure-limited strategies (1, 2). Its successful use for the most severe ARDS

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At a Glance Commentary

Scientific Knowledge on the Subject: Increasing use of extracorporeal membrane oxygenation (ECMO) for acute respiratory failure may increase resource requirements and hospital costs. Better prediction of survival in these patients may improve resource use, allow risk-adjusted comparison of center-specific outcomes, and help clinicians to target patients most likely to benefit from ECMO.

What This Study Adds to the Field: Derived from a population of 2,355 international patients, the Respiratory ECMO Survival Prediction (RESP) score is a robust prediction tool comprising 12 simple pre-ECMO variables that predict survival after initiation of ECMO for respiratory support. It is the first validated international predictive mortality model based on a large population of patients with acute respiratory failure requiring ECMO. In light of the growing use of ECMO, the RESP score is a clinically relevant tool to predict survival for patients receiving ECMO for respiratory failure.

cases during the influenza A(H1N1) pandemic (3, 4) and a positive randomized controlled trial (5) have increased the practice of this salvage therapy over the past decade (6). Despite major technologic advances in design, increasing simplicity of implementation, and devices (1, 2, 7, 8), this therapy is still burdened with a high rate of complications (e.g., bleeding [5, 9–12], infection [13], mechanical complications [11]). In addition, these patients still exhibit a high mortality (5, 9) and are prone to significant long-term physical and neuropsychological impairment (9, 14). Increased use of ECMO, with its associated needs for training expertise and resources, may also increase hospital costs (5). Thus, in the modern era of ECMO support (8), it is necessary to define risk factors for death in these patients prior ECMO initiation, which will in turn allow institutions to appropriately allocate resources and benchmark mortality outcomes. Predictive mortality scores have been recently proposed (9, 15). However, these have several limitations that impede their widespread applicability: the small size of the population used to derive the model (9, 15, 16), restriction to specific groups (e.g., influenza A(H1N1)–induced ARDS, or patients transferred to a referral center) (15, 16), lack of external validation (9), and unknown suitability for patients in other centers (17).

The Extracorporeal Life Support Organization (ELSO) has prospectively maintained a registry of ECMO use in active ELSO centers since 1986. Currently, data from 160 US and 120 other international centers are collected on standardized ELSO forms. Based on the currently collected pre-ECMO assessment data in this large international database, we hypothesized that predictors of hospital survival for patients with adult respiratory failure treated with ECMO could be identified. These would then allow construction of a robust survival prediction model that would have widespread applicability, namely the Respiratory ECMO Survival Prediction (RESP) score.

Methods

Data Collection

We queried the ELSO registry for adult patients who received ECMO primarily for acute respiratory failure from 2000 through 2012. Only data from the primary ECMO run were analyzed including demographic data, pre-ECMO variables, International Classification of Diseases-9 diagnosis codes, procedure and complication codes, year of ECMO run, and hospital outcome. No patient or hospital identifying information was extracted. The pre-ECMO variables included cardiopulmonary resuscitation, blood gases, ventilator settings, and pre-ECMO rescue therapies. High-frequency oscillatory ventilation, nitric oxide neuromuscular blocker agent use, and steroid use before ECMO were reported. Prone positioning is not collected in the ELSO registry. ECMO modes were reported as venoarterial, venovenous including a dual-lumen venovenous cannula (AvalonElite, Maquet, Sweden), or mixed modes (i.e., combinations of venoarterial and venovenous). Two researchers (D.P. and M.S.) independently reviewed all International Classification of Diseases-9 codes. Any discrepancies between the two reviewers were resolved by discussion. Diagnoses for severe acute respiratory failure were collapsed into the following groups: "bacterial pneumonia," "viral pneumonia," "aspiration pneumonitis," "asthma," "trauma/burn," and "others acute respiratory diagnoses." "Obesity" was defined as a body mass index greater than 30 kg/m^2. "Renal dysfunction" included chronic or acute renal insufficiency (e.g., creatinine $>$1.5 mg/dl) with or without renal-replacement therapy. Similarly "heart dysfunction" was defined by chronic or acute heart failure. "Acute associated infection" was defined as a bacterial, viral, parasitic, or fungal infection that did not involve the lung (e.g., intraabdominal sepsis). "Central nervous system (CNS) dysfunction" combined neurotrauma, stroke, encephalopathy, cerebral embolism, and seizure and epileptic syndromes. "Immunocompromised" was defined as hematologic malignancies, solid tumor, solid organ transplantation, human immunodeficiency virus, or cirrhosis. This analysis of deidentified data was approved by the ECMO Registry Committee of ELSO.

