Association of Bleeding and Thrombosis With Outcome in Extracorporeal Life Support*

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Objective: Changes in technology and increased reports of successful extracorporeal life support use in patient populations, such as influenza, cardiac arrest, and adults, are leading to expansion of extracorporeal life support. Major limitations to extracorporeal life support expansion remain bleeding and thrombosis. These complications are the most frequent causes of death and morbidity. As a pilot project to provide baseline data for a detailed evaluation of bleeding and thrombosis in the current era, extracorporeal life support patients were analyzed from eight centers in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network.

Study Design: Retrospective analysis of patients (< 19 yr) reported to the Extracorporeal Life Support Organization registry from eight Collaborative Pediatric Critical Care Research Network centers between 2005 and 2011.

Setting: Tertiary children's hospitals within the Collaborative Pediatric Critical Care Research Network.

Subjects: The study cohort consisted of 2,036 patients (13% with congenital diaphragmatic hernia).

Interventions: None.

Main Results: In the cohort of patients without congenital diaphragmatic hernia (n = 1,773), bleeding occurred in 38% of patients, whereas thrombosis was noted in 31%. Bleeding and thrombosis were associated with a decreased survival by 40% (relative risk, 0.59; 95% CI, 0.53–0.66) and 33% (odds ratio, 0.67; 95% CI, 0.60–0.74). Longer duration of extracorporeal life support and use of venoarterial cannulation were also associated with increased risk of bleeding and/or thrombotic complications and lower survival. The most common bleeding events included surgical site bleeding (17%; n = 306), cannulation site bleeding (14%; n = 256), and intracranial hemorrhage (11%; n = 192). Common thrombotic events were clots in the circuit (15%; n = 274) and the oxygenator (12%; n = 212) and hemolysis (plasma-free hemoglobin > 50 mg/dL) (10%; n = 177). Among patients with congenital diaphragmatic hernia, bleeding and thrombosis occurred in, respectively, 45% (n = 118) and 60% (n = 159), Bleeding events were associated with reduced survival (relative risk, 0.62; 95% CI, 0.46–0.86) although thrombotic events were not (relative risk, 0.92; 95% CI, 0.67–1.26).

Conclusions: Bleeding and thrombosis remain common complications in patients undergoing extracorporeal life support. Further research to reduce or eliminate bleeding and thrombosis is indicated to help improve patient outcome. (*Pediatr Crit Care Med* 2015; 16:167–174)

Key Words: bleeding; cardiopulmonary bypass; complications; extracorporeal life support; extracorporeal membrane oxygenation; thrombosis

Extracorporeal life support (ECLS) is a modified form of cardiopulmonary bypass that provides temporary support to neonates, children, and adults with refractory organ failure (1–3). Over 58,000 patients have been reported to have received ECLS, according to the Extracorporeal Life Support Organization (ELSO) International Registry (4). Changes in technology and the successful use of ECLS in patient populations such as influenza, cardiac arrest, and adults are driving a higher utilization of ECLS in recent years (4–14).

Use of ECLS is accompanied by a significant risk for complications that contribute to risk of death and disability (1–3). Exposure to the extracorporeal circuit induces a prothrombotic state, indicating need for vigilant monitoring of anticoagulation to prevent clotting in the extracorporeal circuit. Traditionally, clinicians rely on unfractionated heparin for anticoagulation. Despite advances in monitoring techniques and treatment of abnormalities in the coagulation cascade during ECLS, bleeding and thrombosis remain predominate complications (15–17). Intracranial hemorrhage and ischemic stroke are the most severe such complications, often resulting in death or significant disability.

The ELSO established a voluntary registry on the clinical use of ECLS (predominantly extracorporeal membrane oxygenation, also known as ECMO) (http://www.elso.org). ELSO implemented the registry to monitor the use of ECLS technology for identification of opportunities to improve practice guidelines and outcomes. Registry data include pre-ECLS clinical characteristics, primary diagnosis, reason for ECLS, ECLS variables, ELSO diagnostic category, complications, and outcome. Although the ELSO database is of great use in descriptions and outcomes of ECLS support, information collected is limited in scope.

