Development of the Pediatric Extracorporeal Membrane Oxygenation Prediction Model for Risk-Adjusting Mortality

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Objectives: To develop a prognostic model for predicting mortality at time of extracorporeal membrane oxygenation initiation for children which is important for determining center-specific risk-adjusted outcomes.

Design: Multivariable logistic regression using a large national cohort of pediatric extracorporeal membrane oxygenation patients.

Setting: The ICUs of the eight tertiary care children's hospitals of the Collaborative Pediatric Critical Care Research Network.

Patients: Five-hundred fourteen children (< 19 yr old), enrolled with an initial extracorporeal membrane oxygenation run for any indication between January 2012 and September 2014.

Interventions: None.

Measurements and Main Results: A total of 514 first extracorporeal membrane oxygenation runs were analyzed with an overall mortality of 45% (*n* = 232). Weighted logistic regression was used for model selection and internal validation was performed using cross validation. The variables included in the Pediatric Extracorporeal Membrane Oxygenation Prediction model were age (pre-term neonate, full-term neonate, infant, child, and adolescent), indication for extracorporeal membrane oxygenation (extracorporeal cardiopulmonary resuscitation, cardiac, or respiratory), meconium aspiration, congenital diaphragmatic hernia, documented blood stream infection, arterial blood pH, partial thromboplastin time, and international normalized ratio. The highest risk of mortality was associated with the presence of a documented blood stream infection (odds ratio, 5.26; CI, 1.90–14.57) followed by extracorporeal cardiopulmonary resuscitation (odds ratio, 4.36; CI, 2.23–8.51). The *C*-statistic was 0.75 (95% CI, 0.70–0.80).

Conclusions: The Pediatric Extracorporeal Membrane Oxygenation Prediction model represents a model for predicting in-hospital mortality among children receiving extracorporeal membrane oxygenation support for any indication. Consequently, it holds promise as the first comprehensive pediatric extracorporeal membrane oxygenation risk stratification model which is important for benchmarking extracorporeal membrane oxygenation outcomes across many centers. (*Pediatr Crit Care Med* 2019; XX:00–00)

Key Words: decision support; extracorporeal membrane oxygenation; pediatric; predictive score model; risk adjustment; risk assessment

Indications for extracorporeal membrane oxygenation (ECMO) include a "reversible condition with a high predicted mortality rate if conventional management is continued" (1). However, the lack of randomized controlled trials and prognostic prediction models complicate prediction of reversibility of the condition and mortality when ECMO is used. Furthermore, mortality is influenced by an increasing complexity of primary diagnoses and comorbid conditions, as well as practice variation (2–5). Discriminating the patient-related risk factors from center-specific practice variation is important for performance benchmarking, observational research, quality improvement, and anticipating mortality across similar patient groups (6–13).

Prediction models have been developed but the target populations of existing models are limited to neonates and pediatric patients with respiratory failure treated with ECMO and these models were developed using only variables captured in the Extracorporeal Life Support Organization (ELSO) registry (2, 14–16). The *C*-statistics of these models range from 0.69 to 0.78 with the best performance achieved in the neonatal respiratory failure population (2, 14–16). Only 35% (712/2,060) of all patients 14 days to 18 years old in the 2016 ELSO registry are represented by current models and of those only 28% (571/2,060) had sufficient data to calculate a score. The percentage of patients for which a score could be applied for the Pittsburgh Index for Pre-ECMO Risk (PIPER), Neonatal Risk Estimate Score for Children Using Extracorporeal Respiratory Support (Neo-RESCUERS),

Pediatric Risk Estimate Score for Children Using Extracorporeal Respiratory Support (Ped-RESCUERS), and Pediatric Pulmonary Rescue with Extracorporeal Membrane Oxygenation Prediction (P-PREP) models were 6%, 8%, 27%, and 31% respectively demonstrating that many pediatric patients cannot be risk-adjusted using current models (2, 14–16). Furthermore, prognostic models for pediatric patients who receive extracorporeal cardiopulmonary resuscitation (eCPR) or require cardiac ECMO do not exist (17). In short, we lack an omnibus risk stratification model that can be applied to both neonates and pediatric patients without being limited to either cardiac or respiratory ECMO and also include those who receive eCPR.

