The impact of mechanical ventilation time before initiation of extracorporeal life support on survival in pediatric respiratory failure: A review of the extracorporeal life support registry*

Michele B. Domico, MD; Deborah A. Ridout, MSc; Ronald Bronicki, MD; Nick G. Anas, MD; John Patrick Cleary, MD; James Cappon, MD; Allan P. Goldman, MRCPCH; Katherine L. Brown, MPH, MRCPCH

Objective: **To evaluate the relationship between duration of mechanical ventilation before the initiation of extracorporeal life support and the survival rate in children with respiratory failure. Extracorporeal life support has been used as a rescue therapy for >30 yrs in children with severe respiratory failure. Previous studies suggest patients who received >7–10 days of mechanical ventilation were not acceptable extracorporeal life support candidates as a result of irreversible lung damage.**

Design: **A retrospective review encompassing the past 10 yrs of the International Extracorporeal Life Support Organization Registry (January 1, 1999, to December 31, 2008).**

Setting: **Extracorporeal Life Support Organization Registry database.**

Patients: **A total of 1325 children (≥ 30 days and ≤ 18 yrs) met inclusion criteria.**

Interventions: **None.**

Measurements and Main Results: **The following pre-extracorporeal life support variables were identified as independently and significantly related to the chance of survival: 1) >14 days of ventilation vs. 0–7 days was adverse (odds ratio, 0.32; $p < .001$); 2) the presence of a cardiac arrest was adverse (odds ratio, 0.56; $p = .001$); 3) pH per 0.1-unit increase was protective (odds ratio, 1.15; $p < .001$); 4) oxygenation index, per 10-unit increase was adverse (odds ratio, 0.95; $p = .002$); and 5) any diagnosis other than sepsis was related to a more favorable outcome. Patients requiring >7–10 or >10–14 days of pre-extracorporeal life support ventilation did not have a statistically significant decrease in survival as compared with patients who received 0–7 days.**

Conclusions: **There was a clear relationship between the number of mechanical ventilation days before the initiation of extracorporeal life support and survival. However; there was no statistically significant decrease in survival until >14 days of pre-extracorporeal life support ventilation was reached regardless of underlying diagnosis. We found no evidence to suggest that prolonged mechanical ventilation should be considered as a contraindication to extracorporeal life support in children with respiratory failure before 14 days. (Pediatr Crit Care Med 2012; 13: 16–21)**

KEY WORDS: extracorporeal membrane oxygenation; extracorporeal life support; respiratory failure; mechanical ventilation; pediatric; Extracorporeal Life Support Organization registry

Extracorporeal life support (ECLS), also known as extracorporeal membrane oxygenation, has been used as a rescue therapy in children with severe respiratory failure for >30 yrs. One of the most arduous tasks for the initiation of ECLS is optimal patient selection. Historically, patients requiring >7–10 days of mechanical ventilation were not considered acceptable ECLS candidates as a result of a marked decline in survival rate and concern for irreversible lung damage (1–3). Current published Extracorporeal Life Support Organization guidelines suggest optimal timing for initiation of ECLS is within the first 7 days of mechanical ventilation (4).

Data from recent studies in adults and children indicate the relationship between number of pre-ECLS ventilation days and outcome is not clear (5–7). Massachusetts General Hospital reviewed 81 adult and pediatric respiratory failure

***See also p. 94.**

From the Department of Pediatrics, Division of Critical Care (MBD, RB, NGA, JC) and Neonatology (JPC), Children's Hospital of Orange County, Orange, CA; the Centre for Paediatric Epidemiology and Biostatistics (DAR), UCL Institute of Child Health, London, UK; and the Cardiac Intensive Care Unit (APG, KLB), Great Ormond Street Hospital for Children NHS Trust, London, UK.

