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Permalink https://escholarship.org/uc/item/2mn4n59j

**Journal** ASAIO Journal, 64(6)

**ISSN** 1058-2916

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Publication Date 2018-11-01

## DOI

10.1097/mat.0000000000000716

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Peer reviewed

# Development and Validation of Extracorporeal Membrane Oxygenation Mortality-Risk Models for Congenital Diaphragmatic Hernia

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The purpose of our study was to develop and validate extracorporeal membrane oxygenation (ECMO)-specific mortality risk models for congenital diaphragmatic hernia (CDH). We utilized the data from the Extracorporeal Life Support Organization Registry (2000-2015). Prediction models were developed using multivariable logistic regression. We identified 4,374 neonates with CDH with an overall mortality of 52%. Predictive discrimination (C statistic) for pre-ECMO mortality model was C = 0.65 (95% confidence interval, 0.62–0.68). Within the highest risk group, based on the pre-ECMO risk score, mortality was 87% and 75% in the training and validation data sets, respectively. The pre-ECMO risk score included pre-ECMO ventilator settings, pH, prior diaphragmatic hernia repair, critical congenital heart disease, perinatal infection, and demographics. For the on-ECMO model, mortality prediction improved substantially: C = 0.73 (95% confidence interval, 0.71-0.76) with the addition of on-ECMO-associated complications. Within the highest risk group, defined by the on-ECMO risk score, mortality was 90% and 86% in the training and validation data sets, respectively. Mortality among neonates with CDH needing ECMO can be reliably predicted with validated clinical variables identified in this study. ECMO-specific mortality prediction tools can allow

Submitted for consideration June 2017; accepted for publication in revised form October 2017.

Disclosure: The authors have no conflicts of interest to report.

This work was supported fully by CHOC/Pediatric Subspecialty Faculty (PSF) Tithe Award and partially by grant UL1 TR001414 from the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), through the Biostatistics, Epidemiology and Research Design Unit University of California Irvine. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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DOI: 10.1097/MAT.000000000000716

risk stratification to be used in research and quality improvement efforts, as well as with caution for individual case management. *ASAIO Journal* 2018; 64:785–794.

#### Key Words: ECMO, CDH, mortality risk, risk score

Despite advances in neonatal care, the mortality rate of infants with congenital diaphragmatic hernia (CDH) treated with extracorporeal membrane oxygenation (CDH-ECMO population) has remained unchanged.<sup>1,2</sup> Accurate discrimination of disease severity in the CDH-ECMO population is required to test and improve current treatment strategies. Mortality risk prediction equations developed for the general CDH population do not discriminate well within the ECMO cohort.3-7 In 2008, Haricharan et al.8 reported a CDH-ECMO mortality prediction score using Extracorporeal Life Support Organization (ELSO) Registry data. The Haricharan score included demographic variables, on-ECMO variables, and support duration >15 days, modeled together as an on-ECMO mortality risk model.8 The Haricharan model has not been externally validated and has not been adopted as a clinical or a research tool. Additional data have since been collected by the ELSO Registry to develop more robust risk models that predict mortality separately before ECMO and during ECMO. More recently, neonatal risk estimate score for children using extracorporeal respiratory support (Neo-RESCUERS) and Pittsburgh index for pre-ECMO risk (PIPER) mortality prediction models were developed inclusive of all neonatal conditions receiving respiratory ECMO.<sup>1,9</sup> However, Neo-RESCUERs and PIPER were not specifically developed for CDH nor validated specifically in a CDH-specific data set. It is well established that CDH has the greatest mortality rate of all other neonatal conditions requiring respiratory ECMO. Furthermore, treatment of CDH with ECMO is inherently more complex given the anatomic complexities associated with herniation of intra-abdominal contents to the thorax and the surgical treatment that is needed to repair the diaphragmatic defect. For all those reasons, we sought to develop and validate ECMO mortality risk models specific for the CDH population.

Given that ECMO is an invasive treatment, ECMO mortality prediction models are most informative when designed to provide mortality risk before exposure to ECMO and then at any time point while the patient is receiving extracorporeal life support. We hypothesized that two separate models would prove to be most relevant in predicting mortality risk associated with ECMO in the CDH population: 1) before initiation of ECMO, and 2) during the course of ECMO. Two separate models were developed to analyze the initial risk mortality associated with ECMO and the risk while on-ECMO. We took into account the possible contributions of pre-ECMO rescue therapies, anatomic variations of CDH, timing of diaphragm repair, comorbidities, ECMO complications, and length of ECMO. Although bedside

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usefulness of such models should never replace clinical acumen, mortality risk models are useful when analyzing and benchmarking patient outcomes and assessing the value of programmatic changes. The ability to benchmark against known pre-ECMO risk and demonstrating a lower on-ECMO risk is the ultimate goal of proving good ECMO therapy. This is why we believed it was critical to provide risk models that sought to independently predict risk of mortality before and during ECMO.