Our aim was to develop and internally validate a comprehensive prognostic model to predict in-hospital mortality for all patients less than 19 years old who received ECMO for any reason, including eCPR, by using pre-ECMO data available in the Bleeding and Thrombosis on ECMO (BATE) dataset (18). We hypothesized that a Pediatric ECMO Prediction (PEP) model could be developed that would be useful for the purposes of risk adjusting to determine center-specific outcomes.

MATERIALS AND METHODS

The prognostic model was developed and internally validated using data originally collected for the BATE study. Permission was requested and granted to obtain access to the BATE dataset, which included 514 first ECMO run data from subjects birth to less than 19 years old enrolled at the eight pediatric hospitals affiliated with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network between December 2012 and September 2014. Our primary outcome was in-hospital mortality in pediatric patients supported with ECMO.

The study was designed following the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement (19) with waiver of informed consent by the Institutional Review Board for every clinical site and the Data Coordinating Center at the University of Utah. All data were collected by trained research coordinators via direct observation, discussion with bedside clinicians, and review of medical records.

Candidate Variables

Potential predictors of mortality were limited to the pre-ECMO variables available in the BATE dataset with missingness less than 10% after imputation. **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/PCC/A904) illustrates the schema used for categorizing diagnostic groups within the BATE dataset which were adapted using previous publications (2–5, 14–16, 20–22). All time-stamped variables were collected within 12 hours prior to ECMO cannulation, and the single data point most proximal and prior to ECMO was used for analysis (**Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/PCC/A905).

Variables Defined

Using clinical judgment at the time of cannulation indications for ECMO were categorized as respiratory, cardiac, or eCPR

which included any subject who went onto ECMO during CPR. ECMO mode was categorized as venoarterial for any mode initially using an arterial cannula and venovenous for any mode initially without an arterial cannula.

Patients less than or equal to 30 days of actual age at time of ECMO cannulation were categorized as neonates, with neonates born at less than 37 weeks gestation defined as pre-term; greater than 30 days to less than 1 year old as infants; greater than or equal to 1 year to less than 12 years old as children; and greater than or equal to 12 years to less than 19 years old as adolescents. Body habitus was determined using weight-for-length percentiles for patients less than 2 years old and body mass index for age percentiles for all others, according to the U.S. Center for Disease Control and Prevention (23). Obesity and underweight cutoffs were defined as greater than or equal to the 95th percentile or less than the 5th percentile, respectively.

Acute diagnoses were the primary conditions requiring ICU admission. Chronic diagnoses were those given to a patient prior to the current hospitalization that were not the primary reason for ICU admission.

Infections were all based on pre-ECMO data and were classified as "documented" (culture or polymerase chain reaction [PCR] testing confirmed the presence of a pathogen) or "suspected" (patient treated with antibiotics for presumed infection despite culture/PCR never performed or negative). Documented infections were further categorized by pathogen and system (blood, respiratory, or other).

The BATE protocol defined organ failure prior to ECMO separately from the indication for ECMO. Cardiovascular failure included those cannulated to venoarterial ECMO and/or receiving vasoactive infusions at the time of cannulation. Hepatic failure was defined as an international normalized ratio (INR) greater than or equal to 2. To determine acute kidney injury (AKI), we presumed baseline creatinine as the median creatinine for age provided the patient did not have known preexisting renal injury or failure, because the first measured serum creatinine in critically ill children may be higher than baseline (24). As described by Zappitelli et al (25), we then calculated the change in creatinine from the presumed baseline and assigned AKI using the Kidney Disease Improving Global Outcomes consensus definition of AKI (26, 27). All patients using renal replacement therapy at baseline or prior to ECMO were analyzed as having "stage II + AKI." Neurologic failure was defined as seizures (clinical or electroencephalography), intracranial hemorrhage, cerebrovascular accident, or stroke.

The Vasoactive-Inotropic Score was calculated at the time of ECMO cannulation (28, 29). Vital sign ranges were categorized based on prior studies (**Supplemental Table 3**, Supplemental Digital Content 3, http://links.lww.com/PCC/A906) (30–33).