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For information regarding this article, E-mail: MDomico@CHOC.org

Index of referenced International Classification of Diseases, 9th Revision (ICD-9) codes:1) Primary or secondary diagnosis of immune deficiency, cancer or transplantation (ICD-9 codes 042–044, 112.4, 112.5, 112.85, 112.89, 116, 117.3, 117.9, 130.4, 136–136.3, 155, 158.0, 163.9, 170.6, 171.4, 189, 191.9, 194.0, 195.1, 200.22, 201.50, 202.1, 202.10, 202.8, 204, 204.0, 204.00, 204.01, 204.1, 205, 205.0, 205.00, 205.01, 205.1, 205.2, 208.0, 238.7, 279.11, 279.12, 279.2, 279.3, 284.8, 284.9, 288.0, 996.8, 996.81, 996.82, 996.83, 996.84, 996.85, V42.6, V42.7, V42.81); 2) cardiac disease (ICD-9 codes 390–397, 402.91, 410–416.99, 417.1, 420.9–429.9, 441–441.2, 444–444.1, 747.8, 759.31, 759.32, 785.51, 996.01, 996.79, V15.1, V45.81); 3) metabolic disorder (ICD-9 codes 220.8, 270.6, 272.4, 275.4, 277.1, 277.6, 330, 359.8); 4) burn (ICD-9 codes e890–899, 942.3–949); 5) diaphragmatic hernia (ICD-9 codes 519.4, 552.3–555.9); 6) primary diagnosis of airway anomaly (ICD-9 codes 162.0, 519.19, 748.2, 748.3); and 7) sepsis or septic shock (ICD-9 codes 36.2, 38–38.9, 771.8, 785.52, 995.91, 995.92).

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ECLS patients from 1990 until 2008. In the subset of patients ventilated >10 days before the initiation of ECLS, the survival rate markedly increased from 21% (from 1990 to 2004) to 67% (from 2005 to 2008). The authors suggested that improved survival may be a reflection of reduced ventilator-associated lung injury with recent ventilation strategies (8).

During the past decade, increased emphasis has been placed on strategies to limit ventilator-induced lung injury. In 2000, the Acute Respiratory Distress Syndrome Network demonstrated that 6-mL/kg tidal volume ventilation was superior to 12 mL/kg (9). Currently, low tidal volume ventilation is widely accepted and practiced. Albeit unproven, most centers use other techniques such as permissive hypercapnia (10), inhaled nitric oxide (11), high-frequency oscillation (12, 13), and surfactant administration (14) in attempts to avert the need for ECLS. There are no studies examining outcome after a protracted pre-ECLS ventilation course during the current decade with the aforementioned interventions widely used.

The aim of this study was to evaluate the relationship between duration of mechanical ventilation before the initiation of ECLS and survival rate in the current era of strategies to attenuate ventilator-induced lung injury. We hypothesized the survival rate for pediatric respiratory ECLS would be similar in patients with short pre-ECLS ventilation courses as compared with children with >10 days of pre-ECLS mechanical ventilation. As part of this investigation, we also sought to explore other significant factors related to survival.

MATERIALS AND METHODS

Data Collection and Study Population. Data were obtained from the Extracorporeal Life Support Organization (ELSO) Registry in Ann Arbor, MI (15). This registry contains data from >4300 pediatric patients with respiratory failure from >130 ECLS centers worldwide. Data reporting to ELSO is approved by each site's institutional review board. Institutional review board exemption for this study was granted by Children's Hospital of Orange County and Great Ormond Street Hospital for Children.

A retrospective review of the ELSO database from January 1, 1999, until December 31, 2008, was performed. All pediatric patients (age defined by the ELSO database as ≥30 days to ≤18 yrs) who required ECLS for respiratory failure were screened. Given the specific study question, we aimed to isolate patients with primary respiratory failure and therefore excluded cases with significant confounding conditions known to decrease ECLS survival (16), where appropriate categorization for analysis would have been extremely challenging. Patients were excluded if they had any of the following conditions: 1) primary or secondary diagnosis of immune deficiency, cancer, or transplantation; 2) cardiac disease; 3) burn; 4) diaphragmatic hernia; or 5) a primary diagnosis of airway anomaly. Any child with a primary diagnosis of cardiac arrest was excluded because these patients may currently be classified as extracorporeal cardiopulmonary resuscitation, a different category in the ELSO database. Children who had a pre-ECLS cardiac arrest, but it was not the primary diagnosis for extracorporeal membrane oxygenation cannulation, were included in the study. Patients who required more than one ECLS course were excluded from the study, because the pre-ECLS ventilator days were not interpretable.

Data examined included the following: patient demographic details, diagnoses, duration of ECLS, survival to hospital discharge or transfer, and time to death or transfer. Pre-ECLS variables included ventilator days, calculated oxygenation index (OI), serum pH, systolic blood pressure, inotrope infusion requirement, cardiac arrest, use of high-frequency ventilation, inhaled nitric oxide use, and surfactant administration.