Statistical Analysis

Analyses were performed with STATA (StataCorp. 2011, Stata Statistical Software: Release 12; StataCorp LP, College Station, TX). Continuous variables were compared with Student *t* test or the Wilcoxon signed rank test, as appropriate. Categorical variables were compared using the chi-square test for equal proportion. The RESP score was constructed using the following steps:

Step 1: *Identification of candidate variable.* Variables relating to patient or treatment factors before initiation of ECMO were considered. Candidate variables for inclusion in the RESP score were identified using logistic regression applied on 2,355 patients with complete data with hospital mortality as the dependent variable. All potential explanatory variables included in the multivariable analyses were subjected to a correlation matrix for analysis of collinearity. Continuous variables were explored for linearity by considering as both quartiles and deciles before being converted into categorical variables for practical purposes.

Step 2: Construction of the RESP score. Logistic regression using bootstrapping methodology with 200 repetitions with replacement and a sample size of 2,000 was used for estimation of the β parameters (regression coefficients) of categorical variables identified in step one (18). This technique involves multiple resampling of the original data and facilitates use of the whole dataset without the need to split into derivation and validation samples. Initial inclusion criteria were set at *P* less than or equal to 0.1 but only variables that retained *P* values less than or equal to 0.05 were retained for calculation of the score. Using the relative contribution of each β parameter (19), practical weights, both positive and negative, were generated with a zero score approximately equating to a 50% risk of death.

Step 3: *Internal validation.* Individual patient scores were generated. Score performance was then reassessed in the original dataset. Model discrimination and calibration were assessed using the

Table 1: Demographic, Pre-ECMO Parameters, and ECMO Settings According to Survival Status for Adult Acute Respiratory Failure

	All Patients (*n* = 2,355)	Status at Hospital Discharge		*P* Value
		Alive (*n* = 1,338)	Dead (*n* = 1,017)	
Age, yr	41 (28–54)	39 (27–51)	45 (30–58)	<0.001
Acute respiratory failure diagnostic groups				
Bacterial pneumonia	487 (21)	319 (24)	168 (17)	0.0001
Viral pneumonia	260 (11)	183 (14)	77 (7)	<0.0001
Aspiration pneumonitis	56 (2)	38 (3)	18 (2)	0.09
Asthma	35 (1)	33 (2)	2 (0)	<0.0001
Trauma	146 (6)	93 (7)	53 (5)	0.08
Others acute respiratory diagnoses	669 (28)	357 (27)	312 (31)	0.03
Others	702 (30)	315 (23)	387 (38)	<0.0001
Immunocompromised*	121 (5)	48 (4)	73 (7)	<0.0001
Renal dysfunction†	429 (18)	189 (14)	240 (24)	<0.0001
Heart dysfunction‡	521 (28)	229 (23)	292 (33)	<0.0001
CNS dysfunction§	190 (8)	37 (3)	153 (15)	<0.0001
Acute associated infection‖	237 (10)	90 (7)	147 (14)	<0.0001
Obesity¶	61 (3)	39 (3)	22 (2)	0.26
Pre-ECMO rescue therapy				
HFOV	241 (10)	130 (10)	111 (11)	0.34
Inhaled nitric oxide	468 (20)	222 (17)	246 (24)	<0.0001
NM blockade agents	1,153 (49)	710 (53)	443 (43)	<0.0001
Steroids	148 (6)	85 (6)	63 (6)	0.02
Bicarbonate infusion	424 (18)	197 (15)	227 (22)	<0.0001
Interval MV-ECMO, h	57 (19–151)	46 (17–128)	75 (24–176)	<0.0001
Cardiac arrest	218 (9)	92 (7)	126 (12)	<0.0001
Pre-ECMO ventilator settings				
Pa_{O_2}/Fi_{O_2}	59 (48–75)	59 (48–76)	58 (48–74)	0.02
Fi_{O_2}	100 (100–100)	100 (100–100)	100 (100–100)	0.98
PIP, cm H_2O	36 (31–43)	36 (31–41)	36 (31–44)	0.035
MAP, cm H_2O	24 (19–30)	25 (19–30)	24 (19–30)	0.53
PEEP	13 (10–16)	14 (10–16)	12 (10–16)	0.21
Pre-ECMO blood gas				
pH	7.25 (7.15–7.35)	7.26 (7.15–7.36)	7.24 (7.15–7.34)	0.01
Pa_{CO_2}, mm Hg	56 (44–73)	54 (43–72)	58 (45–75)	0.02
Pa_{O_2}, mm Hg	57 (46–70)	57 (47–70)	56 (46–69)	0.24
Sa_{O_2}, %	86 (78–92)	87 (79–92)	85 (76–91)	0.0003
ECMO mode				
Venoarterial	547 (23)	219 (16)	328 (32)	<0.0001
Venovenous	1,928 (82)	1,158 (87)	770 (76)	<0.0001
Dual venovenous cannula	500 (21)	352 (26)	148 (15)	<0.0001
Mixed modes	129 (5)	43 (3)	86 (8)	<0.0001
Duration of ECMO support, h	168 (90–306)	170 (105–280)	166 (65–351)	0.12

