

Extracorporeal Membrane Oxygenation Support for Pediatric Burn Patients: Is It Worth the Risk?*

Kelly B. Thompson, MD, USAF¹; Fakhry Dawoud, BS²; Shannon Castle, MD³;
John B. Pietsch, MD⁴; Melissa E. Danko, MD⁴; Brian C. Bridges, MD¹

Objectives: Examine the outcomes of pediatric burn patients requiring extracorporeal membrane oxygenation to determine whether extracorporeal membrane oxygenation should be considered in this special population.

Design: Retrospective cohort study.

Setting: All extracorporeal membrane oxygenation centers reporting to the Extracorporeal Life Support Organization.

Subjects: Pediatric patients (birth to younger than 18 yr) who were supported with extracorporeal membrane oxygenation with a burn diagnosis between 1990 and 2016.

Interventions: None.

Measurements and Main Results: A total of 113 patients were identified from the registry by inclusion criteria. Patients cannulated for respiratory failure had the highest survival (55.7%, $n = 97$) compared to those supported for cardiac failure (33.3%, $n = 6$) or extracorporeal cardiopulmonary resuscitation (30%, $n = 10$). Patients supported on venovenous extracorporeal membrane oxygenation for respiratory failure had the best overall survival at 62.2% ($n = 37$). Important for the burn population, rates of surgical site bleeding were similar to other surgical patients placed on extracorporeal membrane oxygenation at 22.1%. Cardiac arrest prior to cannulation was associated with increased hospital mortality (odds ratio, 3.41; 95% CI, 0.16–1.01; $p = 0.048$). Following cannulation, complications including the need for inotropes (odds ratio, 2.64; 95% CI, 1.24–5.65; $p = 0.011$), presence of gastrointestinal hemorrhage ($p = 0.049$), and hyperglycemia (glucose > 240 mg/dL) (odds ratio, 3.42; 95% CI, 1.13–10.38; $p = 0.024$) were associated with increased mortality. Of patients with documented burn percentage of total body surface area ($n = 19$), survival was 70% when less than 60% total body surface area was involved.

*See also p. 500.

¹Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN.

²Surgical Outcomes Center for Kids (SOCKs), Department of Pediatric Surgery, Monroe Carell Jr Children's Hospital, Nashville, TN.

³Department of Pediatric Surgery, Children's Hospital Los Angeles, Los Angeles, CA.

⁴Department of Pediatric Surgery, Vanderbilt University School of Medicine, Nashville, TN.

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Conclusions: Extracorporeal membrane oxygenation could be considered as an additional level of support for the pediatric burn population, especially in the setting of respiratory failure. Additional studies are necessary to determine the optimal timing of cannulation and other patient characteristics that may impact outcomes. (*Pediatr Crit Care Med* 2020; 21:469–476)

Key Words: burn; extracorporeal life support; Extracorporeal Life Support Organization; extracorporeal membrane oxygenation; pediatric; respiratory failure

Burn injuries are a leading cause of significant morbidity and mortality in the United States with over 1.5 million children younger than 9 years old suffering burn injuries from 2001 to 2010 and 5,842 dying secondary to their injuries (1). In a recent 35-year retrospective review of burn admissions to a major pediatric referral center, most children suffered scald (42%), flame (29%), and contact burns (10%) with 3.1% of those children requiring admission also suffering inhalation injury. Mortality had a bi-modal temporal distribution with 35.3% of deaths occurring within the first 24 hours of admission and being secondary to respiratory failure associated with inhalation injury or shock secondary to delayed or inadequate resuscitation. Deaths occurring between 2 and 15 days after injury were more likely to be secondary to sepsis or respiratory failure. Patients with inhalation injury were 13.6 times more likely to die and suspected nonaccidental injuries increased the chance of mortality by three-fold (2). Improvements in resuscitation, access to specialized pediatric burn care, and early excision and grafting of wounds have improved mortality in pediatric burn patients with an anticipated mortality of approximately 2.8% in the absence of significant inhalation injury, sepsis, or multiple organ dysfunction (3). However, inhalation injury and sepsis leading to acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome, and shock have continued to drive burn-related morbidity and mortality with 60% total body surface area (TBSA) involvement being a predictor of greater complications and mortality in pediatrics (4). Additionally, 30% TBSA has been shown to be a cut point for the initiation of significant pathophysiological responses to burn injury that signal

the start of an immunologic and inflammatory cascade increasing the risk for morbidity and mortality (4, 5).

Extracorporeal membrane oxygenation (ECMO) has demonstrated increased use in the pediatric population for both cardiovascular and respiratory support in recent years (6). Several case reports have suggested survival benefit with the utilization of ECMO in the pediatric burn population complicated by respiratory failure after maximizing other medical management options (7–9). However, studies examining survival benefit of pediatric burn patients with cardiopulmonary failure managed with ECMO are lacking and there are concerns regarding the safety of ECMO in burn surgical patients. Furthermore, patient numbers from prior analyses have been limited, making it difficult to determine applicability of ECMO to the pediatric burn patient. ECMO may provide time for organ function recovery to occur after inhalation injury or other organ dysfunction following burn injury, and therefore, improve survival in this critical patient population. To better understand the feasibility of ECMO utilization in the pediatric burn population, we used the Extracorporeal Life Support Organization (ELSO) (www.elseo.org) registry and examined survival and complication rates for pediatric burn patients who were supported with ECMO.