Data Categorization. The ELSO registry classifies respiratory patients into seven different diagnoses (viral pneumonia, bacterial pneumonia, aspiration pneumonia, acute respiratory distress syndrome postoperative/trauma, acute respiratory distress syndrome not postoperative/trauma, acute respiratory failure nonacute respiratory distress syndrome, and "other"). Patients were classified by diagnoses similar to the ELSO registry with one modification. Patients with any International Classification of Diseases, 9th Revision code consistent with sepsis or septic shock were removed from the "other" category and placed into their own diagnostic category, because previous reports have identified sepsis to be associated with a relatively poor outcome on extracorporeal membrane oxygenation (17, 18).

For additional analytical purposes, we merged these eight diagnostic categories (Table 1) into the following three groups: 1) viral pneumonia; 2) sepsis; and 3) "all others," which includes bacterial pneumonia, aspiration pneumonia, acute respiratory distress syndrome, acute respiratory failure, and all other diagnoses. In keeping with the published literature, an initial exploration of the data indicated that the viral pneumonia group had a higher survival rate than the rest (15). Although a variety of pathologic processes are included in the "all others" group, previously published survival rates are similar for all the diagnoses with the exception of aspiration pneumonia in which there were only 45 patients (15).

Table 1. Patient diagnosis and survival

Diagnosis	Frequency	Survival
Overall survival rate	1352	63%
Viral pneumonia	351	71%
Bacterial pneumonia	218	62%
Aspiration pneumonia	45	73%
ARDS postoperative/trauma	39	64%
ARDS other	115	63%
Acute respiratory failure non ARDS	132	63%
Other	357	61%
Sepsis	95	41%

ARDS, acute respiratory distress syndrome.

For pre-ECLS ventilation duration, four categories were defined for analysis: 0–7 days, >7–10 days, >10–14 days, and >14 days. Categories were selected for analysis (rather than treating ventilation days as a "continuous" variable), because on initial exploration of the data, it was evident that the relationship between pre-ECLS ventilation time and the chance of survival was not linear. This categorization provides a useful aid for clinical interpretation of the data.

Statistical Analysis. Logistic regression was used to examine the relationship between duration of mechanical ventilation (four time categories) before the initiation of ECLS and survival to hospital discharge. Univariate analyses were undertaken in which each of the pre-ECLS factors considered (as listed in Table 2: pre-ECLS ventilation days, inotropes, surfactant, cardiac arrest, inhaled nitric oxide, gender, diagnosis [three categories], ventilation type, oxygenation index, pH, age, systolic blood pressure, and year of ECLS) was used on its own to predict survival to hospital discharge in separate models. These factors were selected *a priori*. In the subsequent adjusted multivariable model, factors identified as important ($p < .05$ in the unadjusted analyses) were simultaneously included as covariates to identify independent predictors of survival.

Fractional polynomials were used to test for any nonlinear relationships between covariates and log odds of survival (19). Except for ventilation duration, there was no evidence of marked nonlinearity; hence, untransformed variables were used.

Multiple imputation was used to handle missing covariate data in the multivariable model, assuming the data were missing at random (20). Five possible values were imputed for each missing value in the multivariable model. The goodness of fit of the logistic models was tested using the Hosmer-Lemeshow test. Results are presented as odds ratios

Table 2. Univariate analysis of factors related with survival to hospital discharge

Pre-ECLS Variable Considered	Odds Ratio	95% Confidence Interval	p
Pre-ECLS mechanical ventilation time[a]			
>7–10 days vs. 0–7 days	0.93	0.63–1.36	.69
>10–14 days vs. 0–7 days	0.88	0.56–1.37	.58
>14 days vs. 0–7 days	0.38	0.24–0.59	<.001
Inotrope infusion	0.70	0.54–0.90	<.01
Surfactant administration	1.03	0.67–1.59	.89
Inhaled nitric oxide use	0.89	0.71–1.11	.31
Pre-ECLS cardiac arrest	0.50	0.36–0.70	<.001
Gender (female vs. male)	1.06	0.85–1.33	.60
Age, yrs	0.99	0.97–1.01	.32
Type of ventilation (high-frequency ventilation vs. conventional)[b]	0.82	0.65–1.02	.07
Oxygenation index per 10 units[c]	0.95	0.91–0.98	<.01
pH per 0.1 units	1.17	1.09–1.25	<.001
Systolic blood pressure per 10 mmHg[d]	1.04	0.99–1.09	.09
Year of ECLS	0.98	0.95–1.02	.39
Diagnosis			
"Other" vs. sepsis	2.40	1.56–3.69	<.001
Viral pneumonia vs. sepsis	3.51	2.19–5.60	<.001

ECLS, extracorporeal life support.