Development and Internal Validation of the PEP Model

Pre-ECMO measurements and characteristics were evaluated as predictors of in-hospital mortality using univariable logistic regression. In order to fully use the variables available to us in the multivariable model, multiple imputation was used to impute missing data. Imputation was performed using a sequence of regression models implemented in IVEware (Imputation and Variance Estimation Software, Version 0.3, Ann Arbor, MI). After imputation, we then excluded any variables that remained missing for greater than 10% of subjects (e.g., vital signs such as blood pressure and heart rate were excluded since they were missing for the 14% of subjects who received eCPR, and imputation of these values would be inappropriate for these subjects). All candidate variables with missingness after imputation of less than 10% were then entered into a bidirectional stepwise selection process with a criterion of p value of less than 0.05 to enter and stay in the final model. The interaction between each variable and the indication for ECMO was considered to allow appropriate modeling in case the relationship between predictors and in-hospital mortality varies by indication. Weighted logistic regression was used for model selection with weights defined uniformly as one of 10 to account for the 10 imputed datasets being used (34). After the variables to be included in the final model were selected, multiple logistic regression was performed separately for each of the 10 imputed datasets. Results were combined, accounting for the amount of imputed data and appropriately inflating the variance of the estimators, using the MIANALYZE procedure in SAS 9.4 (SAS Institute, Cary, NC) (35).

The prediction equation for the probability of in-hospital mortality was defined as the logistic function of the log odds of mortality, as estimated by the model. In order to assess the predictive performance of the model, the C-statistic was generated. Model calibration was tested using the Hosmer-Lemeshow goodness-of-fit test. The model was internally validated using cross validation. Due to the modest sample size, leave-one-out cross validation was used to accurately estimate the C-statistic without the bias that would otherwise occur when using the same dataset to develop and validate a model. The C-statistic for each imputed dataset was obtained, and the results were combined with the MIANALYZE procedure in order to obtain accurate CIs for the C-statistic from the imputed data.

RESULTS

A total of 514 first ECMO runs were analyzed with an overall mortality of 45% ($n = 232$) and a neonatal mortality of 42%. The median duration of ECMO was 5 days (interquartile range [IQR], 2.7–9.4 d). The median time from hospital admission to cannulation was 2 days (IQR, 0.4–7.5 d).

Pre-ECMO characteristics of survivors and nonsurvivors in the BATE dataset are found in Supplemental Table 3 (Supplemental Digital Content 3, http://links.lww.com/PCC/A906). Survival did not differ significantly by sex, race, or ECMO center. The most common acute and chronic diagnoses were congenital cardiovascular disease (38%), respiratory distress/failure (33%), and congenital anomaly/chromosomal defect (23%). Documented infections of any type were found in 16% of subjects. Of the 27 patients with a documented blood stream infection (D-BSI), two were fungal.

Pre-ECMO supportive therapies and laboratory findings by vital status are displayed in **Tables 1** and **2**. Respiratory failure was the most common indication for ECMO (46%); cardiac

TABLE 1. Preextracorporeal Membrane Oxygenation Supportive Therapies by Vital Status