#### **METHODS**

#### Data Source and Cohort

The Children's Hospital Orange County institutional review board approved this study (No. 150969). We queried the ELSO Registry data for neonates whose primary diagnosis was CDH from 2000 to 2015. We omitted data from before 2000 to limit the data to the most current treatment practices. We searched ELSO Registry for secondary international classification of diseases, ninth revision (ICD-9) diagnoses codes to establish dichotomous variables to identify complications/comorbidities. Candidate predictors evaluated for models were selected based on clinical considerations and previous studies.<sup>2,3,6–8,10–16</sup>

#### Candidate Variables

For the pre-ECMO model, we considered the following demographic variables, including gender, pre-ECMO weight, race, gestational age (GA), post-GA, 5 min Apgar, side of CDH, prenatal diagnosis of CDH, CDH repair before ECMO, handbagging, and pre-ECMO arrest; blood gas/ventilator variables included pH,  $pCO_2$  and  $pO_2$ , mean airway pressure (MAP), oxygenation index; pre-ECMO therapies included inotropes, bicarbonate/tromethamine, inhaled nitric oxide, surfactant, neuromuscular blockers, milrinone, sildenafil and steroids; comorbidity variables included critical congenital heart disease, <sup>17,18</sup> multiple congenital anomalies, chromosomal anomalies, perinatal infection, and air leak.

For the on-ECMO model, we identified additional variables including repair of diaphragmatic hernia on-ECMO and ECMO duration, ECMO mode (venoarterial and venovenous)<sup>2</sup> and pump type, and comorbidities including peritonitis, sepsis, and airleak syndrome. We grouped complications by systems or used them individually depending on clinical relevance: mechanical, hemorrhagic (excluding pulmonary hemorrhage which was used independently), cardiac (including stun, tamponade, and need for cardiopulmonary resuscitation (CPR), infectious (positive cultures and white blood cell < 1500), and endocrine complications (glucose < 40 and >240) were grouped. Neurologic complications were divided into seizures (clinical and electrographic) and severe neurologic complications (central nervous system (CNS) hemorrhage, infarct, intraventricular hemorrhage grade 3 and 4); renal complications were separated into two elevated creatinine groups (1.5-3 and >3) and dialysis (hemofiltration, CAVHD).

#### Exclusion Criteria and Missing Values

We excluded patients with missing sex and ECMO mode. We reported results based on mean imputation to address missing values in  $5 \min \text{Apgar}$ , pCO<sub>2</sub>, pO<sub>2</sub>, OI, and duration of ECMO.

Sensitivity analyses were conducted using multiple imputation (10 imputations) as well as on complete data. Missing values in pre-ECMO weight (2.4%) were imputed based on a regression model of nonmissing weight with birth weight (BW) and age (days) as independent variables. Similarly, missing values in GA (4.5%) were imputed based on decile groups of BW. The Henderson–Hasselbalch equation was used to calculate missing pH (3.5%), given known HCO<sub>3</sub> and pCO<sub>2</sub>. MAP (10.2%) was imputed based on a clinical formula as a function of peak inspiratory pressure, respiratory rate, and positive end expiratory pressure. OI was calculated as OI = [(fio<sub>2</sub>×MAP)/pO<sub>2</sub>)], and missing values (10.2%) were obtained using mean imputation.

#### Statistical Methods

The outcome of the prediction models was inpatient mortality during or after ECMO. Patient characteristics were provided as means ± standard deviation (SD) or proportions for continuous and categorical variables, respectively. Prediction scores were developed separately for pre-ECMO and on-ECMO models. The cohort (N = 4,374) was randomly divided into a two-thirds training/development set  $(N_d = 2,912)$  and a onethird test/validation set ( $N_v = 1,462$ ). Prediction models were developed using multivariable logistic regression models. The final models with reduced number of predictors were obtained using backward selection based on the Akaike information criterion.<sup>19</sup> We estimated a linear shrinkage factor ( $\gamma$ ) using the bootstrap method (with 2000 bootstrap replications) applied to the development data set to assess potential model overfitting (optimism).<sup>19–22</sup> The shrinkage factor  $\gamma$  was used to adjust the final prediction models to correct for model over-optimism. Overall model calibration was assessed by the Hosmer-Lemeshow goodness-of-fit test and examination of calibration plots.

Model predictive performance or discrimination was assessed using the C statistic (area under the receiver operating characteristic curve (ROC) curve) on the one-third validation set. The final prediction models (pre- or on-ECMO) were used to estimate the predicted probabilities of death given the characteristics of a new patient given their calibrated risk score (RS), RS =  $\gamma X\beta$ , where X represents patient variables,  $\beta$  are the final model coefficients, and  $\gamma$  is the shrinkage factor. The predicted probability for a new patient was  $1/(1 + e^{-RS})$ . Furthermore, we explored five clinical risk groups (RGs) based on percentiles of the RS (lowest 5%, 5%-25%, 25%-75%, 75%-95%, and highest 5%). The observed mortality in each of the five RGs was assessed in the validation set. Finally, we examined summary statistics of the predictor variables in the five clinical RGs to further understand and identify salient features of patients in each RG. Analyses were performed in R version 3.22 using library RMS and SAS version 9.3.

#### RESULTS

#### **Baseline Characteristics**

Baseline characteristics of the cohort are provided in **Table 1**. The majority were male and white race. The mean pre-ECMO weight was  $3.07 \pm 0.52$  kg and GA was  $38.1 \pm 1.71$ . Average age at cannulation exceeded 2 days, and ECMO duration was nearly 12 days. Overall, mortality reached 52.4% (2291 deaths). Summary of all predictor variables, including pre-ECMO blood gas, ventilator settings, rescue therapies,