MATERIALS AND METHODS

Data Collection and Study Population

The ELSO Registry database (Ann Arbor, MI, July 2016) was retrospectively analyzed to identify mortality and complication rates for pediatric patients (birth to younger than 18 yr) who were supported on ECMO with burn-associated respiratory or cardiopulmonary failure between 1990 and 2016. *International Classification of Diseases*, 9th Revision (ICD-9) codes 940-949.5 were used to identify patients with an associated burn injury. The ELSO registry contains a growing database of clinical and demographic data that has been voluntarily submitted by more than 300 international centers since its inception in 1989. As of 2016, there was information on more than 20,000 pediatric cases requiring ECMO for various diagnoses that led to respiratory or cardiopulmonary failure (10, 11). Participating centers and the data provided to the ELSO registry are de-identified to protect patient privacy. Approval was obtained from the Vanderbilt University Review Board prior to study initiation.

Data analyzed included demographic information, pre-ECMO oxygenation indices (OIs) and Pao_2/FiO_2 ratios calculated from pre-ECMO ventilator and blood gas data, mode and duration of ECMO support, support indication for ECMO (pulmonary, cardiovascular, or extracorporeal cardiopulmonary resuscitation [ECPR]), ECMO complications (patient and mechanical), and survival to hospital discharge as well as pre-ECMO support including ventilator type (conventional, oscillator, or other high frequency ventilation) and need for inotropes prior to cannulation. ECMO complications were based on defined ELSO Registry fields with mechanical complications being defined as complications pertaining to the

ECMO circuit that required intervention, such as a change of circuit components (i.e., oxygenator failure resulting in oxygenator exchange). Patient complications were defined as physiologic complications requiring intervention, such as hemorrhage requiring packed RBC (PRBC) or whole blood transfusion (> 20 mL/kg/calendar day of PRBCs or > 3 units PRBCs/calendar day in neonates and pediatrics) or other intervention such as surgical or endoscopic intervention (12). The main outcome of interest was survival to hospital discharge. ICD-9 codes were reviewed to determine the extent of burn injury as %TBSA when available. Venovenous ECMO was defined as utilization of only venous cannulas during the ECMO run, including double-lumen venous cannulas. Venoarterial ECMO was defined as utilization of a venous and arterial cannula. Venovenous ECMO that was converted to venoarterial ECMO and venoarterial ECMO that was converted to venovenous ECMO were also included in the venoarterial ECMO cohort. Timing or reason for conversion were not included in the ELSO registry. Pre-ECMO OI, Pao_2/FiO_2 ratio, and complication rates were compared among survivors and nonsurvivors for both venovenous and venoarterial groups.

Statistical Analysis

Primary outcome variables were survival and nonsurvival to hospital discharge. Demographic and clinical data, along with pre-ECMO variables and ECMO complications, were analyzed for predictive mortality. Nonparametric continuous variables were analyzed using Mann-Whitney *U* test, while dichotomous and categorical variables were analyzed using chi-square or Fisher exact test depending on indication based on expected cell sizes. Significant variable predictors of mortality were then used to conduct a multivariate binary logistic regression model. Statistical significance was set a priori at *p* value of less than 0.05. All statistical analysis was conducted using IBM SPSS 23.0 statistical software (SPSS, Armonk, NY).

RESULTS

A search of the ELSO database from 1990 to 2016 revealed a total of 113 patients meeting inclusion criteria for the study. Demographics were consistent with other published data regarding pediatric burns in that there were more males ($n = 66$) compared with females ($n = 46$), with a male to female ratio of 1.4:1. The majority of patients were under the age of 5 years with a median age of 2.29 years (interquartile range, 1.04–4.60 yr) (Table 1) (2, 13). There were only 11 children older than or equal to 12 years old and 26 children younger than or equal to 12 months old. Three patients were younger than 30 days old with the youngest being 2 days old and suffering 2nd degree burns to the lower extremities. The median weight was 13 kg with no significant difference between survivors and nonsurvivors (Table 1). There were 54 deaths and 59 survivors for an overall survival to discharge of 52%. Of deaths, 13 patients were decannulated after achieving lung recovery but died of other causes not related to lung injury. Other reasons for decannulation among nonsurvivors were family request ($n = 8$, including two with brain death), diagnosis incompatible with life