Supportive Therapy	Vital Status at Hospital Discharge		Overall (n = 514)
	Dead (n = 232)	Alive (n = 282)	
Primary ECMO indication, n (%)			
Respiratory	83 (36)	154 (55)	237 (46)
Cardiac	105 (45)	102 (36)	207 (40)
Extracorporeal cardiopulmonary resuscitation	44 (19)	26 (9)	70 (14)
Operation in the prior 24 hr, n (%)	89 (38)	89 (32)	178 (35)
CPB in the prior 24 hr, n (%)	78 (34)	70 (25)	148 (29)
ECMO directly from CPB, n (%)	38 (16)	37 (13)	75 (15)
Heparin bolus for cannulation, n (%)	179 (77)	235 (83)	414 (81)
Initial mode of ECMO, n (%)			
Venoarterial	207 (89)	224 (79)	431 (84)
Venovenous	25 (11)	58 (21)	83 (16)
Type of pump, n (%)			
Centrifuge	164 (71)	170 (60)	334 (65)
Roller head	68 (29)	112 (40)	180 (35)
Vasoactive-Inotropic Score[a], n (%)			
None or low	139 (60)	180 (64)	319 (62)
High	93 (40)	102 (36)	195 (38)
Vasoactive bolus, n (%)	50 (22)	44 (16)	94 (18)
Respiratory support	191 (82)	235 (83)	426 (83)
Ventilation, n (%)			
None	30 (14)	38 (14)	68 (14)
Conventional	135 (62)	146 (54)	281 (57)
High frequency	54 (25)	89 (33)	143 (29)
Settings, median (interquartile range)			
Ventilatory rate (beats/min)	28.0 (20.0–35.0)	27.0 (20.0–35.0)	28.0 (20.0–35.0)
Peak inspiratory pressure (cm H_2O)	26.0 (21.0–32.0)	25.0 (21.0–30.0)	26.0 (21.0–31.0)
Exhaled tidal volume (mL)	41.0 (28.0–110.0)	43.9 (27.0–90.0)	43.0 (28.0–100.0)
Set tidal volume (mL)	60.0 (35.0–150.0)	43.0 (30.0–90.0)	50.0 (30.0–104.0)
Positive end-expiratory pressure (cm H_2O)	6.0 (5.0–8.0)	6.0 (5.0–8.0)	6.0 (5.0–8.0)
Pressure support (cm H_2O)	10.0 (8.0–10.0)	10.0 (8.0–10.0)	10.0 (8.0–10.0)
F_{IO_2}	1.0 (0.5–1.0)	1.0 (0.8–1.0)	1.0 (0.6–1.0)
Mean airway pressure (cm H_2O)	14.8 (11.0–20.0)	14.0 (11.0–20.0)	14.3 (11.0–20.0)
Frequency (Hz)	8.0 (6.0–8.0)	7.0 (6.0–8.0)	7.0 (6.0–8.0)
Amplitude (cm H_2O)	41.0 (36.0–50.0)	39.0 (35.0–46.0)	40.0 (35.0–47.0)

CPB = cardiopulmonary bypass, ECMO = extracorporeal membrane oxygenation.
[a]Vasoactive-Inotropic Score: none/low = 0 to < 20, high = ≥ 20.

TABLE 2. Preextracorporeal Membrane Oxygenation Laboratory Findings by Vital Status