This study leveraged the ELSO registry data to evaluate ECLS-related bleeding and thrombotic complications within the Collaborative Pediatric Critical Care Research Network (CPCCRN) of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. The CPCCRN, a network of eight medical centers with a focus on pediatric critical care research, are academic sites with dedicated ICU research personnel, pediatric training programs, have more than 20 ICU beds, and average yearly admissions to the ICU of more than 2,000. All are experienced ECLS centers, supporting more than 20 ECLS-treated patients per year, and each center within CPCCRN is a designated ELSO center of excellence (details at http://www.ELSO.org). Using the ECLS expertise within CPCCRN and the data available within the ELSO registry, we analyzed the bleeding and thrombosis complication rate and the association of such complications with survival. Findings from this study provided baseline data to inform the design of a prospective, observational cohort study of factors associated with bleeding, thrombosis, outcome, anticoagulation regimens, and compliance with center-specific protocols at CPCCRN sites.

METHODS

We analyzed ELSO registry data for pediatric patients (< 19 yr) who underwent ECLS at any of the eight current CPCCRN centers during a 7-year period (2005–2011). The study outcomes were the prevalence of reported bleeding and thrombotic complications (definition described below) and survival to hospital discharge.

Approval to include deidentified data from each center was obtained, and the study was considered exempt by the Institutional Review Board at Phoenix Children's Hospital.

Complications

For this study, bleeding complications extracted from the ELSO registry were identified as bleeding at the cannula site or any surgical site, intracranial hemorrhage, gastrointestinal hemorrhage, or pulmonary hemorrhage. A list of complications tracked within the ELSO database is shown in **Table 1** with those of interest highlighted in bold type. A thrombotic complication was reported clotting of the circuit (bridge, hemofilter, oxygenator, bladder, or "other"), presence of disseminated intravascular coagulation (DIC), and infarction in

TABLE 1. List of Extracorporeal Life Support Organization Mechanical and Patient-Related Complications[a]

Patient-related	Mechanical
Thrombotic	**Clots: oxygenator**
Intracranial infarction (US or CT)	**Clots: bridge**
Hemorrhagic	**Clots: bladder**
Intracranial hemorrhage (US or CT)	**Clots: hemofilter**
Gastrointestinal hemorrhage	**Clots: other**
Cannulation site bleeding	Oxygenator failure
Surgical site bleeding	Raceway rupture
Hemolysis (plasma hemoglobin > 50 mg/dL)	Other tubing rupture
Disseminated intravascular coagulation	Pump malfunction
Pulmonary hemorrhage	Heat exchange malfunction
Cardiopulmonary complications	Air in circuit
Inotropes on extracorporeal life support	Cracks: Connectors
Myocardial stun by echocardiography	Cannula problems
Cardiopulmonary resuscitation required	
Cardiac arrhythmia	
Hypertension requiring vasodilator	
Patent ductusarteriosus	
Tamponade: blood, serous, air	
Pulmonary pneumothorax (requiring treatment)	
Neurologic complications	
Clinical brain death	
Clinical seizures	
Electroencephalography-detected seizures	
Infection	
Renal related	
Continuous arteriovenous dialysis required	
Creatinine (1.5–3.0)	
Creatinine (> 3.0)	
Dialysis required	
Hemofiltration required	
Metabolic related	
Glucose < 40	
Glucose > 240	
Hyperbilirubinemia	
pH < 7.2	
pH > 7.6	

US = ultrasound, CT= computed tomography.

[a] Adapted from International Extracorporeal Life Support Organization registry, with permissions. Complications of interest are noted in boldface font.

the CNS. Hemolysis, defined as a plasma hemoglobin more than 50 mg/dL, was also classified as a thrombotic complication. Of note, specific volume, severity scores, or timing within the ECLS run for observed complications do not exist within the ELSO Registry.

Analysis

Data were analyzed using Stata SE 11.0 (College Station, TX). Descriptive data are presented as median with interquartile range (IQR). The study cohort was stratified based on age: neonatal (< 31 d) and pediatric (age 31 d to 18 yr).

The study outcomes (bleeding and thrombotic complications, survival to discharge) were stratified into four groups based on the indication for ECLS support. These groups were ECMO for respiratory failure, cardiac failure, ECMO applied during cardiopulmonary resuscitation (ECPR), and congenital diaphragmatic hernia (CDH). The mode of ECLS was based on initial method of cannulation as either venoarterial or venovenous. Duration of ECMO and mode of cannulation were compared with complication events and survival outcome using regression to estimate the associated risk (relative risk [RR]; 95% CI). The distribution of ECLS-associated complications and survival were examined and compared between years of ECLS and age groups (neonatal vs pediatric) using chi-square analysis.