#### CDH ECMO RISK SCORE

|--|

Table 1. Predicto	r Variables, In	cluding Baseline	Patient Characteristics
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Protection     Display	Recipients' Characteristics	Entire Cohort (n=4,374), Mean (SD)/Count (%)	Development Set (N=2,912), Mean (SD)/Count (%)	Validation Set (N=1,462), Mean (SD)/Count (%)
Important     Important <t< td=""><td>Pro FOMO</td><td></td><td></td><td>()</td></t<>	Pro FOMO			()
Construction     2222 (\$7.7%)     1688 (68.0%)     3.07 (0.52)     3.05 (0.51)       Race/ethnicity, %     2600 (60.8%)     17.78 (61.1%)     882 (60.3%)       Hispanic     7.77 (17.3%)     5.11 (7.7.5%)     248 (16.3%)       Black     5.22 (12.6%)     3.61 (12.4%)     191 (13.1%)       Gentational age     3.81 (1.71)     3.81 (12.4%)     191 (13.1%)       Apgar at 5 min     6.22 (1.98)     6.23 (1.97)     5.16 (9.7.2%)       Side of hernia     2.33 (3.88)     2.37 (3.97)     2.41 (5.67)       Left     3.17 (7.2.6%)     211 (7.2.8%)     3.93 (1.8%)       Missing     144 (21.6%)     7.83 (1.9.3%)     3.93 (2.7.5%)       Missing     144 (21.6%)     7.83 (1.8.9%)     7.8 (6.9.9%)       Diaphragmatic hernia fixed before ECMO     3.82 (27.6%)     2.41 (3.8%)     7.8 (6.9.9%)       No     3.82 (27.6%)     2.23 (8.1%)     10.6 (6.9.9%)     1218 (8.3.3%)       Yes     2.42 (9.2.9%)     2.41 (8.0.3%)     7.8 (6.9.9%)     13.0 (7.9.8%)       Missing     3.82 (27.7%)     2.83 (8.2.1%)     10.6 (8.4.4%)     14.3 (8.9.8%) <	Pre-ECIMO Demographics			
Weight (pin-ECMO)     3.07 (0.52) <sup>-1</sup> 3.07 (0.52) <sup>-1</sup> 3.07 (0.52) <sup>-1</sup> Multis     260 (00.3%)     1778 (61.1%)     882 (00.3%)       Hispanic     757 (17.3%)     511 (77.5%)     246 (63.8%)       Black     552 (12.6%)     361 (12.4%)     149 (13.1%)       Other     828 (0.5%)     428 (14.9%)     143 (14.8%)       Adjour at 5 min     8.22 (1.98)     2.37 (13.97)     2.41 (8.67)       Side of hernia     3175 (72.6%)     2119 (72.8%)     316 (72.2%)       Post gestational age (days)     2.38 (3.89)     2.37 (13.97)     2.41 (8.67)       Side of hernia     112 (2.4%)     622 (21.5%)     319 (72.5%)     316 (72.2%)       Bath     1.12 (2.4%)     73 (2.4%)     37 (2.5%)     318 (8.2%)     37 (0.5%)     37 (2.5%)     318 (8.4%)     37 (0.5%)     318 (8.4%)     30 (8.2%)     37 (8.6%)     37 (2.5%)     318 (8.4%)     38 (8.2%)     32 (2.5%)     1218 (8.3%)     36 (8.2%)     36 (8.2%)     36 (8.2%)     36 (8.2%)     36 (8.2%)     36 (8.2%)     37 (8.9%)     37 (8.9%)     37 (8.9%)     37 (8.9%)     36 (8.2.9%)	Gender (% male)	2522 (57.7%)	1688 (58.0%)	834 (57.0%)
Receiverthicity, %     Construction     Construction     Construction     Construction       White     2660 (60.856)     17.75 (61.173)     B82 (60.39)       Black     552 (12.396)     511 (17.396)     198 (16.195)       Black     652 (12.696)     361 (12.479)     143 (8.48%)       Other     405 (9.396)     262 (1.097)     2.41 (1.67)       Acguar at min alge (days)     5.22 (1.980)     622 (1.97)     2.41 (1.67)       Side of homina     2.38 (3.880)     2.37 (3.57)     2.41 (1.67)       Side of homina     112 (2.6%)     622 (1.57)     3.19 (2.7)       Bit     112 (2.6%)     623 (1.57)     3.14 (2.67)       Hight     944 (21.6%)     623 (1.57)     319 (7.2%)       Both     112 (2.6%)     623 (1.57)     91 (8.83 .3%)       Missing     313 (7.7%)     237 (8.1%)     101 (8.3%)       No     343 (8.2%)     233 (8.1%)     101 (8.3%)       Yes     226 (6.2%)     138 (8.49)     33 (8.49)       No     3447 (32.5%)     238 (3.27)     344 (8.3.3%)       No <t< td=""><td>Weight (pre-ECMO)</td><td>3.07 (0.52)</td><td>3.07 (0.52)</td><td>3.05 (0.51)</td></t<>	Weight (pre-ECMO)	3.07 (0.52)	3.07 (0.52)	3.05 (0.51)