TABLE 1. Demographic and Clinical Data by Hospital Discharge Status

Variable	Total (<i>n</i> = 113)	Survivors (<i>n</i> = 59)	Nonsurvivors (<i>n</i> = 54)	<i>p</i>
Age, yr	2.29 (1.04–4.60)	2.24 (1.22–4.35)	2.56 (0.93–4.71)	0.765 ^a
Sex, male, <i>n</i> (%)	66 (58.4)	34 (57.6)	32 (59.3)	0.945 (OR, 0.974; CI, 0.46–2.07)
Weight, kg	13.0 (10.0–20.0)	13.0 (10.0–19.8)	14.0 (10.0–20.0)	0.932 ^a
> 200 hr on ECLS, <i>n</i> (%)	52 (46.0)	26 (44.1)	26 (48.1)	0.664 (OR, 1.18; CI, 0.56–2.47)
Hours on ECLS	177.0 (93.5–336.5)	169.0 (105.0–310.0)	192.5 (51.25–369.3)	0.963 ^a
PH	7.24 (7.14–7.33)	7.25 (7.15–7.35)	7.22 (7.11–7.32)	0.206 ^a
Paco ₂	62.0 (45.2–79.0)	63.9 (45.5–78.95)	61.0 (45.2–80.0)	0.982 ^a
Pao ₂	53.0 (43.0–68.0)	53.5 (44.3–69.5)	53.0 (40.0–67.0)	0.389 ^a
Serum bicarbonate level	24.0 (20.0–30.5)	25.0 (20.3–31.5)	22.9 (16.85–29.6)	0.100 ^a
Arterial oxygen saturation	85.0 (74.0–91.6)	86.5 (77.3–93.8)	84.0 (68.5–90.3)	0.241 ^a
Pre-ECLS Fio ₂	100 (100–100)	100 (100–100)	100 (100–100)	0.701 ^a
Pao ₂ /Fio ₂ ratio	54 (43–71)	53.0 (43.75–81.0)	54.0 (41.0–69.7)	0.511 ^a
Oxygenation index	45.24 (28.6–67.7)	45.5 (28.3–67.8)	45.2 (32.6–71.4)	0.724 ^a
Pre-ECLS arrest, <i>n</i> (%)	24 (21.2)	7 (11.9)	17 (31.5)	0.011 (OR, 3.41; CI, 1.29–9.06)
Pre-ECLS inotropes, <i>n</i> (%)	75 (66.4)	36 (61)	39 (72.2)	0.208 (OR, 1.66; CI, 0.75–3.67)
Pre-ECLS milrinone, <i>n</i> (%)	3 (2.7)	2 (3.4)	1 (1.9)	1.000 (OR, 0.54; CI, 0.05–6.11)
Pre-ECLS nitric oxide, <i>n</i> (%)	26 (23)	18 (30.5)	8 (14.8)	0.048 (OR, 0.40; CI, 0.16–1.007)
Pre-ECLS narcotic, <i>n</i> (%)	70 (61.9)	38 (64.4)	32 (59.3)	0.573 (OR, 0.80; CI, 0.38–1.72)
Pre-ECLS bicarb, <i>n</i> (%)	20 (17.7)	9 (15.3)	11 (20.4)	0.477 (OR, 1.42; CI, 0.54–3.75)
Pre-ECLS surfactant, <i>n</i> (%)	1 (0.9)	1 (1.7)	0	1.000
Pre-ECLS high-frequency oscillatory ventilation, <i>n</i> (%)	30 (26.5)	15 (25.4)	15 (27.8)	0.777 (OR, 1.13; CI, 0.49–2.60)
Pre-ECLS neuromuscular blockade, <i>n</i> (%)	57 (50.4)	31 (52.5)	26 (48.1)	0.641 (OR, 0.84; CI, 0.40–1.76)
Pre-ECLS inhalation injury, <i>n</i> (%)	19 (16.8)	10 (18.5)	9 (15.3)	0.643 (OR, 1.26; CI, 0.47–3.39)
Pre-ECLS acute renal failure, <i>n</i> (%)	14 (12.4)	9 (16.7)	5 (8.5)	0.187 (OR, 2.16; CI, 0.68–6.91)
Pre-ECLS sepsis, <i>n</i> (%)	33 (29.2)	15 (27.8)	18 (30.5)	0.750 (OR, 0.88; CI, 0.39–1.98)
% Venoarterial ECLS, <i>n</i> (%)	73 (64.6)	35 (59.3)	38 (70.4)	0.158 (OR, 1.78; CI, 0.80–4.00)
% Venovenous ECLS, <i>n</i> (%)	37 (32.7)	23 (39.0)	14 (25.9)	

ECLS = extracorporeal life support, OR = odds ratio.

^aMann-Whitney *U* *p* value and median with interquartile range reported for nonparametric continuous variables. All other *p* values reported for χ^2 or Fisher exact test analysis with OR and 95% CI.

(*n* = 9, including four with brain death), organ failure (*n* = 23, including four with brain death), and reason not specified (*n* = 1). Seventy-three patients were supported with venoarterial ECMO, while 37 were supported with venovenous ECMO with a survival to discharge of 47.9% (*n* = 35) and 62.2% (*n* = 23), respectively. There was no statistical difference between these groups. Survivors and nonsurvivors were similar in median age (*p* = 0.77), median weight (*p* = 0.93), median hours on ECMO (*p* = 0.96), pre-ECMO OI (*p* = 0.72), and

Pao₂/Fio₂ ratio (*p* = 0.51) (Table 1). Furthermore, ECMO duration of greater than 200 hours, which has been shown in a prior study to be associated with increased mortality in respiratory failure associated with burns and smoke inhalation (14), was not associated with increased mortality (OR, 1.18; 95% CI, 0.56–2.47; *p* = 0.66) (Table 1).

Patients requiring ECMO support for respiratory failure had a higher overall survival (55.7%, *n* = 97) compared to those requiring ECMO for cardiac failure (33.3%, *n* = 6) or

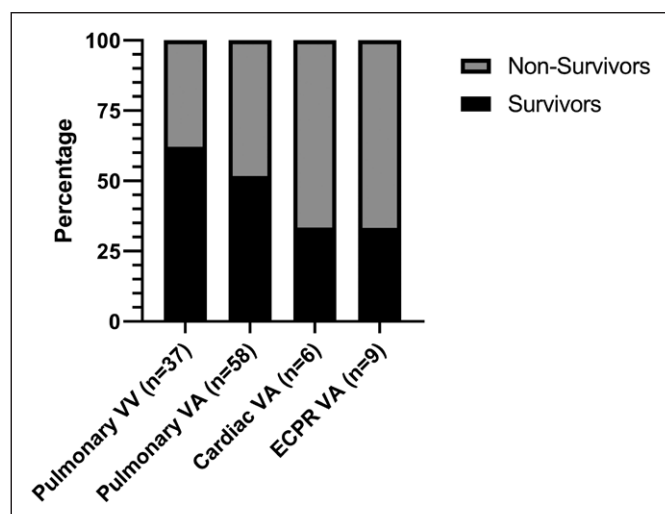


Figure 1. Survival by support indication. ECPR = extracorporeal cardiopulmonary resuscitation, VA = venoarterial, VV = venovenous.