Regression models, with covariates when necessary, were constructed to estimate the RR for the association of complications with survival to hospital discharge. Adjustment for venoarterial was restricted to those in the respiratory setting as venoarterial was used almost exclusively for other indications. Inclusion of potentially significant confounders (e.g., organ dysfunction and severity of illness) was limited by data availability within the ELSO registry. RR ratios are presented with 95% CI. For ordinal independent variables (e.g., year of ECLS and number of complications for individual patients), a linear test for trend was performed. The p values for trend tests (p_{trend}) were derived by entering the ordinal variable as a continuous variable in the model (18). Stratum-specific estimates were obtained when statistical significance was reached. The

TABLE 2. Characteristics of the Study Cohort ($n = 2,036$)

Variable	Percent (%)[a]	n
Male ($n = 2,011$)	56	1,132
Neonatal (non-CDH)	56	1,001
Race/ethnicity ($n = 1,993$)		
Caucasian	48	963
Hispanic	19	385
African-American	22	447
Asian-Pacific Islander	3	68
Other	7	130
Conventional ventilator (non-CDH)	63	772
Indication for extracorporeal life support		
Respiratory	39	784
Neonates	66	520
Pediatric	34	264
Cardiac	36	727
Neonates	51	372
Pediatric	49	355
Extracorporeal cardiopulmonary resuscitation	13	262
Neonatal	42	109
Pediatric	58	153
CDH	13	263

CDH = congenital diaphragmatic hernia.
[a]Percents were rounded to the nearest integer.

statistical significance was defined as an α of 0.05, with two-sided alternative hypotheses.

RESULTS

Over the study period, 2,036 patients were supported with ECLS at eight CPCCRN centers. Of these, 263 received support for CDH. Study cohort details are shown in **Table 2**.

Outcome of Neonatal and Pediatric ECLS Patients (Non-CDH)

Among the non-CDH patients, overall survival to discharge was 56% ($n = 1,001/1,773$), with pediatric survival of 53% and neonatal survival of 59%. The primary indication was respiratory failure in 784 patients (44%), cardiac failure in 727 (41%), and ECPR in 262 patients (15%). Venoarterial support was used in 64% of patients with respiratory failure ($n = 461/722$) and almost exclusively in cardiac failure and ECPR (> 99% of patients).

An increase in survival was noted from 53% in 2005 to 57% in 2011 ($p_{trend} = 0.003$). When a linear effect of year is fitted, annual survival rates for neonatal ($p_{trend}=0.034$) and pediatric ($p_{trend}=0.014$) patients also improved over time; however, an unexplained decrease in survival is noted among pediatric patients from 61% in 2010 to 49% in 2011. Survival did not vary between CPCCRN centers ($p = 0.294$) among neonatal ($p = 0.854$) or pediatric ($p = 0.244$) patients.

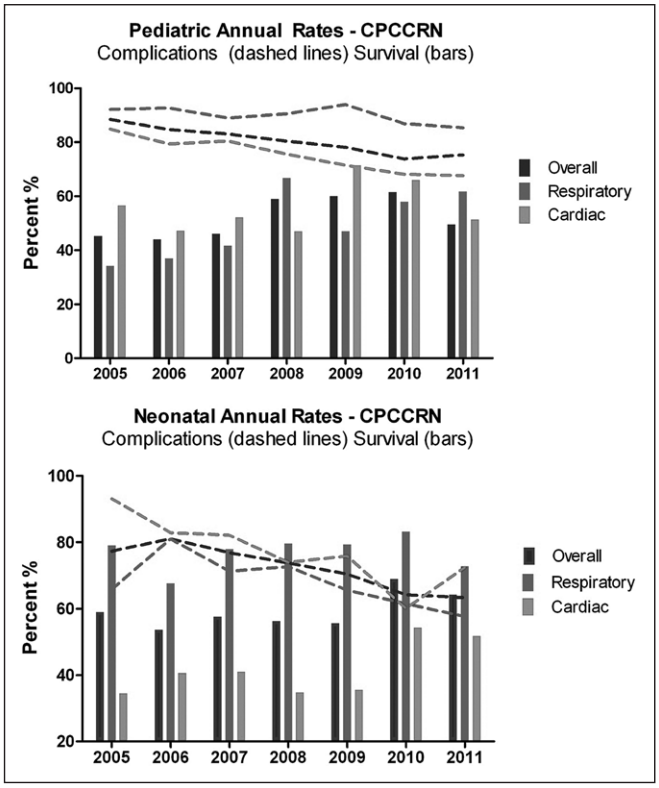

Figure 1. Annual survival and complication rates (excludes cases of congenital diaphragmatic hernia). CPCCRN = Collaborative Pediatric Critical Care Research Network.