White     2660 (06.8%)     1776 (61.1%)     B82 (06.3%)       Hispanic     757 (17.3%)     511 (17.5%)     246 (16.8%)       Black     552 (12.6%)     361 (12.4%)     143 (18.4%)       Gestational age     33 (17.1)     36.1 (1.27)     83.0 (1.89)       Abar at 5 mil age (days)     2.26 (2.8%)     2.27 (3.97)     50.0 (7.2%)       Side of herria     3175 (72.6%)     2119 (72.8%)     1056 (72.2%)       Right     944 (21.6%)     625 (1.5%)     371 (2.5%)       Both     112 (2.6%)     75 (2.6%)     372 (2.5%)       Prenatal diagnosis     2267 (60.7%)     2008 (62.6%)     178 (64.8%)       Diagranatic hernia fixed before ECMO     3023 (82.8%)     204 (62.2%)     148 (64.9%)       Ves     226 (52.5%)     161 (5.5%)     50 (64.9%)       Missing     388 (7.7%)     237 (81.9%)     104 (83.9%)       Ves     246 (52.9%)     161 (5.5%)     66 (4.4%)       Maising     231 (2.7%)     236 (2.3%)     132 (4.3%)       Missing     33.2 (2.80.0)     33.0 (2.9.3)     33.2 (3.6)       Yes	Race/ethnicity. %	0.01 (0.02)	0.01 (0.02)	
Hispanic     757 (17.3%)     611 (17.5%)     246 (16.8%)       Black     552 (12.6%)     361 (12.4%)     191 (13.1%)       Other     405 (9.3%)     262 (9.0%)     143 (9.8%)       Gestational age     351 (17.1)     36.1 (1.72)     86.08 (1.69)       Post gestational age (days)     2.28 (3.88)     2.237 (3.37)     2.41 (3.67)       Stat gestational age (days)     2.236 (3.88)     2.216 (3.98)     1056 (72.2%)       Flight     944 (21.6%)     75 (2.6%)     319 (21.8%)       Bath     112 (2.6%)     75 (2.6%)     37 (2.5%)       Missing     143 (3.3%)     93 (3.2%)     50 (3.4%)       Prentatal diagnosis     2867 (66.0%)     1909 (65.6%)     978 (66.9%)       No     3623 (82.8%)     2406 (82.6%)     101 (6.9%)     104 (93.8%)       Ves     226 (52%)     161 (5.5%)     103 (6.9%)     103 (8.9%)       Ves     226 (52%)     161 (5.5%)     36 (2.4%)     30 (8.9%)       Ves     226 (5.2%)     161 (5.5%)     36 (2.2.5)     36 (2.2.5)       Masing     101 (2.3%)     82 (2.7.5	White	2660 (60.8%)	1778 (61.1%)	882 (60.3%)
Black     552 (12.6%)     361 (12.4%)     191 (13.1%)       Other     405 (635%)     262 (9.0%)     143 (9.8%)       Gestational age     36.1 (1.71)     36.1 (1.72)     38.08 (1.69)       Apgar at 5 min     6.22 (1.49)     6.23 (1.67)     6.16 (2.01)       Note of gestational age (days)     2.38 (3.88)     2.37 (3.97)     2.41 (3.67)       Side of hermia     112 (2.6%)     75 (2.5%)     37 (2.5%)       Both     112 (2.6%)     75 (2.5%)     37 (2.5%)       Prenatal diagnosis     2887 (66.0%)     199 (65.6%)     97 (66.5%)       No     362 (82.8%)     2405 (82.6%)     1218 (83.3%)       Yes     413 (9.4%)     270 (9.3%)     143 (8.8%)       Missing     388 (7.7%)     297 (8.1%)     101 (6.9%)       Missing     110 (2.3%)     68 (2.3%)     38 (2.3%)       Pater Arrance bardore ECMO     361 (8.3%)     231 (7.9%)     101 (6.9%)       Pre-ECM blood gas     71.7 (0.17)     7.17 (0.17)     7.18 (0.17)       p.O.     68.6 (27.76)     68.8 (27.5%)     38 (2.3%)       Pre-ECM ventilat	Hispanic	757 (17.3%)	511 (17.5%)	246 (16.8%)
Other     405 (9.3%)     262 (0.0%)     143 (9.8%)       Gestational age     38.1 (1.71)     38.1 (0.72)     38.0 (0.16)       Post gestational age (days)     2.38 (2.88)     2.37 (3.97)     2.41 (3.67)       Side of herria     175 (72.6%)     2119 (72.8%)     1056 (72.2%)       Laft     917 (72.6%)     625 (2.5%)     310 (71.8%)       Hight     944 (21.6%)     625 (2.5%)     310 (71.8%)       Missing     143 (3.3%)     93 (2.5%)     50 (2.4%)       Pronatal diagnosis     2280 (60.0%)     1999 (65.6%)     1218 (63.3%)       Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)       Yes     413 (0.4%)     7270 (3.3%)     143 (0.8%)       Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)       Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)       Vas     226 (5.2%)     268 (92.1%)     1364 (93.3%)       Yas     226 (5.2%)     268 (92.1%)     136 (8.48)       Masing     101 (2.3%)     68 (92.7%)     53 (2.3%)       Yas     222 (2.0.0)     39.0	Black	552 (12.6%)	361 (12.4%)	191 (13.1%)