ECPR (30%, $n = 10$). Patients who were supported on venovenous ECMO for respiratory failure had the best overall survival at 62.2% ($n = 23$) and those cannulated to venoarterial ECMO for respiratory failure had a survival of 51.7% ($n = 30$) (Fig. 1). Notably, there were 19 patients (16.8%) carrying an ICD-9 code indicative of inhalation injury; however, the mechanism of injury and the method by which inhalation injury was diagnosed were not available in the registry. All 19 were cannulated for respiratory support. Ten of these patients died indicating a mortality in this subgroup of 52.6%; however, inhalation injury was not associated with mortality (OR, 1.26; 95% CI, 0.47–3.39; $p = 0.64$).

One-hundred patients suffered mechanical or patient-related complications. There were 293 complications in the venoarterial group ($n = 73$, 55 mechanical, 238 patient) versus 144 in the venovenous group ($n = 37$, 33 mechanical, 111 patient). Overall per patient complication rates between venoarterial and venovenous groups were similar (4.01 vs 3.89; $p = 0.101$). Rates of surgical site bleeding, defined as bleeding from a surgical site other than ECMO cannulation sites (12), for venovenous ECMO and venoarterial ECMO were similar 13.5% ($n = 5$) and 24.7% ($n = 18$), respectively (OR, 2.095; 95% CI, 0.71–6.18; $p = 0.17$). Surgical site bleeding was not associated with mortality (OR, 1.53; 95% CI, 0.63–3.74; $p = 0.35$). The need for renal replacement therapy (RRT) defined as receiving either hemofiltration, dialysis or continuous arteriovenous hemodialysis, during ECMO support was not associated with increased mortality, as 37.3% of nonsurvivors required RRT versus 53.7% of survivors with an OR of 1.95 (95% CI, 0.92–4.14; $p = 0.08$). Additionally, culture-proven infection during the ECMO course or a diagnosis of sepsis were not associated with increased mortality with odds ratios (ORs) of 2.06 (95% CI, 0.84–5.06; $p = 0.11$) and 0.876 (95% CI, 0.388–1.98; $p = 0.75$), respectively.

Several factors were found to be significantly associated with mortality. Cardiac arrest prior to cannulation was associated with increased mortality with an OR of 3.41 (95% CI,

1.29–9.06; $p = 0.011$). There was a trend for the use of nitric oxide prior to cannulation to be associated with a decrease in mortality with an OR of 0.40 (95% CI, 0.16–1.01; $p = 0.048$) (Table 1). Following cannulation, complications including the need for inotropes (OR, 2.64; 95% CI, 1.24–5.65; $p = 0.011$), presence of gastrointestinal hemorrhage ($p = 0.049$), and hyperglycemia (glucose > 240 mg/dL) (OR, 3.42; 95% CI, 1.13–10.38; $p = 0.024$) were associated with increased mortality (Table 2).

A multivariate logistic regression model utilizing factors with statistical significance from chi-square or Fisher exact test analysis was performed to identify predictive factors that may be associated with survival. Only a history of pre-extracorporeal life support (ECLS) arrest was found to be significantly associated with survival showing a decreased association (OR, 0.30; 95% CI, 0.10–0.89; $p = 0.03$). Pre-ECLS nitric oxide use, need for inotropes on ECMO, gastrointestinal hemorrhage on ECMO, and hyperglycemia (glucose > 240 mg/dL) were all included in the model and did not reach statistical significance (Table 3).

Documentation of TBSA involved was only noted in 19 patients. Of this small cohort, overall survival was 70% when less than 60% TBSA was involved with improved survival rates associated with lower %TBSA involvement (Fig. 2).

DISCUSSION

ECMO has had increasing utilization in pediatrics since the successful use by Bartlett et al (15) in 1975 for neonatal respiratory failure (6). In recent years, there have been several studies looking at the feasibility of ECMO for respiratory failure in the setting of burn injury in the pediatric population and despite these studies, questions remain regarding its utilization in this special population (7–9, 16–19). Given the mortality associated with significant burns in the pediatric population, there may be a subset for which ECMO would be a life-saving modality. This is the first study to investigate the use of ECMO in pediatric patients that have suffered burn injury that not only examines outcomes with respiratory failure but also attempts to examine outcomes with cardiopulmonary failure. As the ELSO Registry has accrued more patient numbers since the last analysis completed by Askegard-Giesmann et al (8) in 2010, this study intends to clarify several questions regarding the use of ECMO in the pediatric burn population, namely, whether or not ECMO is beneficial in the pediatric burn population and are there factors that may determine which patients are appropriate to support with ECMO.