Definition of abbreviations: CNS = central nervous system; ECMO = extracorporeal membrane oxygenation; HFOV = high-frequency oscillation ventilation; ICU = intensive care unit; MAP = mean airway pressure; MV = mechanical ventilation; NM = neuromuscular; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; Sa_{O_2} = arterial oxygen saturation.

Data are given as n (%) or median (interquartile range).

*"Immunocompromised" is defined as hematologic malignancies, solid tumor, solid organ transplantation, human immunodeficiency virus, and cirrhosis.

†"Renal dysfunction" is defined as chronic or acute renal insufficiency (e.g., creatinine >1.5 mg/dl) with or without renal-replacement therapy.

‡"Heart dysfunction" is defined as chronic or acute heart failure.

§"CNS dysfunction" diagnosis combined neurotrauma, stroke, encephalopathy, cerebral embolism, and seizure and epileptic syndrome.

‖"Acute associated infection" is defined as another bacterial, viral, parasitic, or fungal infection that did not involve the lung.

¶"Obesity" was defined as a body mass index greater than 30 kg/m^2.

area under the receiver operating characteristic (ROC) curve and the Hosmer-Lemeshow C statistic with associated *P* value, respectively (20). Further sensitivity analyses were undertaken to determine the performance of the RESP score in specific subgroups (early [pre-2009] and late [2009–2012], viral pneumonitis, and patients with missing data not initially included in the development dataset).

Step 4: *External validation.* The external validation of the RESP score was performed on the dataset of 140 multicenter French patients used to create the PRESERVE score (9). Because the use of neuromuscular blockade agents was not collected in the PRESERVE dataset, a score of 0 was attributed to this item. Similarly, plateau pressure (i.e., >30 cm H_2O marked by −1) instead of peak pressure was used in the external validation of the RESP score. Performance of the RESP score and the simplified acute physiology score (SAPS) II and the sepsis-related organ failure assessment (SOFA) score at intensive care unit (ICU) admission were assessed using the area under the ROC curve.

Table 2: Pre-ECMO Factors Associated with Survival to Hospital Discharge (Candidate Factors for the RESP Score) in Multivariate Analysis

Pre-ECMO Support	Odds Ratio (95% CI)	*P* Value
Age	0.98 (0.97–0.99)	<0.0001
Immunocompromised*	0.64 (0.42–0.95)	0.029
Bacterial pneumonia	2.12 (1.63–2.75)	<0.0001
Viral pneumonia	2.26 (1.62–3.14)	<0.0001
Asthma	17.7 (3.72–83.8)	<0.0001
Trauma and burn	1.82 (1.22–2.71)	0.003
Aspiration pneumonitis	3.45 (1.82–6.53)	<0.0001
Others acute respiratory diagnoses	1.29 (1.02–1.62)	0.032
Central nervous system dysfunction†	0.15 (0.10–0.22)	<0.0001
Acute nonpulmonary-associated infection‡	0.46 (0.34–0.62)	<0.0001
Renal dysfunction§	0.77 (0.61–0.98)	0.038
Cardiac arrest	0.62 (0.45–0.85)	0.003
Mechanical ventilation time prior to initiation of ECMO, d	0.989 (0.980–0.998)	0.017
Neuromuscular blockade agents	1.40 (1.14–1.66)	0.001
Inhaled nitric oxide	0.68 (0.54–0.85)	0.001
Bicarbonate infusion	0.69 (0.54–0.88)	0.002
Peak inspiratory pressure	0.992 (0.986–0.998)	0.009
Pa_{CO_2}	0.996 (0.993–0.999)	0.020

Definition of abbreviations: CI = confidence interval; ECMO = extracorporeal membrane oxygenation; RESP = Respiratory ECMO Survival Prediction.
n = 2355 patients.
*"Immunocompromised" is defined as hematologic malignancies, solid tumor, solid organ transplantation, human immunodeficiency virus, and cirrhosis.
†"Central nervous system dysfunction" diagnosis combined neurotrauma, stroke, encephalopathy, cerebral embolism, and seizure and epileptic syndrome.
‡"Acute nonpulmonary-associated infection" is defined as bacterial, viral, parasitic, or fungal infection that did not involve the lung.
§"Renal dysfunction" is defined as chronic or acute renal insufficiency (e.g., creatinine >1.5 mg/dl) with or without renal-replacement therapy.