Laboratory Test	Vital Status at Hospital Discharge		
	Dead (*n* = 232), Median (IQR)	Alive (*n* = 282), Median (IQR)	Overall (*n* = 514), Median (IQR)
Lactate (mmol/L)	5.1 (1.8−9.9)	3.0 (1.6−6.9)	4.0 (1.7−8.0)
pH	7.3 (7.1−7.4)	7.3 (7.2−7.4)	7.3 (7.1−7.4)
Pao_2 (mm Hg)	48.5 (34.2−95.1)	53.0 (37.0−89.7)	52.0 (35.2−93.7)
$Paco_2$ (mm Hg)	50.0 (38.4−66.9)	50.0 (39.0−66.0)	50.0 (38.8−66.8)
Pao_2/Fio_2 ratio	73.8 (37.4−175.3)	61.2 (37.4−142.5)	64.0 (37.4−153.3)
Oxygenation index	24.4 (8.3−49.2)	30.2 (12.5−50.0)	28.3 (10.9−50.0)
Prothrombin time (s)	18.0 (14.7−21.7)	16.0 (13.3−18.5)	16.8 (13.8−19.7)
Partial thromboplastin time (s)	46.9 (34.8−65.9)	41.5 (32.7−53.0)	43.7 (33.4−58.4)
International normalized ratio	1.6 (1.3−2.0)	1.4 (1.2−1.7)	1.5 (1.2−1.8)
Fibrinogen (mg/dL)	210.5 (136.5−284.5)	238.0 (177.0−320.0)	217.0 (156.0−306.0)
Leukocytes ($10^3/\mu L$)	13.7 (8.9−18.5)	13.8 (8.8−19.1)	13.8 (8.8−19.0)
Hemoglobin (g/dL)	13.2 (11.1−15.0)	13.3 (11.4−15.4)	13.2 (11.2−15.3)
Platelets ($10^3/\mu L$)	180.5 (109.0−253.0)	172.0 (120.0−237.0)	174.0 (114.0−248.0)
Sodium (mmol/L)	140.0 (136.0−145.0)	140.0 (136.0−145.0)	140.0 (136.0−145.0)
Potassium (mmol/L)	4.0 (3.5−4.6)	3.7 (3.3−4.3)	3.8 (3.4−4.4)
Chloride (mmol/L)	104.0 (99.0−109.0)	104.0 (99.0−109.0)	104.0 (99.0−109.0)
Blood urea nitrogen (mg/dL)	15.0 (8.0−26.0)	16.0 (10.0−23.0)	16.0 (9.0−24.0)
Creatinine (mg/dL)	0.6 (0.4−0.9)	0.6 (0.4−0.8)	0.6 (0.4−0.9)
Glucose (mg/dL)	127.0 (94.0−202.0)	138.0 (101.0−183.0)	135.5 (98.0−188.0)
Albumin (g/dL)	2.7 (2.1−3.2)	2.6 (2.2−3.2)	2.6 (2.2−3.2)
Alkaline phosphatase (IU/L)	118.0 (83.0−154.5)	119.5 (76.0−199.0)	118.5 (80.0−174.0)
Alanine aminotransferase (IU/L)	36.0 (18.0−99.0)	30.5 (21.0−54.0)	32.0 (20.0−68.0)
Aspartate aminotransferase (IU/L)	92.5 (44.5−320.5)	66.0 (35.0−130.0)	71.5 (39.0−180.0)
Total bilirubin (mg/dL)	2.3 (1.0−4.3)	2.0 (0.6−5.2)	2.2 (0.7−4.6)

IQR = interquartile range, IU = international units.

failure and eCPR respectively accounted for 40% and 14% of the total. Overall mortality for venovenous ECMO was significantly lower than for venoarterial ECMO (30% vs 48%; $p = 0.003$).

Univariable analysis and missingness of candidate variables included in the PEP model prior to and after imputation are found in **Table 3**, with a complete list of candidate variables found in **Supplemental Table 4** (Supplemental Digital Content 4, http://links.lww.com/PCC/A907). Variables excluded because they were missing after imputation, that is, not applicable in greater than 10% of the cohort were vital signs (mean, systolic, and diastolic arterial blood pressure and heart rate) as these were not applicable in eCPR subjects (14%); baseline ventilator settings were not applicable in nonintubated subjects (13%). Indication for ECMO of the nonintubated patients were respiratory 1.4%, cardiac 8.4%, and eCPR 3.5%.

Similarly, indices using Pao_2 were excluded as they were not relevant in patients with congenital heart disease with the potential of intracardiac shunting (56%). Of these excluded variables only mean arterial pressure was associated with mortality by univariate analysis ($p = 0.024$) but was not significant by multivariate analysis using full case selection. An analysis performed excluding subjects who received eCPR also found that vital signs were not independently predictive of mortality.

Table 4 displays the PEP model. The variables retained after final multiple logistic regression analysis included age (preterm neonate, full-term neonate, infant, child, and adolescent), indication for ECMO, meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), D-BSI, pH in arterial blood, activated partial thromboplastin time (aPTT), and INR. The highest risk of mortality was associated with D-BSI (odds ratio [OR], 5.26; CI, 1.90–14.57) followed by eCPR (OR, 4.36;

TABLE 3. Univariable Analyses of Preextracorporeal Membrane Oxygenation Candidate Predictors of In-Hospital Mortality Included in the Multivariable Model