Gestational age     38.1 (1.71)     38.1 (1.72)     38.09 (1.69)       Apgar at 5 min     6.22 (1.99)     6.23 (1.97)     6.19 (2.01)       Post gestational age (days)     2.38 (3.89)     2.37 (3.97)     2.41 (3.67)       Loft     3175 (72.99)     2119 (72.976)     316 (71.976)     316 (71.976)       Loft     3175 (72.996)     219 (72.976)     317 (1.977)     316 (1.976)       Missing     143 (3.376)     93 (2.276)     37 (1.987)     50 (3.476)       Prenatal (dagnosis     2857 (160.976)     210 (66.976)     1218 (63.376)     108 (1.9376)       No     3623 (82.986)     2405 (82.676)     1218 (83.376)     104 (83.376)     104 (83.376)       Missing     338 (7.776)     270 (1.376)     108 (1.9376)     143 (8.496)     104 (82.9376)     136 (82.376)       Missing     226 (5.256)     168 (62.2376)     138 (8.196)     33 (3.376)     33 (3.376)     33 (3.376)       ProteCMO sociagas     7.17 (0.17)     7.17 (0.17)     7.17 (8.017)     138 (8.196)     33 (2.876)       Missing     3192 (73.096)     2116 (72.796)     168 (2.676)	Other	405 (9.3%)	262 (9.0%)	143 (9.8%)
Apgar at 5 min     6.22 (1.98)     6.23 (1.97)     6.19 (2.01)       Pest gestational age (days)     2.38 (3.88)     2.37 (3.87)     2.41 (3.67)       Left     3175 (72.6%)     2119 (72.8%)     315 (21.8%)       Both     112 (2.6%)     6.25 (21.5%)     315 (21.8%)       Both     12 (2.5%)     75 (2.5%)     37 (2.5%)       Prestati diagnosis     2.887 (60.9%)     1009 (6.6%)     978 (66.9%)       Diaphorgmatic hernia fixed before ECMO     383 (7.7%)     237 (8.1%)     101 (6.9%)       Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)       Missing     101 (2.3%)     88 (2.3%)     33 (2.3%)       Patient arrested before ECMO     331 (8.3%)     231 (7.7%)     33 (2.3%)       Patient arrested before ECMO     331 (8.3%)     231 (7.7%)     33 (2.3%)       Patient arrested before ECMO     331 (2.7%)     30 (2.9%)     33 (2.3%)       Poc.     92 2 (20.00)     39.06 (23.8)     35 (7.8%)     33 (2.3%)       Patient arrested before ECMO     318 (2.7%)     107 (7.7 (3.6%)     107 (7.7 (3.6%)       MAP     64.80 (7.7%)	Gestational age	38.1 (1.71)	38.1 (1.72)	38.09 (1.69)
Post gestational age (days)     2.38 (3.89)     2.37 (3.97)     2.41 (3.67)       Left     3175 (72.6%)     2119 (72.8%)     1066 (72.2%)       Both     112 (2.6%)     75 (2.6%)     37 (2.5%)       Missing     113 (2.3%)     33 (3.2%)     50 (3.4%)       Prenatal diagnosis     2867 (66.0%)     1909 (65.6%)     1718 (63.3%)       No     433 (9.4%)     270 (9.3%)     143 (9.8%)       Ves     2265 (56.0%)     237 (8.1%)     101 (6.9%)       Handbagging     338 (7.7%)     231 (7.9%)     136 (4.83.3%)       No     4047 (92.5%)     268 (92.1%)     136 (4.9%)     136 (4.9%)       PrescMO bood gas     7     7.17 (0.17)     7.17 (0.17)     7.18 (0.17)       PH     7.17 (0.17)     7.17 (0.17)     7.18 (0.17)     16.6 (4.4%)       pCO_     68.86 (2.76)     68.29 (2.56)     68.79 (2.8.16)     99.5 (2.8.6)     39.5 (2.8.3)       PH     7.17 (0.17)     7.17 (0.17)     7.18 (0.17)     16.6 (4.48)     10.6 (2.9.36)     39.5 (28.29)       PGC     68.36 (2.76)     68.39 (2.56)     68.79	Apgar at 5 min	6.22 (1.98)	6.23 (1.97)	6.19 (2.01)
Side of hernia     1eft     3175 (72.6%)     2119 (72.8%)     1056 (72.2%)       Right     944 (21.6%)     625 (21.5%)     319 (21.8%)       Both     112 (2.6%)     75 (2.6%)     57 (2.5%)       Missing     143 (3.3%)     93 (3.2%)     50 (3.4%)       Diaphragmatic hernia fixed before ECMO     8623 (82.8%)     2405 (82.6%)     1218 (83.3%)       No     3623 (82.8%)     2405 (82.6%)     1248 (83.3%)       Yes     413 (3.4%)     270 (2.5%)     146 (9.8%)       Hindbagging     0447 (82.5%)     2683 (82.1%)     136 (83.8%)       Yes     226 (5.2%)     161 (5.5%)     66.4%)       Missing     101 (2.3%)     68 (2.3%)     33 (2.3%)       Patient arrested before ECMO     361 (8.3%)     231 (7.9%)     130 (8.9%)       PC-C     68.66 (27.76)     68.89 (27.56)     68.79 (28.16)       pCO     39.22 (29.00)     39.06 (29.36)     39.53 (28.9)       HFOV     3192 (73.0%)     2116 (72.7%)     1076 (73.6%)       MAP     16.55 (4.28)     16.5 (4.17)     16.64 (4.48)       Oxagop	Post gestational age (days)	2.38 (3.88)	2.37 (3.97)	2.41 (3.67)