Results

There were 3,522 ECMO runs for respiratory failure in 3,376 patients reported to ELSO during this 13-year period. Of these, 2,355 had complete data available for analysis. Their distribution per year and respective survival is detailed in Figure E1 in the online supplement. A total of 1,338 patients (57%) were alive at hospital discharge after a median of 170 (105–280) hours on ECMO. Venovenous ECMO was the sole mode used for 82% of patients (Pa_{O_2}/FI_{O_2} ratio 59 [48–75] mm Hg), and was instituted after a median of 57 (19–151) hours of mechanical ventilation with high positive end-expiratory pressure level (13 [10–16] cm H_2O), neuromuscular blocker agents (49%), inhaled nitric oxide (20%), and high-frequency oscillatory ventilation (10%). Of note, 9% of the patients received an ECMO for respiratory failure following a cardiac arrest. As shown in Table 1, bacterial pneumonia, viral pneumonia, trauma, and asthma were more frequent among the survivors' group.

Initial multivariate analysis performed on 2,355 patients retained older age, cardiac arrest before ECMO, CNS dysfunction, renal dysfunction, immunocompromised status, associated nonpulmonary infection, the use of inhaled nitric oxide and bicarbonate infusion, longer mechanical ventilation duration before initiation of ECMO, higher Pa_{CO_2}, and higher peak inspiratory pressure (PIP) as independent risk factors at the time of ECMO institution associated with hospital mortality (Table 2). Conversely, bacterial pneumonia, viral pneumonia, aspiration pneumonia, asthma, trauma and burn, and the use of neuromuscular blocking agents were protective factors (Table 2). The RESP score was developed and validated using these "candidate variables" (*see* Table E1). The full description of the RESP score is shown in Table 3. An online calculator is available at www.respscore.com.

It is composed of 12 pre-ECMO items: age, immunocompromised status, mechanical ventilation time before initiation of ECMO, acute respiratory failure diagnosis group, CNS dysfunction, acute nonpulmonary-associated infection, neuromuscular blocking agents, nitric oxide use, bicarbonate infusion, cardiac arrest, Pa_{CO_2}, and PIP (Table 3). Renal dysfunction, although initially identified as a candidate for inclusion, was not independently predictive of survival and was not included in the final RESP score. Predicted hospital survival in the original cohort according to the RESP score is described in Figure 1A. Cumulative predicted hospital survival were 92, 76, 57, 33, and 18% for five RESP score risk classes I (≥6), II (3–5), III (−1 to 2), IV (−5 to −2), and V (≤ − 6), respectively (Table 3, Figure 1A). Representation of the individual predicted survival at every level of the RESP score with 95% confidence interval (CI) (together with observed survival from the ELSO dataset) is provided in Figure 2. The RESP score was also

Table 3: The RESP Score at ECMO Initiation

Parameter	Score
Age, yr	
18 to 49	0
50 to 59	−2
⩾60	−3
Immunocompromised status*	−2
Mechanical ventilation prior to initiation of ECMO	
<48 h	3
48 h to 7 d	1
>7 d	0
Acute respiratory diagnosis group (select only one)	
Viral pneumonia	3
Bacterial pneumonia	3
Asthma	11
Trauma and burn	3
Aspiration pneumonitis	5
Other acute respiratory diagnoses	1
Nonrespiratory and chronic respiratory diagnoses	0
Central nervous system dysfunction†	−7
Acute associated (nonpulmonary) infection‡	−3
Neuromuscular blockade agents before ECMO	1
Nitric oxide use before ECMO	−1
Bicarbonate infusion before ECMO	−2
Cardiac arrest before ECMO	−2
Pa_{CO_2}, mm Hg	
<75	0
⩾75	−1
Peak inspiratory pressure, cm H_2O	
<42	0
⩾42	−1
Total score	−22 to 15

Hospital Survival by Risk Class		
Total RESP Score	**Risk Class**	**Survival**
⩾6	I	92%
3 to 5	II	76%
−1 to 2	III	57%
−5 to −2	IV	33%
⩽−6	V	18%

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; RESP = Respiratory ECMO Survival Prediction.
An online calculator is available at www.respscore.com.
*"Immunocompromised" is defined as hematological malignancies, solid tumor, solid organ transplantation, human immunodeficiency virus, and cirrhosis.
†"Central nervous system dysfunction" diagnosis combined neurotrauma, stroke, encephalopathy, cerebral embolism, and seizure and epileptic syndrome.
‡"Acute associated (nonpulmonary) infection" is defined as another bacterial, viral, parasitic, or fungal infection that did not involve the lung.

calculated for the 1,021 patients who had incomplete data and had not initially been included in the score development (Figure 3).