[a]Data available for 1289 patients; [b]data available for 1211 patients; [c]data available for 975 patients; [d]data available for 1153 patients.

Table 3. Patient characteristics (n = 1352)

Overall survival rate	63%
Male/female	53%/47%
Median age, yrs (25–75% IQR)	1.4 (0.3–7.1)
Median weight, kg (25–75% IQR)	10.9 (4.5–26)
Pre-ECLS median oxygenation index (25–75% IQR)	45 (31–62)
Pre-ECLS ventilator days, median (25–75% IQR)	2.9 (1–6.7)
Median duration of ECLS, hrs (25–75% IQR)	201 (109–352)

ECLS, extracorporeal life support; IQR, interquartile range.

(ORs) for survival to hospital discharge with 95% confidence intervals and p values. A value of $p < .05$ was deemed significant. The statistics package Stata (College Station, TX) was used for all analyses.

RESULTS

From 1999 until 2008, a total of 2,360 pediatric respiratory patients were reported to the ELSO registry. Of these, only 1,352 patients met inclusion criteria and are the subject of this analysis. Patient demographics are shown in Table 3. The median age was 1.4 yrs with an overall survival rate of 63%. Males accounted for 53% of the patients. The pre-ECLS median OI was 45 and the median pre-ECLS ventilation duration was 2.9 days (ranges listed in Table 3). One of the largest groups (n = 351) was viral pneumonia with a survival rate of 71%. Sepsis had the lowest survival rate of 41% (n = 95). Patient diagnoses, frequency, and survival rates are listed in Table 1.

The most frequent pre-ECLS intervention was inotrope infusions, used by 73% of patients. Additional therapies included inhaled nitric oxide (48%), high-frequency ventilation (46%), and surfactant administration (7%). Twelve percent of children (n = 157) had a pre-ECLS cardiac arrest (Fig. 1).

Univariate analysis of factors related to survival is shown in Table 2. Pre-ECLS ventilation >14 days compared with ventilation <7 days (OR, 0.38; $p < .001$), inotrope use (OR, 0.70; $p < .01$), sepsis as a primary diagnosis compared with "other" diagnoses (viral OR, 3.51; "other" OR, 2.40; $p < .001$), higher OI (OR, 0.95; $p < .01$), lower pH (OR, 1.17; $p < .001$), and the presence of a pre-ECLS cardiac arrest (OR, 0.50; $p < .001$) were significantly related to a reduced chance of survival when each was considered in isolation. The continuous variables OI (per 10 units), pH (per 0.1 unit), age (per year), systolic blood pressure (per 10 mm Hg), and year of ECLS (per year) were each included as a simple continuous term in a univariate regression model so that for example in the case of OI, the odds of survival fell by 5% (0.05) for each 10-unit incremental increase in OI.

A multivariable logistic regression analysis identified the following pre-ECLS variables as independently and significantly related to the chance of survival: 1) >14 days of mechanical ventilation vs. 0–7 days was adverse (OR, 0.32; $p < .001$), 2) the presence of a cardiac arrest was adverse (OR, 0.56; $p = .001$); 3) pH per 0.1-unit increase was protective (OR, 1.15; $p < .001$); 4) OI per 10-unit increase was adverse (OR, 0.95; $p = .002$); and 5) any diagnosis other than sepsis was related to a more favorable outcome (viral OR, 3.14; others OR, 2.24; $p \leq .001$) (Table 4). Patients with >7–10 or >10–14 pre-ECLS ventilation days did not have a statistically significant decrease in survival rate as compared with patients who received 0–7 pre-ECLS ventilator days after adjustment for other factors. There was no statistically significant decrease in survival rate until >14 days of pre-ECLS ventilation was reached regardless of underlying diagnosis and other variables. The Hosmer-Lemeshow test indicated the overall fit of this model was good ($p = .2$).

Estimated probabilities, with 95% confidence intervals, were generated for the full multivariable model and results are presented graphically for each of the three diagnostic categories in Figure 2 based on whether the patient did or did not have a pre-ECLS cardiac arrest, because this was a significant factor in the multivariable model. Some numeric explanations of the plots are provided subsequently.