Factors Associated With Outcome in Non-CDH Patients

Median duration of ECLS was 131 hours (IQR, 73–216). For every 10 hours of ECMO, the risk of complications and death increased (RR, 1.005; 95% CI, 1.003–1.007; RR, 1.005; 95% CI, 1.003–1.007, respectively). Among patients supported for respiratory failure, venoarterial cannulation mode increased the risk of complications (RR, 1.15; 95% CI, 1.04–1.26) and death (RR, 1.86; 95% CI, 1.42–2.44).

Complication rates for neonatal and pediatric patients steadily declined over the study years ($p_{trend} < 0.001$) (**Fig. 1**). Bleeding complications occurred in 33% of neonates and 45% of pediatric patients. Thrombotic complications (840 events) occurred in 29% of neonates and 33% of pediatric patients.

Bleeding and thrombosis were associated with decreased survival (RR, 0.59; 95% CI, 0.53–0.66) and 33% (RR, 0.67; 95% CI, 0.60–0.74), respectively. The most common bleeding events included surgical site bleeding (17%; $n = 306$), cannulation site bleeding (14%; $n = 256$), and intracranial hemorrhage (11%; $n = 192$). Thrombotic events included clots in the circuit (15%; $n = 274$), clots in the oxygenator (12%; $n = 212$), hemolysis (free hemoglobin > 50 mg/dL) (10%; $n = 177$), intracranial infarction (4%; $n = 74$), and DIC (3%; $n = 59$) (**Fig. 2**).