Mortality for respiratory failure was shown to be similar in this study (55.7%, $n = 97$) when compared to that reported for all pediatric respiratory indications (58%) (6). However, survival was lower for cardiac support (33%, $n = 6$) and ECPR (30%, $n = 10$) than that reported for all pediatric patients requiring ECMO for cardiac support or ECPR (51% and 41%, respectively) (6). Of those undergoing ECPR and not surviving (70% of ECPR patients), four had findings consistent with brain death and two suffered CNS hemorrhage or infarct by ultrasound or head CT which have been shown to be associated

TABLE 2. Complications by Hospital Discharge Status

Complication	Total, n = 113, n (%)	Survivors, n = 59, n (%)	Nonsurvivors, n = 54, n (%)	p
Cardiac arrhythmia	10 (8.8)	3 (5.1)	7 (13)	0.190 (OR, 2.78; CI, 0.68–11.35)
Cardiopulmonary resuscitation on ECLS	5 (4.4)	1 (1.7)	4 (7.4)	0.191 (OR, 4.64; CI, 0.50–42.88)
Inotropes on ECLS	55 (48.7)	22 (37.3)	33 (61.1)	0.011 (OR, 2.64; CI, 1.24–5.65)
Hypertension requiring vasodilators	16 (14.2)	8 (13.6)	8 (14.8)	0.848 (OR, 1.11; CI, 0.39–3.19)
Pneumothorax requiring treatment	11 (9.7)	4 (6.8)	7 (13)	0.268 (OR, 2.05; CI, 0.56–7.43)
Surgical site bleeding	25 (22.1)	11 (18.6)	14 (25.9)	0.352 (OR, 1.53; CI, 0.63–3.74)
Cannulation bleeding	16 (14.2)	8 (13.6)	8 (14.8)	0.848 (OR, 1.11; CI, 0.39–3.19)
Gastrointestinal hemorrhage	4 (3.5)	0	4 (7.4)	0.049
Infection, culture positive	26 (23)	10 (16.9)	16 (29.6)	0.110 (OR, 2.06; CI, 0.84–5.06)
Renal replacement therapy	51 (45.1)	22 (37.3)	29 (53.7)	0.080 (OR, 1.95; CI, 0.92–4.14)
CNS hemorrhage	7 (6.2)	3 (5.1)	4 (7.4)	0.708 (OR, 1.49; CI, 0.32–7.00)
Glucose < 40 on ECLS	3 (2.7)	1 (1.7)	2 (3.7)	0.605 (OR, 2.23; CI, 0.20–25.33)
Glucose > 240 on ECLS	18 (15.9)	5 (8.5)	13 (24.1)	0.024 (OR, 3.42; CI, 1.13–10.38)
pH < 7.2 on ECLS	12 (10.6)	5 (8.5)	7 (13)	0.439 (OR, 1.61; CI, 0.48–5.41)
pH > 7.6 on ECLS	2 (1.8)	2 (3.4)	0	0.497
Mechanical, clot related	26 (23)	13 (22)	13 (24.1)	0.797 (OR, 1.12; CI, 0.47–2.70)
Mechanical, non-clot related	35 (31)	19 (32.2)	16 (29.6)	0.768 (OR, 0.89; CI, 0.40–1.97)

ECLS = extracorporeal life support, OR = odds ratio.

with a mortality of 79% (11). Additionally, pre-ECLS arrest was found to have a significant association with brain death with an OR of 21.75 (95% CI, 4.23–111.97; $p < 0.001$) as 80% of patients with a diagnosis of brain death suffered at least one pre-ECLS arrest. However, only a small number of burn patients were cannulated for cardiac failure or ECPR, so it is difficult to make clinically applicable inferences in these groups.

Venoarterial ECMO was used almost twice as often as venovenous ECMO despite most patients being cannulated for respiratory support (86%). Whether type of cannulation was dictated by surgeon or institutional preference, patient physiology at the time of cannulation, or a combination of these and other factors cannot be discerned from the ELSO Registry. Regardless,

TABLE 3. Binary Log Regression of Predictive Variables of Survival

Variable	p	OR (95% CI)
Pre-ECLS arrest	0.03	0.30 (0.10–0.89)
Pre-ECLS nitric oxide	0.09	2.42 (0.87–6.74)
Inotropes on ECLS	0.17	0.56 (0.24–1.29)
Gastrointestinal hemorrhage	0.99	
Glucose > 240 on ECLS	0.17	0.43 (0.13–1.43)

ECLS = extracorporeal life support, OR = odds ratio. Nagelkerke $r^2 = 0.636$.

there was no statistical difference in mortality between these two groups. Patients cannulated with venovenous ECMO for respiratory support had a higher survival at 62.2% compared to those cannulated to venoarterial ECMO for respiratory support (51.7%) which may indicate that those cannulated to venoarterial ECMO for respiratory failure had other physiologic findings worrisome for the potential need for cardiac support placing them at a higher mortality risk at the initiation of ECMO. Prior studies have shown that there is a trend for venoarterial ECMO to have lower survival than venovenous ECMO when used for