In Figure 2*A*, we show the estimated probability of survival for children without a pre-ECLS cardiac arrest based on diagnosis and the number of ventilation days before ECLS support.

- For sepsis patients, there were few cases pre-ECLS ventilated beyond 7 days (nine of 68); therefore, the estimates should be viewed with caution. No estimated probability is provided for sepsis cases >14 days because all four cases died. In sepsis patients with 0–7 days of pre-ECLS ventilation, the estimated probability of survival was 46% (n = 59) and at >7–10 days of ventilation, the survival dropped to 40% (n = 3).
- For patients with "other" respiratory diagnoses and without a pre-ECLS cardiac arrest, the estimated probability of survival at 0–7 days of preceding mechanical ventilation was 67% (n = 604). A similar patient with >7–10, >10–14, and >14 days of ventilation had survival

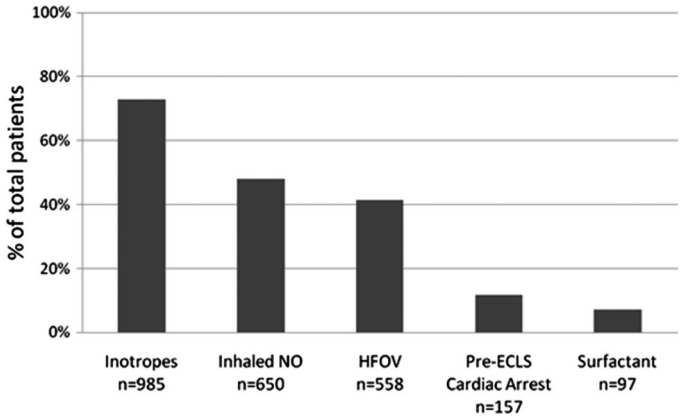

Figure 1. Pre-extracorporeal life support (*ECLS*) interventions. *NO*, nitric oxide; *HFOV*, high-frequency ventilation.

Table 4. Multivariable regression analysis identifying factors independently associated with survival to hospital discharge

Pre-ECLS Variable Considered	Odds Ratio	95% Confidence Interval	*p*
Pre-ECLS mechanical ventilation time			
>7–10 days vs. 0–7 days	0.78	0.51–1.19	.25
>10–14 days vs. 0–7 days	0.70	0.44–1.10	.12
>14 days vs. 0–7 days	0.32	0.20–0.51	<.001
Pre-ECLS cardiac arrest	0.56	0.40–0.80	.001
Oxygenation index per 10 units	0.95	0.92–0.98	.002
pH per 0.1 units	1.15	1.09–1.23	<.001
Diagnosis			
"Other" vs. sepsis	2.24	1.44–3.42	<.001
Viral pneumonia vs. sepsis	3.14	1.92–5.14	<.001

ECLS, extracorporeal life support.

rates of 61% (n = 59), 59% (n = 45), and 40% (n = 52), respectively.

- A child with the diagnosis of viral pneumonia and 0–7 days of ventilation had a survival rate of 76% (n = 199). Patients with viral pneumonia with >7–10 days of ventilation (n = 51) and >10–14 days of ventilation (n = 36) had survival rates of 71% and 68%, respectively. It was not until >14 days that the estimated probability of survival decreased to 50% (n = 20).

In Figure 2*B*, we show a similar graph with the estimated probability of survival based on diagnosis and days of pre-ECLS mechanical ventilation with the exception that all patients had a cardiac arrest before ECLS support.

DISCUSSION

This study evaluated the relationship between duration of preceding mechanical ventilation and outcome in children with respiratory failure requiring ECLS within the past 10 yrs. We found no significant decline in survival rate until the patient required >14 days of pre-ECLS ventilation regardless of the underlying diagnosis and other factors. In certain categories (viral pneumonia), even patients ventilated >14 days before ECLS had a survival rate of ≥50%. Despite the use of ELSO registry data, the results do reflect small numbers in some categories and this must be considered during interpretation.

Outcome in children with severe primary respiratory failure receiving ECLS was related to severity of illness as determined by higher OI and worse acidosis, the causation of respiratory failure (diagnosis), the presence of a pre-ECLS cardiac arrest, and the duration of pre-ECLS ventilation if this is prolonged >14 days. The number of pediatric patients annually receiving ECLS for respiratory failure has remained relatively constant over the past decade in the ELSO registry and case selection for this group is challenging; we consider that these new data useful for clinicians and will assist in the process of case selection for ECLS.