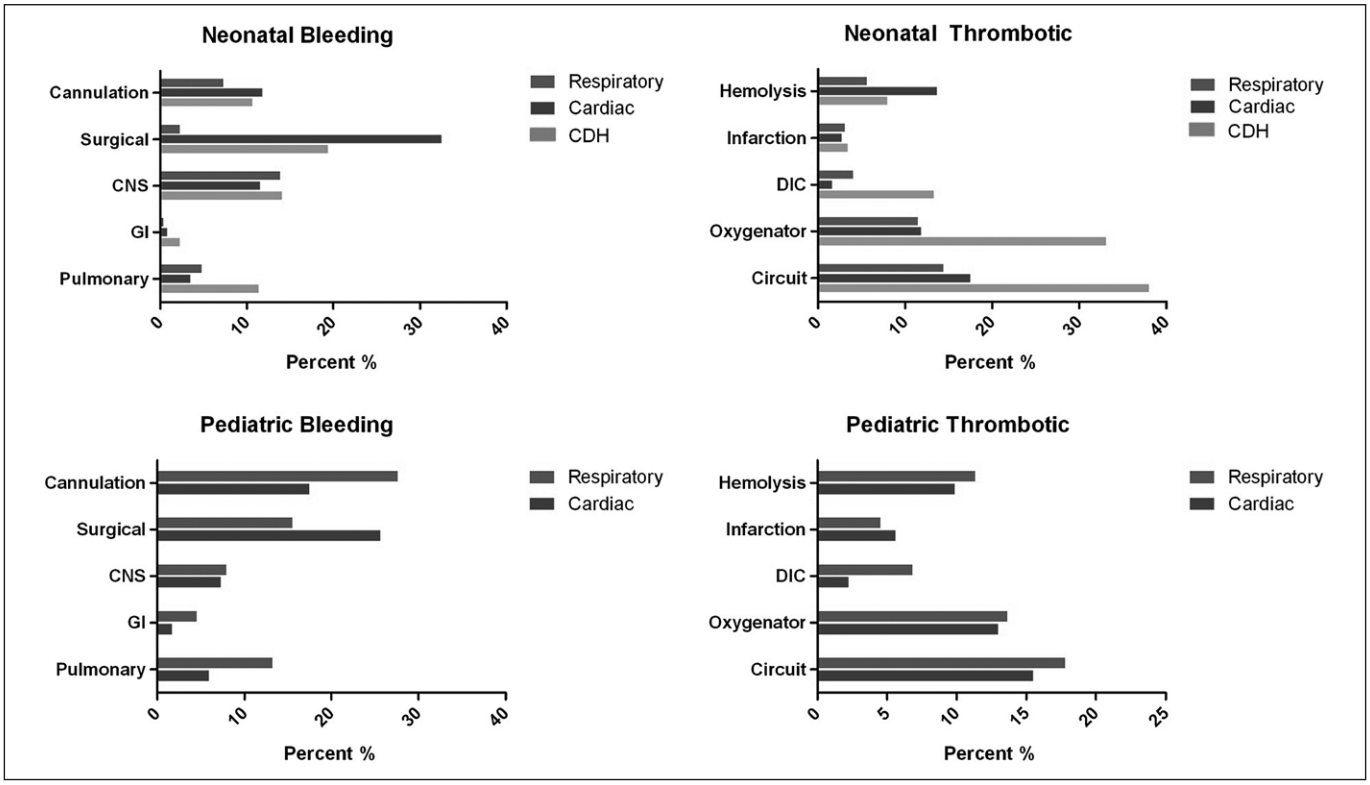

Figure 2. Prevalence of bleeding and thrombotic complications. CDH = congenital diaphragmatic hernia, DIC = disseminated intravascular coagulation, GI = gastrointestinal.

Patients Requiring ECLS for Respiratory Failure

Survival to discharge in patients supported for respiratory failure was 68% (n = 530/784), with neonatal survival of 77% and 50% in pediatric patients. The annual survival rates trended upward; however, this was not statistically significant (p_{trend} = 0.053). Increased survival was noted in pediatric respiratory patients (p_{trend} = 0.005), but neonatal survival was unchanged over time (p_{trend} = 0.380).

The prevalence of bleeding and thrombotic-related complications in neonatal and pediatric patients requiring respiratory support is presented in **Figure 2**. Among neonatal patients, bleeding occurred in 25% (n = 131) and thrombosis in 27% (n = 141). Bleeding events were associated with decreased survival (RR_{adj}, 0.68; 95% CI, 0.58–0.80) as were thrombotic events (RR_{adj}, 0.79; 95% CI, 0.69–0.92). Compared with neonatal patients, pediatric patients had a higher prevalence of bleeding (50%, n = 131; $p < 0.001$) and thrombotic (37%, n = 98; p = 0.004) complications. Bleeding complications in pediatric patients were associated with a decrease in survival likelihood (RR_{adj}, 0.67; 95% CI, 0.51–0.87).

An increased number of bleeding complications were associated with decreased likelihood of survival for both neonatal and pediatric patients (p_{trend} = 0.001) (**Table 3**). The frequency of thrombotic-related complications was associated with reduced survival in neonatal patients (p_{trend} = 0.009) but was not associated with survival for pediatric patients (p_{trend} = 0.274).

Patients Requiring ECLS for Cardiac Failure

Survival in patients receiving ECLS for cardiac failure was 49% (n = 353/727), increasing from 44% in 2005 to 52% in 2011 (p_{trend} = 0.010) (**Fig. 1**). Bleeding and thrombotic-related events were noted in 43% of patients (n = 316) and 33% of patients (n = 237), respectively. Overall survival for neonates was 40% as compared with 57% in pediatric patients ($p < 0.001$). Annual survival rates for neonatal and pediatric patients were unchanged (p_{trend} = 0.136 and p_{trend} = 0.133, respectively). Bleeding events were associated with reduced survival for neonates and pediatric cardiac patients by 33% (RR_{adj}, 0.67; 95% CI, 0.51–0.88) and 32% (RR_{adj}, 0.68; 95% CI, 0.55–0.83), respectively. A similar decrease in survival likelihood associated with thrombotic complications was noted for both neonatal patients (RR_{adj}, 0.56; 95% CI, 0.38–0.82) and pediatric patients (RR_{adj}, 0.63; 95% CI, 0.49–0.82).

The bleeding and thrombotic-related complications in patients who underwent ECLS for cardiac failure are presented in **Figure 2**. Increasing frequency of bleeding and thrombotic-related complications were also associated with decreased survival ($p_{trend\ (all)} < 0.01$) (**Table 4**).