Internal validation of the RESP score demonstrated reasonable discrimination (c = 0.73 [95% CI, 0.71–0.75]) and good calibration with a Hosmer-Lemeshow C statistic of 12.81 (P = 0.12). In addition, despite an improvement in survival from 52% to 60% between the early time period cohort (n = 891; 2000–2008) and the late time period cohort (n = 2,355; 2009–2012), respectively, the RESP score exhibited similar performance across both periods (c = 0.75 [95% CI, 0.72–0.78] in 2000–2008 and c = 0.73 [95% CI, 0.70–0.75] in 2009–2012, respectively) (*see* Figure E2). Performance of the RESP score in the 260 patients with viral pneumonia, of whom 183 (70%) were also subcategorized as due to influenza, was compared with other diagnoses (*see* Figure E3). Performance was similar in both groups, with an area under the ROC curve of 0.73 (95% CI, 0.65–0.80) in the viral pneumonia group and 0.73 (95% CI, 0.71–0.76) in the other diagnostic groups, respectively.

Predicted hospital survival in the external validation cohort according to the RESP score is described in Figure 1B. Overall observed survival was much lower in risk class V and VI (i.e., RESP score ⩽ −2) than in risk class III, II, and I (i.e., RESP score ⩾ −1) (15.5 vs. 91.5%, respectively). The external validation of the RESP score on the PRESERVE dataset exhibited excellent performance (c = 0.92 [95% CI, 0.89–0.97]) in contrast to much poorer discrimination of the SAPS II (c = 0.60 [95% CI, 0.51–0.70]) and SOFA scores (c = 0.58 [95% CI, 0.48–0.67]) in the PRESERVE data. Graphic representation of the RESP score, SAPS II, and SOFA discrimination performance is shown in Figure E4.

Discussion

To our knowledge, this is the largest report of patients who have received ECMO for severe acute respiratory failure and comprises 2,355 patients from multiple countries over a 13-year period. This large population has allowed creation of a well-calibrated and discriminatory survival model comprising twelve pre-ECMO variables (RESP score; http://www.respscore.com).

Prognostic Factors of Hospital Discharge

Our study suggests that the diagnosis group has a strong impact on survival. Although scarce (35 cases in 12 yr), ECMO for acute severe asthma exhibited a very high survival rate (33 of 35, 94%). Similarly, viral pneumonia was independently associated with hospital survival (odds ratio, 2.26; 95% CI, 1.62–3.14; $P < 0.0001$) (Table 2) and thus highly weighted in the RESP score (Table 3). Forty percent (104 of 260) of the cases of viral pneumonia were recorded in 2009 and are likely caused by influenza A (H1N1). The Australian and New Zealand Intensive Care Society (3), the British (4), and the French REVA groups (10) all reported low mortality (25–36%) despite extreme clinical severity at the time of the ECMO establishment (e.g., median Pa_{O_2}/FI_{O_2} ratio to 56 mm Hg despite 18 cm H_2O of positive end-expiratory pressure and median

lung injury score of 3.8 in the Australian and New Zealand Intensive Care Society study) (3). However the performance of the RESP score was similar in the viral pneumonia group and in other diagnostic groups. Comparative analysis of worldwide results published on ECMO suggested that the best results were obtained for patients treated in expert centers with a sufficient number of patients and in countries where the ECMO activity was organized and regulated (21–23). Moreover, the very recent analysis of large pediatric databases confirmed a significant relationship between the volume of patients treated by center and the prognosis (24–26). Our study regroups ECMO experience in acute respiratory failure of more than 280 centers worldwide. Because of deidentified data, we did not examine center-specific outcomes. However, it is possible that centers included in the ELSO registry might not be representative of all ICUs that use ECMO for patients with acute respiratory failure according to the high survival rate (57%) compared with those reported in recent publications (16). The RESP score may now allow individual centers to compare their outcomes against an international standard.