	In-hospital mortality			
Variables	OR (95% CI)	p	% Missing Pre-Imputation	% Missing Post-Imputation
Primary extracorporeal membrane oxygenation indication		< 0.001	0	0
Respiratory	Reference			
Cardiac	1.91 (1.30–2.80)			
Extracorporeal cardiopulmonary resuscitation	3.14 (1.81–5.46)			
Age		0.001	0	0
Pre-term neonate	3.71 (1.93–7.15)			
Full-term neonate	Reference			
Infant	1.75 (1.11–2.74)			
Child	1.43 (0.85–2.40)			
Adolescent	1.67 (0.88–3.19)			
Acute diagnoses				
Congenital diaphragmatic hernia	2.03 (1.15–3.58)	0.014	0	0
Meconium aspiration syndrome	0.10 (0.03–0.28)	< 0.001	0	0
Infection				
Level of evidence				
Documented	1.34 (0.83–2.16)	0.233	0	0
Pathogen				
Bacterial	1.82 (0.99–3.37)	0.055	0	0
Viral	0.70 (0.35–1.43)	0.327	0	0
System				
Blood	3.71 (1.54–8.93)	0.003	0	0
Respiratory	0.80 (0.46–1.41)	0.442	0	0
Other	2.44 (0.22–27.12)	0.467	0	0
Labs				
pH	0.32 (0.10–1.02)	0.054	18	0
Partial thromboplastin time (s)	1.13 (1.04–1.22)	0.003	36	0
International normalized ratio	1.99 (1.36–2.90)	< 0.001	37	0

OR = odds ratio.

Five-hundred fourteen records were analyzed in models for in-hospital mortality. Analysis based on nonimputed data.

CI, 2.23–8.51). In contrast, a diagnosis of MAS was protective (OR, 0.18; CI, 0.05–0.63).

A total of 27 subjects had D-BSI prior to ECMO. Mortality by infection type was 14 of 20 bacterial, four of five viral, and two of two fungal. Of the seven survivors, four used venoarterial ECMO. The most common organisms isolated in the blood stream were *Staphylococcus aureus* (*n* = 4) and *Streptococcus pneumoniae* (*n* = 4) followed by adenovirus and *Escherichia coli* (*n* = 2 each). Both patients with adenovirus had chronic immune dysfunction. Only one subject grew *Staphylococcal epidermidis*. Fevers occurred in equal proportions (8%) of those with and without a D-BSI prior to ECMO. The median time from blood culture last drawn to cannulation for those with D-BSI was 22.3 hours (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/PCC/A905).

The *C*-statistic was 0.75 (95% CI, 0.70–0.80) and the Hosmer-Lemeshow *p* value was 0.94, indicating modest model discrimination. When evaluating subjects without imputed data

TABLE 4. Multivariable Model of In-Hospital Mortality

Variables	OR (95% CI)	p
Indication for ECMO		< 0.001
Extracorporeal cardiopulmonary resuscitation	4.36 (2.23–8.51)	
Cardiac	2.42 (1.46–4.02)	
Respiratory	Reference	
Age		0.031
Pre-term neonate	3.10 (1.52–6.33)	
Full-term neonate	Reference	
Infant	1.47 (0.87–2.48)	
Child	1.11 (0.60–2.07)	
Adolescent	1.44 (0.67–3.07)	
Congenital diaphragmatic hernia	3.11 (1.49–6.49)	0.002
Meconium aspiration syndrome	0.18 (0.05–0.63)	0.007
Baseline pH in arterial blood	0.22 (0.06–0.80)	0.022
Partial thromboplastin time (increase of 10 s)	1.07 (1.00–1.14)	0.048
International normalized ratio	1.45 (0.95–2.23)	0.085
Documented blood infection prior to ECMO	5.26 (1.90–14.57)	0.001

ECMO = extracorporeal membrane oxygenation, OR = odds ratio.

Estimated probability of mortality is $p = e^x/(1 + e^x)$, where x = 9.081 + 0.887 (indication = cardiac) + 1.468 (indication = extracorporeal cardiopulmonary resuscitation) + 1.132 (age = pre-term neonate) + 0.378 (age = infant) + 0.109 (age = child) + 0.360 (age = adolescent) + 1.138 (congenital diaphragmatic hernia) − 1.710 (meconium aspiration syndrome) − 1.534 (pH in arterial blood) + 0.0064 (partial thromboplastin time [s]) + 0.357 (international normalized ratio) + 1.659 (documented blood infection) is the log odds of mortality from the multivariable model. Using leave-one-out cross validation to prevent small-sample bias, the area under the receiver operating characteristic curve is 0.75 (0.70–0.80).