Patients Requiring ECLS for Cardiopulmonary Resuscitation

ECLS was initiated for ECPR in 15% of the non-CDH cohort (n = 262), of which 42% were neonates (median age among neonates, 7 d [IQR, 4–12]). Survival among ECPR patients to discharge was 45% and was unchanged across the study years (p_{trend} = 0.282).

Bleeding and thrombotic complications occurred in 38% of patients with ECPR (n = 99) and 29% of patients with ECPR (n = 77), respectively. Bleeding rates were

similar between neonates and pediatric patients (37% vs 39%; $p = 0.759$), as was the prevalence of thrombosis (30% vs 29%; $p = 0.790$). In neonates, bleeding complications were associated with reduced survival (RR_{adj}, 0.45; 95% CI, 0.23–0.86) but thrombosis was not ($p = 0.124$). In pediatric patients, bleeding complications were not associated with survival ($p = 0.187$). The presence of thrombotic complications, however, was associated with reduced survival (RR_{adj}, 0.59; 95% CI, 0.37–0.95)

TABLE 3. Frequency[a] of Complications During Extracorporeal Life Support for Respiratory Support and Relative Risk of Survival (Excludes Cases of Congenital Diaphragmatic Hernia)

	Bleeding					Thrombosis				
Variable	*n*	% (*n*)	% Survival	Survival RR[b]	95% CI	*n*	% (*n*)	% Survival	Survival RR[b]	95% CI
Neonatal	0	75 (389)	84	1.00	–	0	73 (379)	82	1.00	–
	1	22 (115)	57	0.72	0.61–0.85	1	16 (85)	62	0.80	0.67–0.95
	2+	3 (16)	31	0.36	0.16–0.84	2	6 (33)	67	0.83	0.63–1.08
				$p < 0.001$[a]		3+	4 (23)	57	0.72	0.48–1.08
									$p = 0.009$[a]	
Pediatric	0	50 (133)	61	1.00	–	0	63 (166)	52	1.00	–
	1	33 (87)	45	0.75	0.57–0.98	1	22 (58)	50	0.95	0.70–1.29
	2+	17 (44)	27	0.47	0.27–0.81	2	10 (26)	50	1.08	0.73–1.61
				$p = 0.001$[a]		3+	5 (14)	21	0.47	0.17–1.29
									$p = 0.274$[a]	

RR = relative risk.
[a]A linear test for trend was performed.
[b]Adjusted for duration of extracorporeal life support (hours) and mode of administration (venoarterial and venovenous).
Dashes indicate that 0 is the reference value.

TABLE 4. Frequency[a] of Complications During Extracorporeal Life Support for Cardiac Support and Relative Risk of Survival[a] (Excludes Cases of Congenital Diaphragmatic Hernia)

	Bleeding					Thrombosis				
Variable	*n*	% (*n*)	% Survival	Survival RR[b]	95% CI	*n*	% (*n*)	% Survival	Survival RR[b]	95% CI
Neonatal										
	0	57 (211)	49	1.00	–	0	68 (251)	49	1.00	–
	1	28 (103)	35	0.80	0.59–1.07	1	20 (75)	21	0.51	0.32–0.81
	2+	16 (58)	19	0.45	0.26–0.77	2	8 (29)	31	0.78	0.45–1.35
				$p < 0.001$[a]		3+	5 (17)	12	0.36	0.09–1.35
									$p = 0.014$[a]	
Pediatric										
	0	56 (200)	69	1.00	–	0	67 (239)	67	1.00	–
	1	31 (109)	42	0.66	0.52–0.83	1	20 (70)	41	0.67	0.50–0.89
	2+	13 (46)	43	0.73	0.52–1.02	2	10 (35)	31	0.57	0.34–0.93
				$p = 0.003$[a]		3+	3 (11)	27	0.58	0.23–1.47
									$p = 0.002$[a]	

RR = relative risk.
[a]A linear test for trend was performed.
[b]Adjusted for the duration of extracorporeal life support (hours).
Dashes indicate that 0 is the reference value.