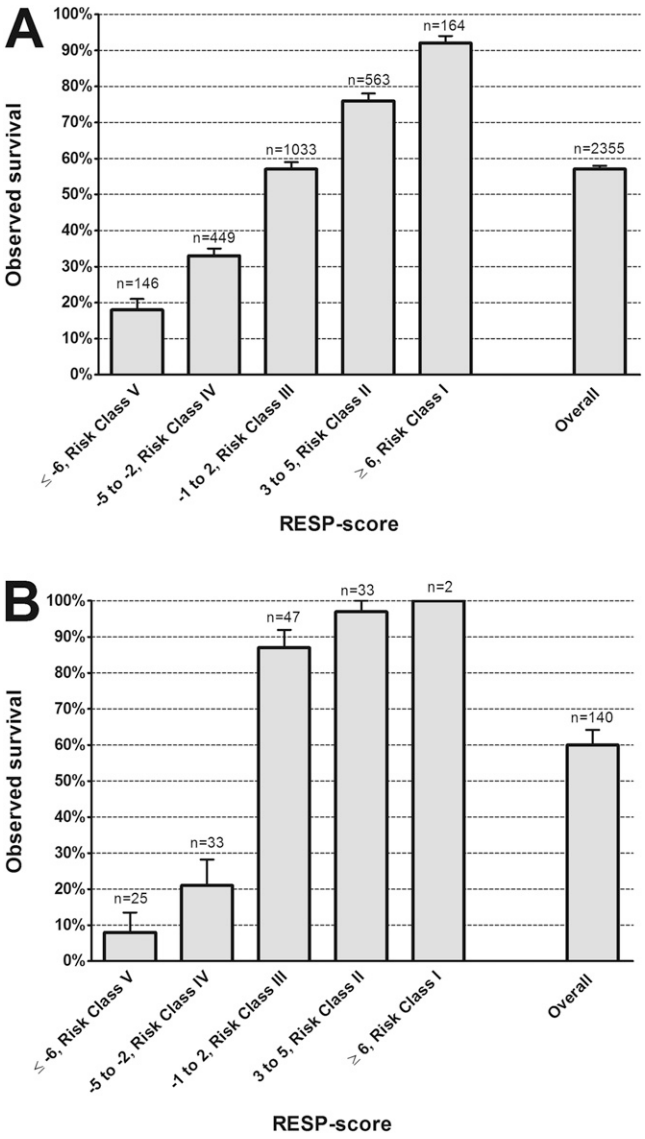

Figure 1. (*A*) Hospital survival percentage in original cohort according to the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score at extracorporeal membrane oxygenation initiation for severe acute respiratory failure. (*B*) Hospital survival percentage in the external validation cohort according to the RESP score. n = number of patients in the study who had particular RESP score values. Survival percentage is expressed as mean and 95% confidence interval. The external validation cohort was extracted from Reference 9.

As in our study, older age (9, 11, 27–29), a greater number of days of mechanical ventilation before the ECMO establishment (9, 11, 27, 28), and a higher number of extrapulmonary organ failures (9, 11, 27–29) were frequently associated with poor outcome in patients with severe acute respiratory failure treated with ECMO. It is worth noting that both "CNS dysfunction" and "acute nonpulmonary-associated infection" were strongly related to hospital mortality and thus heavily impacted the RESP score (Table 3). Although severe hypoxemia is a frequent indication for initiating ECMO, once the decision to undertake this therapy has been made, the initial oxygenation status itself does not seem to be associated with outcome (9). By contrast, a higher PIP and a higher Pa_{CO_2} before ECMO institution were associated with mortality and thus represented in the RESP score. Although the ELSO registry records PIP, positive end-expiratory pressure, and mean airway pressure, only PIP was independently predictive of survival in our analysis. Plateau pressure was not specifically available. Thus, it is unknown if as a better marker of trans-pulmonary pressure, its inclusion in the RESP score might have further enhanced predictive ability.