(complete case analysis; $n = 298$), the C-statistic improved only to 0.78. The prediction equation for probability of mortality is $p = e^x/(1 + e^x)$, where x = 9.081 + 0.887 (indication = cardiac) + 1.468 (indication = eCPR) + 1.132 (age = pre-term neonate) + 0.378 (age = infant) + 0.109 (age = child) + 0.360 (age = adolescent) + 1.138 (CDH) − 1.710 (MAS) − 1.534 (pH in arterial blood) + 0.0064 (aPTT) + 0.357 (INR) + 1.659 (D-BSI) is the log odds of mortality from the multivariable model. An online calculator is available at www (domain to be provided following manuscript acceptance).

Figure 1 displays the distribution of patients across the estimated risk of mortality and the calibration plot for observed to expected mortality demonstrating good calibration across all risk categories, notably including the lowest and highest.

DISCUSSION

The PEP prognostic model provides an in-hospital mortality prediction model for all respiratory, cardiac, or eCPR ECMO candidates less than 19 years old. Of all currently existing pediatric ECMO risk adjustment models, only Neo-RESCUERS, which is limited to neonates with respiratory failure, has a higher C-statistic (0.75 vs 0.78).

The PEP model is unique from previously published models because of the omnibus approach of incorporating "all" pediatric subjects who received ECMO for any indication, including eCPR subjects. Our model allows for centers to benchmark performance using all patients who receive ECMO. Additionally, we identified three unique covariates associated with mortality: INR, aPTT, and D-BSI. Commensurate with prior publications, we found patient age, ECMO mode, neonatal diagnoses of MAS or CDH, and severity of acidosis pre-ECMO to be associated with mortality (2, 5, 14–16).

The odds of death conferred from a D-BSI in the PEP model exceeded all other variables. The antibiotic status of those with a D-BSI prior to ECMO is unknown, suggesting that perhaps source control prior to ECMO could be improved. Only one patient grew a coagulase-negative staphylococcus organism suggesting that the infections were not merely contaminants. Usual screening methods such as fevers and leukocytosis may be insufficient given that fevers were not a sensitive marker for D-BSI, and WBC count was not independently associated with mortality. Additionally, studies evaluating the physiologic benefits and ECMO practices in the setting of blood stream infections including the variation related to antibiotic use and rapid screening is warranted.

The use of ECMO to reverse cardiac arrest is mechanistically plausible as ECMO restores both perfusion and oxygenation. The benefit of ECMO in the setting of infection is less clear given that the mainstay of treatment for infection is source control which may be more difficult to achieve and maintain on ECMO.

In prior studies, hepatic failure has been associated with greater mortality (2, 5). It remains unknown whether attempts to
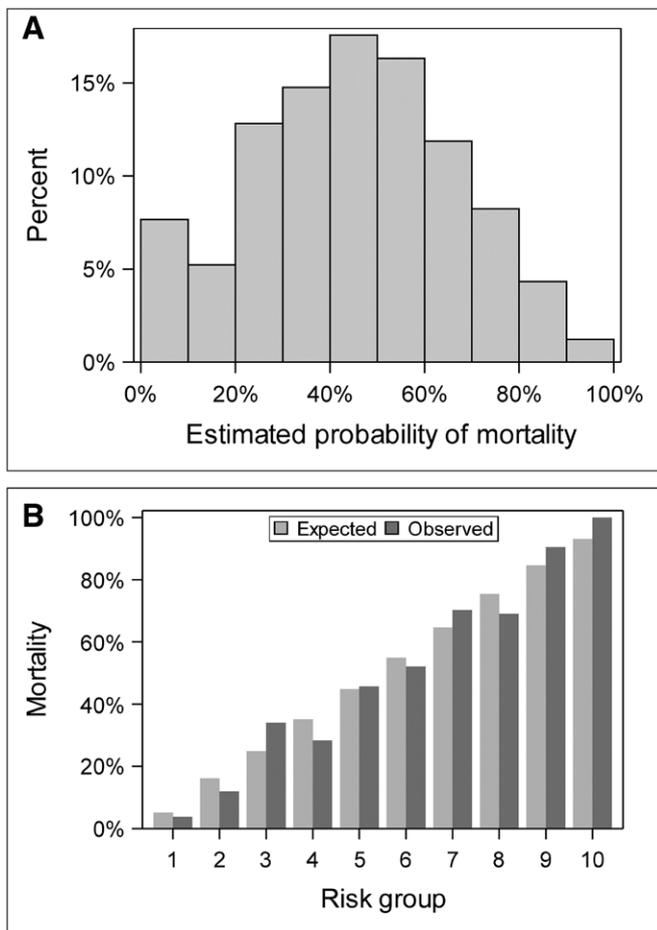
Figure 1. Distribution of estimated probability of mortality (**A**) and the calibration plot for observed to expected mortality by risk group (**B**). An even distribution and good calibration is demonstrated across all risk groups.