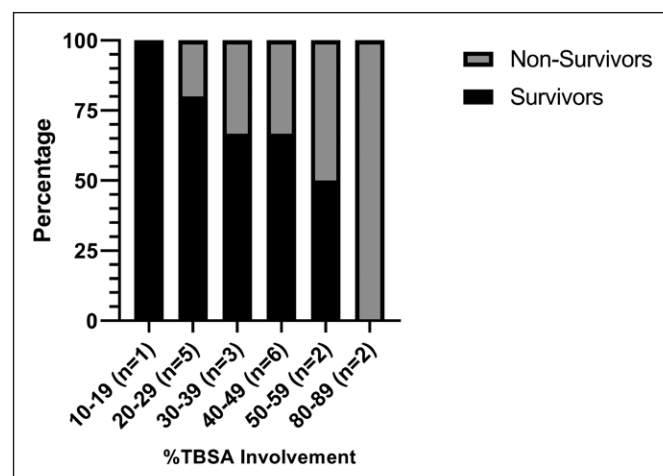


Figure 2. Survival by burn involvement. TBSA = total body surface area.

respiratory support and our study further supports this finding (20, 21). Furthermore, the cause of respiratory failure is not elucidated by the registry data. OI can be affected by chest wall trauma or burn injury, inhalation injury, fluid resuscitation, sepsis, and many other factors. It is likely that fluid overload played a significant part in the development of respiratory failure as only a small number ($n = 19$) had inhalation injury, trauma ($n = 2$), or sepsis/infection ($n = 33$), which are known causes for ARDS. For these patients, continuous RRT could be deployed concurrently with ECMO to allow for lung recovery as well as judicious fluid removal in the setting of respiratory failure.

There were no statistically significant differences in the overall complication rates between venoarterial and venovenous ECMO. The most common mechanical complication was clot development within the circuit necessitating a replacement of a circuit component or the circuit itself. The most common patient complication was the requirement of inotropes for blood pressure support while on ECMO. Surgical site bleeding occurred at a higher rate (21%) than that reported by ELSO for other patients supported for respiratory failure (10%) (11). However, surgical site bleeding in the burn population was less than that reported for pediatric medical patients on ECMO for cardiac support (32%) and pediatric cardiac patients following cardiac surgery (45%) as reported in a recent study by Werho et al (22) and further supported by data reported by Dalton et al (23). This finding supports a bleeding risk that is less than that of pediatric patients supported on ECMO for cardiac support or following cardiac surgery. The risk of bleeding may be decreased by utilizing lower anticoagulation goals if the patient's burns have not been excised and grafted at the time of cannulation (9). Once excision and grafting have been completed, the risk of bleeding is decreased and anticoagulation goals can be raised to normal institutional goals at that time (24).

Following cannulation, hyperglycemia (glucose > 240 mg/dL), gastrointestinal hemorrhage, and inotrope requirement were all found to be significantly associated with mortality. Inotrope requirement was found to be associated with increased mortality in a recent adult study investigating the use of ECMO in the adult burn population (25), and our study further supports this finding. Interestingly, the diagnoses of sepsis or culture proven infection, which might increase the need for inotropes, were not associated with mortality. Multiple studies have demonstrated that hyperglycemia in critical illness is also associated with increased mortality which is also supported by our analysis (26). The burn population is certainly at risk for hyperglycemia of critical illness and a study by Gore et al (27) in 2010 demonstrated the deleterious effects of hyperglycemia in the pediatric burn population including increased risk for fungemia, poor wound healing, and mortality. Finally, it is not surprising that gastrointestinal hemorrhage is associated with increased mortality, as this finding has been well documented in the literature with data supporting significant mortality in the burn population when gastrointestinal hemorrhage occurs in the setting of burn shock or sepsis or significant multiple organ dysfunction (28).

Noteworthy factors that were not associated with mortality include severity of lung injury as indicated by Pao_2/FiO_2 ratio

or OI, need for oscillatory ventilation, presence of inhalation injury, sepsis, need for RRT, or ICD-9 diagnosis of acute renal failure. Interestingly, the use of nitric oxide prior to cannulation showed a trend toward decreased mortality. Various studies have demonstrated improved Pao_2/FiO_2 ratios with the use of nitric oxide in ARDS in burns; however, none have demonstrated mortality benefit from its use (29, 30) and patients in our study still ultimately required cannulation onto ECMO.

Of the 113 patients identified in the ELSO Registry with a burn injury, only 19 had ICD-9 codes linked to %TBSA (Fig. 2); however, the timing and method by which %TBSA was calculated was not provided by the ELSO registry. Two patients had greater than 80% TBSA burn involvement and had a mortality of 100%. Survival was 73% with less than 50% TBSA involvement and 70% with less than 60% TBSA involvement. These findings are consistent with the mortality cut point of 60% for pediatric burn patients highlighted by Jeschke et al (4) in a prior study from 2015. Given the limited number of patients with documented %TBSA, it is difficult to make clinical judgments regarding %TBSA, but perhaps 60% TBSA involvement could be considered a clinical cut point for initiation of ECMO support for pediatric burn patients. Certainly, 80% TBSA has a high likelihood of mortality, and ECMO is unlikely to be of benefit to these patients. However, other diagnostic, social, and clinical data should take priority when deciding to use ECMO in the pediatric burn population as %TBSA, especially early in the course of injury, is typically unreliable (31).