TABLE 5. Frequency[a] of Complications During Extracorporeal Life Support for Congenital Diaphragmatic Hernia and Relative Risk of Survival

	Bleeding					Thrombosis				
Variable	*n*	% (*n*)	% Survival	Survival RR[a]	95% CI	*n*	% (*n*)	% Survival	Survival RR[a]	95% CI
Neonatal										
	0	55 (145)	50	1.00	–	0	40 (104)	48	1.00	–
	1	34 (89)	33	0.65	0.46–0.91	1	29 (75)	37	0.90	0.62–1.31
	2	11 (29)	24	0.53	0.27–1.04	2	18 (48)	38	0.95	0.61–1.48
				$p = 0.006$		3	14 (36)	36	0.92	0.55–1.52
									$p = 0.740$	

RR = relative risk.
[a]A linear test for trend was performed.
[b]Adjusted for the duration of extracorporeal life support (hours).
Dashes indicate that 0 is the reference value.

In the ECPR subgroup, the most common source of bleeding was at surgical sites (16%; $n = 41/262$) while thrombotic complications from hemolysis (12%; $n = 32/262$) and clots in the circuit (12%; $n = 32/262$) predominated.

Patients Requiring ECLS for CDH

Overall survival for patients with CDH was 41% ($n = 109/263$). No increase in survival was noted over the study time period ($p_{trend} = 0.876$). Bleeding and thrombotic complications in the CDH group were found in 45% ($n = 118$) and 60% ($n = 159$), respectively. Bleeding complications were associated with reduced survival (RR, 0.62; 95% CI, 0.46–0.86) although thrombotic complications were not (RR, 0.92; 95% CI, 0.67–1.26). Increasing frequency of bleeding complications were also associated with reduced survival likelihood ($p_{trend} = 0.006$) (**Table 5**).

DISCUSSION

In this retrospective analysis of ELSO registry data from clinical sites in CPCCRN, we identified a trend toward increased survival between 2005 and 2011. The majority of improvement is in patients receiving ECLS for respiratory support, as those with ECPR, CDH, and cardiac support had fairly static survival rates over the study period. Such an improvement is encouraging, given that patients receiving ECLS for respiratory failure in the current era are reported to have more comorbidities adversely affecting survival (19).

The reason for poor survivability of neonatal CDH patients receiving ECLS remains elusive. Reports of improved survival due to scoring systems for severity of CDH and treatment or surgical regimens have been limited to single-center studies (20–23). Fatal bleeding events are high among this patient population, and the occurrence of thrombotic events may reflect anticoagulation efforts (24). Our analysis of patients treated within CPCCRN sites found no association between thrombotic events and survival. The absence of an association raises the question about the presence of subclinical thrombus similar to those identified in postmortem examinations of adult populations (25, 26).

Data from this report are subject to limitations similar to those noted in previous reports based on ELSO registry data. Data available for analysis did not allow correlation between timing of bleeding and/or thrombotic events and other factors, such as anticoagulation status, organ failure severity, or specific data on administration of blood products. Similarly, although veno-arterial support during ECLS for respiratory support was associated with decreased survival, this may be related to pre-ECLS severity factors or other details rather than the mode itself (27, 28), but specific data points to establish this association are not available within the registry. Outcome measures were limited to survival. Nonetheless, this focused evaluation from academic sites with large ECMO populations and long experience is useful to inform the field of factors associated with outcome in the current era. Our findings highlight a lack of success in development of anticoagulation regimens and ECMO practices and processes to limit or eliminate the occurrence of bleeding and thrombosis.

The variability in ECMO practice between centers remains an ongoing limitation to research on ECLS. The ability to develop studies aimed at a specific anticoagulation regimen or intervention is confounded by nonstandardized ECMO equipment and management algorithms. Perhaps, the time has come to standardize ECMO practice and procedures to aid scientific research and advance the field. This novel approach in ECMO has not been implemented in the past and represents a paradigm shift in ECMO practice, as most centers have developed their own unique practices (29).

To achieve the goal of eliminating bleeding and thrombosis-related death during ECMO, investigations must employ rigorous, prospective observational designs to systematically gather data at a more granular level than is currently available. ELSO is currently revising the registry data fields to strengthen variable definitions (e.g., complications) and to add fields which would allow more exact severity-of-illness scoring as well as identify timing of complications during the ECMO course. This analysis was conducted in preparation for a multicenter trial of bleeding and thrombosis during ECMO among CPCCRN

sites. By capitalizing on the CPCCRN infrastructure, the author and collaborators are in pursuit of a framework to standardize ECMO practice—from circuitry to anticoagulation algorithms to patient management—in order to design and implement scientifically rigorous studies. Successful implementation of such a process within ECLS will open the door for similar efforts throughout critical care medicine (30, 31).

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