normalize these prolonged clotting tests prior to ECMO initiation would alter the increased mortality risk; however, these data suggest that early and deliberate screening for pre-ECMO liver injury using INR and aPTT may improve pre-ECMO risk stratification.

Due to missingness greater than 10% after imputation, the PEP model notably excludes some variables that are clinically appealing or have been predictive in prior models including measures of oxygenation and vital signs. It is important to remember that oxygenation is largely determined by the clinician's preference for escalating support and is not driven by protocol. Furthermore, vital signs in the setting of sedation and interventions such as dexmedetomidine and cooling do not accurately reflect the patient's state or degree of illness. Nonetheless, we did perform a separate multivariate analysis using only full case selection to allow for inclusion of vital signs which also demonstrated no significant association with mortality.

Implications

The value of the PEP model is that it can be applied to all pediatric ECMO patients without excluding for age or ECMO indication. Thus, it may afford improved discrimination into the center-specific processes that influence survival across cohorts that are currently not evaluated with existing models

as well as anticipate and benchmark mortality for similar ECMO cohorts (10, 11, 36).

The PEP model performance decreases from 0.75 to 0.73 (95% CI, 0.69–0.77; $p < 0.05$) when using only variables available in the ELSO registry at time of model development (age, indication, CDH, MAS, D-BSI, and baseline arterial pH) suggesting that the collection of pre-ECMO aPTT and INR could improve calibration of risk among ELSO centers. External validation using the ELSO registry and prospective validation is warranted.

Limitations

The results must be interpreted within the limitations of the study design. First, because there is no comparison database of non-ECMO patients with similar illnesses, the findings only apply to pediatric cohorts for whom ECMO is chosen as a therapy and is not intended for individual patient predictions or selection for ECMO. Second, the model is limited to covariates available in the BATE database. Therefore, it is possible that other nonmeasured exposures such as antibiotic use might serve as better predictors or were covariants with variables included in our model. For example, center infrastructure covariates were not analyzed (20). Third, misclassification may have been introduced because many of the diagnostic categories used lack explicit definitions. Fourth, a larger sample size may detect a mortality difference across centers (36–38). Fifth, the data collection concluded in 2014 and calibration over time will be required given that pre-ECMO care and patient factors continue to evolve (2, 5).

Finally, missingness prior to imputation was not proportional across all variables, and therefore, may not have been missing at random. Vital signs were not included in the final model because they were not recorded during eCPR which represented greater than 10% of subjects; however, none of them were independently predictive by multivariate analysis using full case selection or after excluding patients who received eCPR. The finding that the *C*-statistic using full case selection was relatively similar to the findings using the imputed data (0.75 vs 0.78) further mitigates the concerns related to the missingness of values and the use of imputation.

CONCLUSIONS

The PEP model represents a model to prognosticate in-hospital mortality for all patients less than 19 years old who receive ECMO for any indication. Because it is not limited to any narrow group of patients (e.g., neonates with respiratory failure), it can be applied to all patients at a single institution or across institutions which is a current limitation of all existing models. It expands upon current models by including commonly monitored variables not previously available in the ELSO registry such as INR and aPTT. Consequently, it is anticipated that the model will be most useful for risk stratifying patient-specific features that influence ECMO mortality in order to improve benchmarking of ECMO performance.

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