Although this study is the first pediatric study to include sufficient numbers for ECMO use for respiratory failure in the setting of burn injury, there are several weaknesses to this study. First, the number of patients supported for cardiac support or ECPR was low and not adequate to draw applicable conclusions for these two patient populations regarding utility or prognostication. Additionally, a large proportion of patients supported for ECPR suffered severe neurologic injury further skewing the analysis toward mortality for this subgroup. Continued data collection and increased ECMO utilization will likely lead to increased numbers of patients falling into these two categories. However, it will likely remain difficult to draw helpful conclusions for years to come. Second, determining the optimal timing of ECMO cannulation as it relates to initial excision and grafting is unable to be determined by this study due to lack of data in the ELSO registry as timing of cannulation from injury and initiation of resuscitation or surgical interventions were not included in the data. Furthermore, whether trauma or assault were associated with mortality is difficult to assess with this study as only two patients were identified by ICD-9 codes as having suffered traumatic injury. This information is, again, limited by the data submitted by individual ELSO centers as it is likely that more than two patients had associated trauma or assault. Additionally, we are unable to identify if ECMO utilization impacts the bi-modal distribution of deaths secondary to burns as timing of ECMO cannulation in relation to initial injury was not recorded by the ELSO database. However, a

study by Williams et al (3) from 2009 continued to demonstrate a bi-modal distribution of mortality for burn patients despite advances in burn management when ECMO is not used with those dying within the first 48 hours succumbing to shock and brain death and those dying later succumbing to sepsis from multi-drug resistant organisms and respiratory failure. Of our cohort, most patients who died were supported with ECMO for more than 48 hours (73.7% of venoarterial and 85.7% of venovenous), so there may be an effect on late deaths that we are unable to capture due to the lack of timing of cannulation information. More thorough data analysis may be possible in the future as the ELSO registry has undergone recent changes in its data collection practices. Since September 2016, the ELSO database has expanded to request additional information from participating centers regarding timing of ECMO cannulation, timing of complications, and severity of illness and organ dysfunction scores at admission. Additionally, the database will include more robust diagnostic codes due to the utilization of *International Classification of Diseases*, 10th Revision codes and will improve on its data collection with multiple logical checks and prompts (11). These changes should provide more data to further clarify pre-cannulation factors that may predict mortality such as %TBSA at admission. Third, this is a retrospective analysis of registry data which is subject to reporting and selection bias with burn specific data missing from the registry and is inherently reliant on accurate and complete data reporting. Errors and omissions in reporting must be assumed to be accurate for the purposes of analysis and may skew results. Clinical information regarding patient status at the time of cannulation or withdraw of support is limited to the data provided by the registry and makes it difficult to draw conclusions regarding ECMO utilization in burn patients with the same veracity that a prospective study would be able to achieve. Fourth, we used a broad age range for the study inclusion (birth to 18 yr) in order to capture an adequate number of patients for analysis. Given the obvious differences between infants and adolescents, it might have been difficult to draw specific conclusions about ECMO while utilizing such a wide-ranging population. However, based on the data provided, the median age was approximately 2.29 years old (Table 1) with no significant difference noted between survivors and nonsurvivors. Furthermore, only a limited number of patients were identified as being younger than 12 months old or older than 12 years old. More specifically, there were only 11 children older than or equal to 12 years old and 26 children younger than or equal to 12 months old. Based on this, the authors feel we are able to draw reasonable conclusions regarding the study. Finally, we included data over an extensive time period (1990–2016) in order to have sufficient patient numbers to be able to draw reasonable conclusions about the utility of ECMO. Given the broad time period of study, it becomes increasingly difficult to isolate individual

factors that may impact outcomes as there have been significant advances in ECMO technology and management that may also impact survival. In a summary report by Thiagarajan et al (6) encompassing data from 1989 to 2016, survival rates for pediatric patients supported with ECMO for various respiratory and cardiac indications improved from 1989 to 2009 likely secondary to increased center experience and improvements in technology such as more efficient centrifugal pumps, bio-compatible surface coatings, avoidance of silicone oxygenators, and use of dual lumen cannulas. However, in a summary report from ELSO by Barbaro et al (11) examining the registry data from 2009 to 2016, pediatric ECMO survival rates by support type remained relatively unchanged. Regarding our data from burn patients, from 1990 to 2016, there was no significant change for overall mortality with most years having a mortality of approximately 50%. Furthermore, data regarding the specifics of the circuit components used for each ECMO run were not available for review.

CONCLUSIONS

Our analysis indicates that ECMO should be considered for support in the pediatric burn population when maximal medical therapy has been provided without improvement in clinical status. Concerns over increased bleeding risk from burn sites, although valid, hopefully are lessened with this analysis as surgical site bleeding was not associated with increased mortality and was better than that experienced by other surgical patients supported by ECMO. This is likely partially due to early and aggressive wound excision and grafting becoming the standard of burn care. Overall survival for pediatric burn patients requiring ECMO support for respiratory failure is comparable to other pediatric ECMO patients with those supported by venovenous ECMO having the highest survivability. As such, ECMO could be considered as an additional level of support for the pediatric burn population, especially in the setting of respiratory failure when burns are limited to less than 60% TBSA. Additional studies are necessary to determine the optimal timing of ECMO support and other patient characteristics that may impact outcomes.