The timing of ECMO institution is still a matter of debate. However, a considerable body of clinical studies (9, 11, 27, 28) suggests that the greater number of days of mechanical ventilation before ECMO initiation, the poorer is the outcome. The RESP score and the PRESERVE score (9) demonstrated 7 days of mechanical ventilation before ECMO as a time point beyond which there is a reduction in survival. Additionally, we demonstrated a beneficial impact of early use of ECMO (<48 h), which may now lead to earlier consideration of ECMO (Table 3) (9). Ongoing randomized trials may also help to confirm this finding (30). This also highlights the need to understand how and when to use other potential rescue therapies (e.g., prone positioning, neuromuscular blocker agents, and nitric oxide) with and before ECMO. Recently, positive impacts of neuromuscular blocking agents and prolonged prone-positioning sessions on 90-day survival were demonstrated by two landmark publications (31, 32). To date,

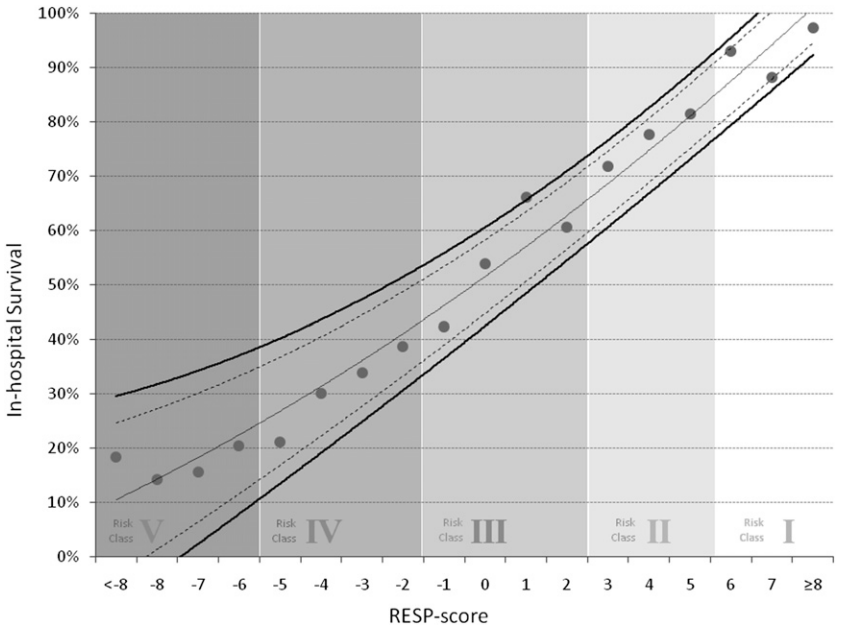

Figure 2. Individual observed survival regarding the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score within 95% confidence interval. Each *dot* represents the observed survival percentage in the study population (n = 2,355) used to derive the RESP score. *Curved dotted gray lines* and *curved black lines* represent 95 and 99% confidence intervals, respectively, for predicted survival at each score level.

despite a transient improvement in oxygenation in adults with ARDS, no survival benefit or reduction in ventilator-free days has been observed with inhaled nitric oxide (33). Moreover, it was even associated with a higher mortality within the RESP score. Prone positioning is not currently collected in the ELSO registry. Of note, only 49% and 20% of the patients in our study were recorded as receiving neuromuscular blockers or nitric oxide, respectively. Interestingly, use of neuromuscular blocking agents before ECMO was associated with a better in-hospital survival (Table 2), and then translated into a positive score in the RESP score (Table 3). Papazian and coworkers (32) demonstrated that 48 hours of intravenous cisatracurium besylate significantly improved outcomes of patients with ARDS. However, we were not able to specify the timing and the duration of the neuromuscular blockers received before ECMO institution in our study.

The RESP Score

The main objective of this study was to develop and validate a robust predictive survival score model on a large international population. Potential roles for such scores include helping clinicians select appropriate candidates for ECMO, informing family members of likely prognosis, and facilitating risk-adjusted comparison of center-specific outcomes. Several predictive mortality risk models are currently available. The ECMOnet score, published by the Italian network in 2012, was first developed on 60 patients with influenza A(H1N1)-associated ARDS and was secondarily validated on a cohort of 74 influenza A(H1N1) international patients. This score was developed and validated on a specific ARDS population, which may be a barrier to widespread use of this score with other diagnoses. Recently, the PRESERVE score was constructed from 140 ECMO-treated patients with ARDS admitted to three French ICUs (9). Although highly discriminatory with an area under the ROC curve of 0.89 (95% CI, 0.83–0.94) in the derivation set, no external validation was performed and it may therefore be subject to "over-fitting." It is notable that 4 of 12 items in the RESP score were also present in the PRESERVE score: age, immunocompromised status, mechanical ventilation time before initiation of ECMO, and PIP or plateau pressure.

The external validation of the RESP score on the PRESERVE data exhibited excellent performance (i.e., area under the ROC curve 0.92 [95% CI, 0.89–0.97]), which was considerably better than the "classical" ICU severity scores, SAPS II and SOFA. However, the scores were not performed at the same time in the ICU course (i.e., ICU admission vs. the day of ECMO cannulation). A delay between ICU admission and ECMO cannulation may have further emphasized these discrepancies in performance. Nevertheless, our findings suggest that the RESP score may be more useful than "classical" ICU severity scores in decision making about patients with severe respiratory failure where ECMO has been considered.