Left 3175 (72.8%) 2119 (72.8%) 1056 (72.3%) Both 112 (2.6%) 625 (2.5%) 37 (2.5%) Both 112 (2.6%) 75 (2.6%) 37 (2.5%) Missing 143 (3.3%) 33 (3.2%) 50 (3.4%) Prenatal diagnosis 2867 (66.0%) 1909 (65.6%) 978 (66.9%) No 36623 (82.8%) 2405 (82.6%) 1218 (83.3%) Yes 413 (9.4%) 270 (9.3%) 143 (9.8%) Missing 3338 (7.7%) 237 (8.1%) 101 (6.9%) Handbagging 407 (2.2%) 2683 (92.1%) 136 (93.3%) Yes 226 (5.2%) 151 (5.5%) 65 (4.4%) Yes 226 (5.2%) 2683 (92.1%) 136 (93.3%) Yes 226 (2.3%) 221 (7.9%) 130 (8.9%) Pre-ECMO blood gas 7,17 (0.17) 7,17 (0.17) 7,18 (0.17) Pro-CoMO ventilator settings 39.22 (9.00) 39.06 (29.36) 39.53 (28.29) HFOV 3132 (73.0%) 2116 (72.7%) 1076 (73.8%) MAP 1655 (4.28) 155 (4.17) 166 4 (4.48) Oxygenation index 53.38 (33.47) 53.61 (33.07) 52.92 (34.25) Pre-ECMO ventilator settings 132 (73.0%) 2560 (87.9%) 1288 (88.1%) Oxygenation index 53.38 (33.47) 53.61 (33.07) 52.92 (34.25) Pre-ECMO ventilator settings 142 (53.9%) 156 (4.17) 166 4 (4.48) Oxygenation index 53.38 (33.47) 53.61 (33.07) 52.92 (34.25) Pre-ECMO rescue therapy Inotropes (vasopressor/inotropic drugs/ 39.48 (88.0%) 2560 (87.9%) 1288 (88.1%) Oxygenation index 53.55 (81.3%) 2350 (80.7%) 1268 (82.4%) Nitric oxide 3555 (81.3%) 2350 (80.7%) 126 (82.4%) Nutric oxide 3555 (81.3%) 126 (7.6%) 121 (7.7%) Siteratal Text 726 (16.6%) 4400 (15.5%) 246 (16.8%) Purton USA 727 (22.59) 177 (6.1%) 12 (7.7%) Siteratal 150 (1.1%) 31 (1.1%) 19 (1.3%) Other 72.2% 05 (22.7%) 12 (7.7%) Diaphragmatic hemia fixed during ECMO Ne 72.2% 05 (22.7%) 127 (7.6%) Purp type 72 ECMO mode and pump type 120 ECMO mode and pu	Side of hernia			
Right     944 (21,6%)     625 (21,5%)     319 (21,8%)       Both     112 (26%)     75 (26%)     37 (2,5%)       Missing     143 (3,3%)     93 (3,2%)     50 (3,4%)       Diaphragmatic hernia fixed before ECMO	Left	3175 (72.6%)	2119 (72.8%)	1056 (72.2%)
Both     112 (2,6%)     75 (2,6%)     37 (2,5%)       Missing     143 (3,3%)     93 (2,5%)     50 (3,4%)       Prenatal diagnosis     2887 (66,0%)     1909 (65,6%)     978 (66,9%)       No     3623 (82,8%)     2405 (82,6%)     1218 (83,3%)       Missing     338 (7,7%)     237 (8,1%)     101 (8,9%)       Handbagging     101 (8,2%)     2683 (92,1%)     1364 (93,3%)       Yes     228 (5,2%)     161 (5,5%)     65 (4,4%)       Missing     101 (2,3%)     68 (2,3%)     33 (2,3%)       Patient areasted before ECMO     361 (3,5%)     217 (9,7%)     100 (8,9%)       Pre-MO biood ga     7,17 (0,17)     7,18 (0,17)     68,79 (28,1%)       pCo     68,86 (27,6)     66,80 (27,5%)     68,70 (28,64)     266 (23,60)     33,53 (28,29)       Pre-ECMO ventilator settings     39,22 (29,00)     39,06 (29,36)     39,53 (28,29)     39,53 (28,29)       Pre-ECMO venciliator settings     39,22 (29,00)     39,06 (29,36)     39,53 (28,29)       Pre-ECMO venciliator settings     39,22 (29,00)     39,06 (29,36)     31,63,417)     16,64 (4,48)	Right	944 (21.6%)	625 (21.5%)	319 (21.8%)
Missing     143 (3.3%)     99 (3.2%)     50 (3.4%)       Prenatal diagnosis     2887 (66.9%)     1906 (65.6%)     978 (66.9%)       Diaphragmatic hernia fixed before ECMO     3623 (82.8%)     2405 (82.6%)     1218 (83.3%)       Yes     413 (9.4%)     270 (9.3%)     143 (9.8%)     101 (6.9%)       Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)     164 (93.3%)       No     4047 (92.5%)     2683 (92.1%)     1364 (93.3%)     Yes       Missing     101 (2.3%)     68 (2.3%)     332 (2.3%)     TAT (7.9%)     130 (8.9%)       Pre-ECMD blood gas     717 (0.17)     7.17 (0.17)     7.18 (0.17)     P.18 (2.2%)     105 (2.2%)     107 (7.6%)       PD-     Pre-ECMD vantilator settings     712 (2.7%)     107 (7.6%)     107 (7.6%)     107 (7.6%)       MAP     15.5 (4.17)     16.64 (4.4%)     20.5 (2.8.9%)     468 (32.9%)     22.9 (2.0.0)     20.9 (2.9.0)     20.9 (2.9.0)     20.9 (2.9.0)     20.8 (2.8.17)     16.64 (4.4%)     20.5 (2.8.9%)     107 (7.6%)     107 (7.6%)     10.7 (7.6%)     10.7 (7.6%)     10.8 (8.1.7)     16.64 (4.4%)	Both	112 (2.6%)	75 (2.6%)	37 (2.5%)