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For information regarding this article, E-mail: kelly.b.thompson6.mil@mail.mil

REFERENCES

1. Palmieri TL: Pediatric burn resuscitation. *Crit Care Clin* 2016; 32:547–559

2. Saeman MR, Hodgman EI, Burriss A, et al: Epidemiology and outcomes of pediatric burns over 35 years at Parkland Hospital. *Burns* 2016; 42:202–208
3. Williams FN, Herndon DN, Hawkins HK, et al: The leading causes of death after burn injury in a single pediatric burn center. *Crit Care* 2009; 13:R183
4. Jeschke MG, Pinto R, Kraft R, et al: Inflammation and the Host Response to Injury Collaborative Research Program: Morbidity and survival probability in burn patients in modern burn care. *Crit Care Med* 2015; 43:808–815
5. Jeschke MG, Herndon DN: Burns in children: Standard and new treatments. *Lancet* 2014; 383:1168–1178
6. Thiagarajan RR, Barbaro RP, Rycus PT, et al; ELSO member centers: Extracorporeal Life Support Organization Registry International Report 2016. *ASAIO J* 2017; 63:60–67
7. Pierre EJ, Zwischenberger JB, Angel C, et al: Extracorporeal membrane oxygenation in the treatment of respiratory failure in pediatric patients with burns. *J Burn Care Rehabil* 1998; 19:131–134
8. Askegard-Giesmann JR, Besner GE, Fabia R, et al: Extracorporeal membrane oxygenation as a lifesaving modality in the treatment of pediatric patients with burns and respiratory failure. *J Pediatr Surg* 2010; 45:1330–1335
9. Goretsky MJ, Greenhalgh DG, Warden GD, et al: The use of extracorporeal life support in pediatric burn patients with respiratory failure. *J Pediatr Surg* 1995; 30:620–623
10. Watson JA, Englum BR, Kim J, et al: Extracorporeal life support use in pediatric trauma: A review of the National Trauma Data Bank. *J Pediatr Surg* 2017; 52:136–139
11. Barbaro RP, Paden ML, Guner YS, et al: Pediatric Extracorporeal Life Support Organization Registry International Report 2016. *ASAIO J* 2017; 63:456–463
12. Rycus P: Extracorporeal Life Support Organization: ELSO database definitions. 2018. Available at: <https://www.else.org/Portals/0/Files/PDF/ELSO%20Database%20Definitions%202018-2-1.pdf>. Accessed July 1, 2018
13. Krishnamoorthy V, Ramaiah R, Bhananker SM: Pediatric burn injuries. *Int J Crit Illn Inj Sci* 2012; 2:128–134
14. Asmussen S, Maybauer DM, Fraser JF, et al: Extracorporeal membrane oxygenation in burn and smoke inhalation injury. *Burns* 2013; 39:429–435
15. Bartlett RH, Gazzaniga AB, Toomasian J, et al: Extracorporeal membrane oxygenation (ECMO) in neonatal respiratory failure. 100 cases. *Ann Surg* 1986; 204:236–245
16. Kane TD, Greenhalgh DG, Warden GD, et al: Pediatric burn patients with respiratory failure: Predictors of outcome with the use of extracorporeal life support. *J Burn Care Rehabil* 1999; 20:145–150
17. Cedidi C, Hierner R, Pichlmaier M, et al: Survival of severe ARDS with five-organ system failure following burns and inhalation injury in a 15-year-old patient. *Burns* 2003; 29:389–394
18. Hilt T, Graves DF, Chernin JM, et al: Successful use of extracorporeal membrane oxygenation to treat severe respiratory failure in a pediatric patient with a scald injury. *Crit Care Nurse* 1998; 18:63–72
19. Lessin MS, el-Eid SE, Klein MD, et al: Extracorporeal membrane oxygenation in pediatric respiratory failure secondary to smoke inhalation injury. *J Pediatr Surg* 1996; 31:1285–1287
20. 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
21. Zabrocki LA, Brogan TV, Statler KD, et al: Extracorporeal membrane oxygenation for pediatric respiratory failure: Survival and predictors of mortality. *Crit Care Med* 2011; 39:364–370
22. Werho DK, Pasquali SK, Yu S, et al; Extracorporeal Life Support Organization Member Centers: Hemorrhagic complications in pediatric cardiac patients on extracorporeal membrane oxygenation: An analysis of the Extracorporeal Life Support Organization Registry. *Pediatr Crit Care Med* 2015; 16:276–288
23. Dalton HJ, Garcia-Filion P, Holubkov R, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network: Association of bleeding and thrombosis with outcome in extracorporeal life support. *Pediatr Crit Care Med* 2015; 16:167–174
24. Xiao-Wu W, Herndon DN, Spies M, et al: Effects of delayed wound excision and grafting in severely burned children. *Arch Surg* 2002; 137:1049–1054
25. Burke CR, Chan T, McMullan DM: Extracorporeal life support use in adult burn patients. *J Burn Care Res* 2017; 38:174–178
26. Brealey D, Singer M: Hyperglycemia in critical illness: A review. *J Diabetes Sci Technol* 2009; 3:1250–1260
27. Gore DC, Chinkes D, Heggors J, et al: Association of hyperglycemia with increased mortality after severe burn injury. *J Trauma* 2001; 51:540–544
28. Zhou YP, Zhou ZH, Xue JZ: Burns complicated with gastrointestinal haemorrhage—an analysis of 70 cases. *Burns* 1993; 19:150–152
29. Musgrave MA, Fingland R, Gomez M, et al: The use of inhaled nitric oxide as adjuvant therapy in patients with burn injuries and respiratory failure. *J Burn Care Rehabil* 2000; 21:551–557
30. Sheridan RL, Hurford WE, Kacmarek RM, et al: Inhaled nitric oxide in burn patients with respiratory failure. *J Trauma* 1997; 42:629–634
31. Monstrey S, Hoeksema H, Verbelen J, et al: Assessment of burn depth and burn wound healing potential. *Burns* 2008; 34:761–769