Patients who received >7–10 days of mechanical ventilation have traditionally not been considered ECLS candidates as a result of concern for irreversible lung damage. Despite these guidelines, the ELSO registry indicates that a proportion of patients were placed on ECLS after longer periods of pre-ECLS ventilation; however, information indicating the basis on which such patients were selected is unavailable. A study by Pranikoff et al (3) in 1997 retrospectively reviewed 36 adult patients with respiratory failure placed onto ECLS. They found survival rate was inversely associated with the number of pre-ECLS ventilation days with a 50% mortality predicted after 5 days of mechanical ventilation. Data published in the neonatal population at the same time failed to demonstrate the similar mortality rates. In 1996, a study by Lewis and colleagues (21) sought to characterize the outcome and respiratory morbidity for newborns placed on ECLS after >7 days of ventilation. They found an increased risk of mortality and bronchopulmonary dysplasia with increased time on the ventilator; however, at 14 days, the predicted probability of survival was 53%. The authors felt it was reasonable to consider application of ECLS to neonates who received up to 14 days of mechanical ventilation. Predictors of outcome from 124 children in the United Kingdom requiring respiratory ECLS indicated a significantly higher mortality for patients presenting with shock and increased OI (6). Significant pre-ECLS independent predictors of survival in adults include age, gender, pH, PaO_2/FIO_2 ratio, and days of mechanical ventilation (22).

The pediatric respiratory failure category of the ELSO registry is recognized to be diverse in terms of diagnoses in comparison to the cardiac and neonatal respiratory groups; this issue represents a challenge in terms of data analysis. The survival rate for children included in this study (63% to hospital discharge) exceeds that reported in previous evaluations of pediatric respiratory ECLS (23, 24). We suspect this is a reflection of our exclusion criteria, which removed certain high-risk patients. In an attempt to isolate children with primary respiratory failure, patients with other confounding disease (such as cardiac or immunocompromised conditions) were excluded, because we considered that inclusion of these diverse and complex patients would not assist us with the main study question. Unfortunately, this was approximately 40% of the patients; the largest single excluded group (n = 450) had pri-