Prenatal diagnosis     2887 (66.0%)     1909 (65.6%)     978 (66.9%)       No     3623 (82.8%)     2405 (82.6%)     1218 (83.3%)       No     3623 (82.8%)     2405 (82.6%)     1218 (83.3%)       Missing     338 (7.7%)     237 (8.1%)     139 (9.8%)       No     4047 (92.5%)     2683 (92.1%)     1346 (93.3%)       Yes     226 (52.9%)     161 (5.5%)     66 (4.4%)       Missing     101 (2.3%)     68 (2.3%)     33 (2.3%)       P4     7.17 (0.17)     7.17 (0.17)     7.18 (0.17)       pCO     68.86 (27.76)     68.88 (27.56)     68.79 (22.16)       pC     39.22 (29.00)     93 06 (92.36)     39.53 (22.9)       Pre-ECMO ventilator settings     116 (72.7%)     1076 (73.6%)       MAP     16.55 (4.28)     15.6 (4.77)     16.64 (4.48)       Oxygenation index     53.38 (34.77)     53.61 (3.30,70)     52.22 (34.25)       Pre-ECMO rescue therapy     1160 (72.7%)     1076 (73.6%)     486 (33.2%)       Inotropse (vasopressor/instropic drugs/     3848 (88.0%)     2560 (87.9%)     1288 (88.1%)       Oxygena	Missing	143 (3.3%)	93 (3.2%)	50 (3.4%)
Diaphragmatic hernia fixed before ECMO     3623 (82.8%)     2405 (82.6%)     1218 (83.3%)       No     343 (9.4%)     270 (9.3%)     143 (9.8%)       Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)       No     4047 (92.5%)     2683 (92.1%)     1364 (93.3%)       Yes     226 (5.2%)     161 (5.5%)     65 (4.4%)       Missing     101 (2.3%)     66 (2.3%)     33 (2.3%)       Patient arcsted before ECMO     361 (8.3%)     231 (7.9%)     130 (8.9%)       Pre-ECMO bood gas     717 (0.17)     7.17 (0.17)     7.18 (0.17)       pCO2     68.86 (27.66)     68.48 (27.56)     66.79 (22.16)       pO.     39.22 (29.00)     39.06 (29.36)     39.53 (28.29)       Pre-ECMO vantilator settings     16.55 (4.28)     15.6 (4.17)     16.64 (4.46)       Oxygenation index     53.38 (33.47)     53.61 (33.07)     52.92 (34.25)       Pre-ECMO forescue therapy     76     16.66 (60.87%)     486 (32.9%)       Pre-ECMO forescue therapy     726 (16.6%)     480 (16.57%)     246 (16.8%)       Minricovide doutarmine/penephytine)     258 (68.0%) <t< td=""><td>Prenatal diagnosis</td><td>2887 (66.0%)</td><td>1909 (65.6%)</td><td>978 (66.9%)</td></t<>	Prenatal diagnosis	2887 (66.0%)	1909 (65.6%)	978 (66.9%)
No     36/23 (82.8%)     2406 (82.6%)     1218 (83.3%)       Yes     413 (9.4%)     270 (9.3%)     1218 (83.3%)       Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)       Handbagging     7     68.3 (92.1%)     101 (6.9%)       No     4047 (92.5%)     66.1 (5.5%)     65 (4.4%)       Missing     101 (2.3%)     68 (2.3%)     33 (2.3%)       Patient arrested before ECMO     36 (8.8%)     231 (7.9%)     130 (8.9%)       PH     7.17 (0.17)     7.18 (0.17)     6.8.7 (9.2.5%)     68.7 (9.2.5%)       PCO,     68.86 (27.76)     68.89 (27.56)     68.7 (9.2.8%)       PA     7.17 (0.17)     7.18 (0.17)     6.6.4 (4.4%)       Xoxygenation index     53.38 (3.4.7)     53.61 (33.0.7)     52.92 (8.2.9)       Pre-ECMO ventilator settings     116 (72.7%)     1076 (73.6%)     MAP       Inotropes (vasopressor/inotropic drugs/     3848 (88.0%)     2560 (87.9%)     1228 (88.1%)       Orsygenation index     53.58 (13.3%)     2560 (87.9%)     1228 (88.1%)       Inotropes (vasopressor/inotropic drugs/     2484 (88.0%)	Diaphragmatic hernia fixed before ECMO			
Yes     413 (9.4%)     270 (9.3%)     143 (9.3%)       Missing     38 (7.7%)     237 (8.1%)     101 (6.9%)       Handbagging	No	3623 (82.8%)	2405 (82.6%)	1218 (83.3%)
Missing     338 (7.%)     237 (5.%)     101 (6.3%)       Handbagging	Yes	413 (9.4%)	270 (9.3%)	143 (9.8%)