Study Strengths and Limitations

Our study's strengths are the large international population studied, the detailed pre-ECMO parameters on patients with acute severe respiratory failure, and a predictive survival model on ECMO validated internally and externally on various acute respiratory failure diagnosis groups. However, there are some limitations. First, the study lasts for a 13-year period with an improvement of overall survival between 2000 and 2008, and 2009 and 2012 (*see* Figure E2). During the past decade, new generations of ECMO devices have been developed (8) and a landmark randomized trial has been published (5). Therefore, we cannot exclude that global management of ECMO for severe acute respiratory failure may have changed during the study's period and may also change before the potential application of the RESP score into clinical practice. It is possible that the RESP score in common with other scoring systems will lose calibration over time and may need further adaptation in future (34). However, because nearly two-thirds (1,464 of 2,355) of the patients used to construct the score were from the most recent 4 years (2009–2012), it is likely the RESP score reflects contemporary clinical practices. Second, although reporting one of the largest populations of ECMO with adult acute respiratory failure published to date, it is worth noting that prone positioning use is not reported in the pre-ECMO therapy section of the ELSO registry. According to the recent positive effect of prone positioning in both the PROSEVA trial (31) and the PRESERVE score (9), this omission could have affected our results. Third, lung infection without further details was reported by 28% of the population. The possible inclusion of patients with bacterial

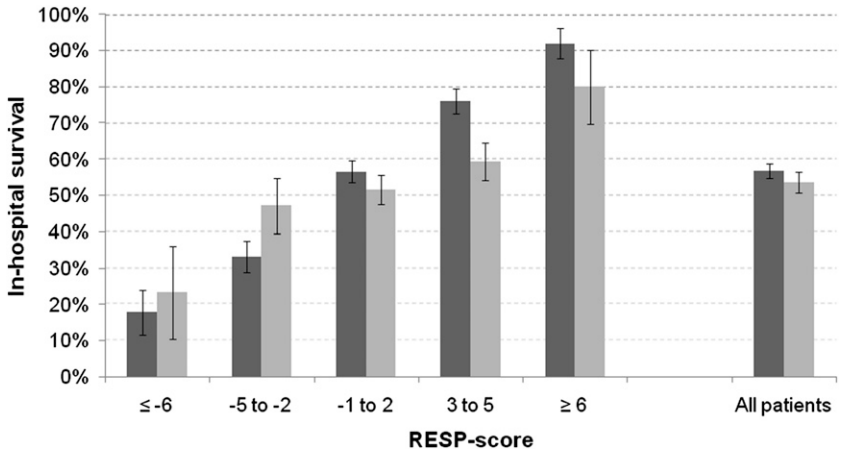

Figure 3. Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score calculated for the 1,021 patients who had incomplete data and had not initially been included in the score development. Observed survival is expressed as mean and standard deviation. Missing RESP score variables were allocated zero score. *Dark gray* = 2,355 patients used to develop score; *light gray* = 1,021 patients (i.e., remainder who have one or more missing values for the score).

or viral pneumonia in this "other acute respiratory diagnoses" group may affect external application of the RESP score. Fourth, excluding blood gases, no pre-ECMO biologic data are currently available in the ELSO registry. Modern well-calibrated and highly discriminatory risk prediction models for critically ill patients are derived from large datasets, which include extensive physiologic and biochemical information to enhance severity of illness assessment (35). The SOFA score or its biologic components have been associated with outcome in three recent studies aimed at developing mortality risk models in ECMO (9, 15, 16). More detailed biologic and chronic health data may have enhanced the accuracy of our model (15). Fifth, all items of the RESP score were not recorded in the external validation dataset (i.e., neuromuscular blocker use, plateau pressure instead of peak pressure). Finally, it is worth remembering that the RESP score has been developed on patients already on ECMO. It has not been validated for prediction of survival in a more general population of patients with severe acute respiratory failure where ECMO has not (yet) been instituted.

In conclusion, the overall hospital survival of 2,355 patients with severe acute respiratory failure extracted from an international cohort over a 13-year period was 57%. The RESP score offers, through 12 simple pre-ECMO items, a relevant and validated tool to predict survival for patients receiving ECMO for respiratory failure. Further international prospective studies aiming to evaluate the performance of the RESP score are now warranted. ■

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

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