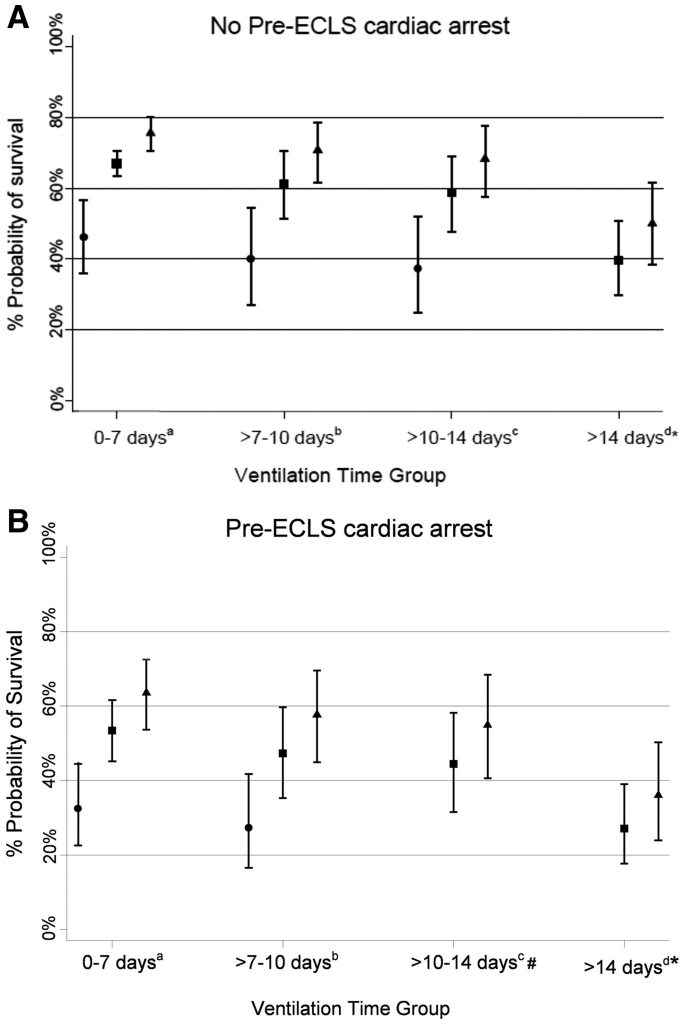

Figure 2. *A,* Estimated probability of survival time (mean ± 95% confidence interval) in patients without a pre-extracorporeal life support (*ECLS*) cardiac arrest based on diagnosis and days of pre-ECLS mechanical ventilation. Sepsis patients are represented in this graph by *circles*; "other" by *squares*; and viral pneumonia by *triangles*. Total patients included in each time group: 862,[a] 113,[b] 87,[c] 76.[d] *No sepsis survivors with >14 days pre-ECLS ventilation. *B,* Estimated probability of survival (mean ± 95% confidence interval) in patients who had a pre-ECLS cardiac arrest based on diagnosis and days of pre-ECLS mechanical ventilation. Sepsis patients are represented in this graph by circles; "other" by squares; and viral pneumonia by triangles. Total patients included in each time group: 125,[a] 14,[b] 4,[c] 8.[d] #No sepsis cases with 10–14 days pre-ECLS ventilation. *No sepsis survivors with >14 days pre-ECLS ventilation.

mary cardiac disease. The appearance in the ELSO registry of so many children with cardiac disease as recipients of respiratory ECLS was a surprise to us and illustrates the reason we elected to exclude these patients from our study. Individual diagnoses included cardiac failure/congestive heart failure (n = 96), cardiogenic shock (n = 40), cardiomyopathy (n = 28), tetralogy of Fallot (n = 52), ventricular septal defect (n = 48), pulmonary atresia (n = 39), and hypoplastic left heart syndrome (n = 35). This section of the database cannot distinguish between children with congenital heart defects that have been completely repaired vs. palliated nor does the database determine timing of congenital heart surgery in relation to ECLS, increasing the challenge of categorizing them for analysis.

Limitations. This was a retrospective database review with associated limitations inherent of databases. The ELSO registry is a voluntary database and there is no standardized quality measurement for the accuracy of data reported. The diagnostic data in the ELSO registry does not require verification (for example, a diagnosis of viral pneumonia is not necessarily culture-proven). Also, there may be other pre-ECLS hospital-acquired morbidities unaccounted for in the database, which may have been present in patients who received ECLS after prolonged mechanical ventilation.

In this study group, there were 155 children ventilated >10 days before ECLS. Selection bias may have occurred because current guidelines do not recommend ECLS after >7–10 days of mechanical ventilation; therefore, clinicians placing those children onto ECLS after prolonged ventilator support presumably had justification. We are unable to comment on ventilator settings and OI during the entire pre-ECLS mechanical ventilation course in these children. The database does not take into account cumulative mean airway pressure and fraction of inspired oxygen (oxygen index days), which may play an important role. The database only records the highest ventilatory requirements in the 6 hrs preceding extracorporeal membrane oxygenation cannulation. Regional variations of ventilator management pre-ECLS occur, but we intentionally included patients worldwide to account for this. In addition, there are no long-term outcome data for survivors including chronic lung disease or quality of life. Also, there are many patients considered for ECLS who ultimately never go on it. The database does not allow us to draw conclusions regarding the outcome of patients who did not require ECLS.

It is possible that evolving technical expertise with the ECLS circuit and its maintenance has contributed to overall improved survival rates over the past decade. This was not explored in the current study.

CONCLUSIONS

There is a clear relationship between the number of mechanical ventilation days before initiation of ECLS and survival in pediatric respiratory failure. However, deeming a child unsuitable for ECLS solely based on 7–10 days of preceding mechanical ventilation is not supported in this study population. Given the favorable outcome, we suggest children with up to 14 days of pre-ECLS ventilation are viable candidates for ECLS and there may be carefully selected patients who received >14 days of ventilation who could still be considered candidates for ECLS. It is possible that current strategies to attenuate ventilator-induced lung injury have improved survival rates for patients with prolonged pre-ECLS venti-

lation time. This new data may assist clinicians with the challenge of selecting suitable ECLS candidates.

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REFERENCES

1. Moler FW, Palmisano J, Custer JR, et al: Extracorporeal life support for pediatric respiratory failure: Predictors of survival from 220 patients. *Crit Care Med* 1993; 21: 1604–1611
2. Green TP, Moler FW, Goodman DM, et al: Probability of survival after prolonged extracorporeal membrane oxygenation in pediatric patients with acute respiratory failure. Extracorporeal Life Support Organization. *Crit Care Med* 1995; 23:1132–1139
3. Pranikoff T, Hirschl RB, Steimle CN, et al: Mortality is directly related to the duration of mechanical ventilation before the initiation of extracorporeal life support for severe respiratory failure. *Crit Care Med* 1997; 25: 28–32
4. ELSO Guidelines for Cardiopulmonary Extracorporeal Life Support. Version 1:1. Ann Arbor, MI, Extracorporeal Life Support Organization, Ann Arbor, April 2009. Available at: http://www.elso.med.umich.edu. Accessed February 1, 2009
5. Swaniker F, Kolla S, Moler F, et al: Extracorporeal life support outcome for 128 pediatric patients with respiratory failure. *J Pediatr Surg* 2000; 35:197–202
6. Brown KL, Walker G, Grant DJ, et al: Predicting outcome in ex-premature infants supported with extracorporeal membrane oxygenation for acute hypoxic respiratory failure. *Arch Dis Child Fetal Neonatal Ed* 2004; 89:F423–F427
7. Pathan N, Ridout DA, Smith E, et al: Predictors of outcome for children requiring respiratory extra-corporeal life support: Implications for inclusion and exclusion criteria. *Intensive Care Med* 2008; 34:2256–2263
8. Nehra D, Goldstein AM, Doody DP, et al: Extracorporeal membrane oxygenation for nonneonatal acute respiratory failure: The Massachusetts General Hospital experience from 1990 to 2008. *Arch Surg* 2009; 144:427–432
9. The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342:1301–1308
10. Halbertsma FJ, Vaneker M, Pickkers P, et al: Hypercapnic acidosis attenuates the pulmonary innate immune response in ventilated healthy mice. *Crit Care Med* 2008; 36: 2403–2406
11. Dobyns EL, Cornfield DN, Anas NG, et al: Multicenter randomized controlled trial of the effects of inhaled nitric oxide therapy on gas exchange in children with acute hypoxemic respiratory failure. *J Pediatr* 1999; 134: 406–412
12. Derdak S, Mehta S, Stewart TE, et al: High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: A randomized, controlled trial. *Am J Respir Crit Care Med* 2002; 166:801–808
13. Ferguson ND, Chiche JD, Kacmarek RM, et al: Combining high-frequency oscillatory ventilation and recruitment maneuvers in adults with early acute respiratory distress syndrome: The Treatment with Oscillation and an Open Lung Strategy (TOOLS) Trial pilot study. *Crit Care Med* 2005; 33:479–486
14. Willson DF, Thomas NJ, Markovitz BP, et al: Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: A randomized controlled trial. *JAMA* 2005; 293:470–476
15. Registry of the Extracorporeal Life Support Organization (ELSO). Ann Arbor, MI, ELSO, January 2009
16. Gupta M, Shanley TP, Moler FW: Extracorporeal life support for severe respiratory failure in children with immune compromised conditions. *Pediatr Crit Care Med* 2008; 9:830–835
17. Weber T, Kountzman B: Extracorporeal membrane oxygenation for nonneonatal pulmonary and multiple-organ failure. *J Pediatr Surg* 1998; 33:1605–1609
18. Luyt D, Pridgeon J, Brown J, et al: Extracorporeal life support for children with meningococcal septicaemia. *Acta Paediatr* 2004; 93:1608–1611
19. Royston P, Altman D: Regression using fractional polynomials of continuous covariates: Parsimonious parametric modeling. *Appl Stat* 1994; 43:429–467
20. Little R, Rubin D: Statistical Analysis With Missing Data. New York, J. Wiley & Sons, 1987
21. Lewis DA, Gauger P, Delosh TN, et al: The effect of pre-ECLS ventilation time on survival and respiratory morbidity in the neonatal population. *J Pediatr Surg* 1996; 31: 1110–1114
22. Hemmila MR, Rowe SA, Boules TN, et al: Extracorporeal life support for severe acute respiratory distress syndrome in adults. *Ann Surg* 2004; 240:595–605
23. Zahraa JN, Moler FW, Annich GM, et al: Venovenous versus venoarterial extracorporeal life support for pediatric respiratory failure: Are there differences in survival and acute complications? *Crit Care Med* 2000; 28:521–525
24. Moler FW, Custer JR, Bartlett RH, et al: Extracorporeal life support for pediatric respiratory failure. *Crit Care Med* 1992; 20: 1112–1118