Handbagging     1364 (93.3%)       No     4047 (92.5%)     2683 (92.1%)     1364 (93.3%)       Yes     226 (5.2%)     161 (5.5%)     65 (4.4%)       Missing     101 (2.3%)     682 (2.3%)     33 (2.3%)       Patient arrested blood gas     717 (0.17)     7.18 (0.17)     7.18 (0.17)       pCQ     68.86 (27.76)     68.89 (27.56)     66.79 (28.16)       pOQ     68.68 (27.76)     68.99 (27.56)     66.79 (28.16)       pDQ     68.56 (27.76)     68.99 (27.56)     66.79 (28.16)       pDQ     68.56 (27.76)     68.59 (27.76)     68.57 (28.16)       pDQ     39.02 (29.00)     39.06 (29.36)     1076 (73.6%)       MAP     16.55 (4.28)     16.5 (4.17)     16.64 (4.48)       Oxygenation index     53.38 (33.47)     53.61 (33.07)     52.92 (44.25)       Par-ECMO rescue therapy     Inotropes (vasopressor/inotropic drugs/     3548 (68.0%)     2560 (87.9%)     1288 (68.1%)       Inotropes (vasopressor/inotropic drugs/     3548 (68.0%)     2560 (87.9%)     126 (82.4%)       Nutrico oxide     3355 (61.3%)     230 (00.7%)     126 (82.4%) <td>Missing</td> <td>338 (7.7%)</td> <td>237 (8.1%)</td> <td>101 (6.9%)</td>	Missing	338 (7.7%)	237 (8.1%)	101 (6.9%)
NO     404/ (25.3%)     2653 (25.1%)     161 (5.5%)     65 (4.4%)       Missing     101 (2.3%)     68 (2.3%)     33 (2.3%)       Patient arrested before ECMO     361 (8.3%)     231 (7.9%)     130 (8.9%)       PH     7.17 (0.17)     7.17 (0.17)     7.18 (0.17)       pCQ     68.86 (27.76)     68.89 (27.56)     68.79 (28.16)       pQ,     39.22 (29.00)     39.06 (29.36)     39.53 (28.29)       Pre-ECMO ventilator settings     16.55 (4.28)     16.5 (4.17)     16.64 (4.48)       Oxygenation index     53.38 (33.47)     53.61 (33.07)     52.92 (34.25)       Pre-ECMO rescue therapy     10.55 (4.28)     16.5 (4.17)     16.64 (4.48)       Inotropes (vasopressor/intorpic drugs/ sa848 (88.0%)     2560 (87.9%)     1288 (88.1%)       dopamine/dobutamine/epinephrine/     728 (16.5%)     2350 (80.7%)     128 (86.1%)       Nifric oxide     3553 (55.0%)     161 (15.5%)     246 (16.8%)       Neuromuscular blockers     2358 (56.0%)     168 (15.7%)     120 (7.7%)       Sildenafil     50 (1.1%)     177 (61.9%)     82 (65.9%)       Micharitic oxide <t< td=""><td>Handbagging</td><td></td><td>0000 (00 10/)</td><td>1004 (00.00())</td></t<>	Handbagging		0000 (00 10/)	1004 (00.00())
Hissing     220 (22.79)     101 (537)     00 (4.47)       Missing     101 (2.3%)     68 (2.3%)     33 (2.3%)       Patient arrested blood gas     7.17 (0.17)     7.18 (0.17)     7.18 (0.17)       pCQ,     68.86 (27.76)     68.89 (27.56)     68.79 (28.16)       pCQ,     68.66 (27.76)     68.89 (27.56)     68.79 (28.16)       pD,     39.22 (29.00)     39.06 (29.36)     39.53 (28.29)       Pre-ECMO ventilator settings     116 (72.7%)     1076 (73.6%)       HFOV     3192 (73.0%)     2116 (72.7%)     1076 (73.6%)       MAP     16.55 (4.28)     16.5 (4.17)     16.64 (4.48)       Oxygenation index     53.38 (33.47)     53.61 (33.07)     52.92 (34.25)       Pre-ECMO rescue therapy     100 toppies (vasopressor/inotropic drugs/ 358 (80.5%)     2560 (87.9%)     1288 (86.1%)       Inotropses (vasopressor/inotropic drugs/ 3555 (81.3%)     2350 (80.7%)     1205 (82.4%)     316 (15.5%)     246 (16.8%)       Surfactant     726 (16.6%)     480 (15.5%)     246 (16.8%)     120 (82.4%)     1205 (82.4%)     130 (1.3%)     54 (3.7%)     234 (61.8.9%)     112 (7.7%)     8	NO Xaa	4047 (92.5%)	2683 (92.1%)	1364 (93.3%)
Missing     101 (2.3%)     060 (2.3%)     33 (2.3%)       Patient arrested before ECMO     361 (8.3%)     231 (7.9%)     130 (8.9%)       Pre-ECMO blood gas     7.17 (0.17)     7.17 (0.17)     7.18 (0.17)       pD     68.86 (27.76)     68.89 (27.56)     68.79 (28.16)       pO     39.22 (29.00)     39.06 (29.36)     39.53 (28.29)       Pre-ECMO ventilator settings     116 (72.7%)     1076 (73.6%)       MAP     16.55 (4.28)     16.5 (4.17)     16.64 (4.48)       Oxygenation index     53.38 (33.47)     53.61 (33.07)     52.92 (34.25)       Pre-ECMO rescue therapy     Inotropes (vasopressor/inotropic drugs/     3848 (88.0%)     2560 (87.9%)     1288 (88.1%)       Inotropes (vasopressor/inotropic drugs/     3845 (78.5%)     486 (33.27%)     120 (22.4%)       Surfactant     726 (16.8%)     480 (16.5%)     226 (24.8%)       Nitric oxide     355 (61.3%)     220 (7.8%)     112 (7.7%)       Sidenafi     50 (1.1%)     31 (1.1%)     19 (1.3%)       Surfactant     726 (16.8%)     480 (16.5%)     226 (7.8%)       Nutric oxide     259 (5.9%) </td <td>Yes</td> <td>226 (5.2%)</td> <td>161 (5.5%)</td> <td>65 (4.4%)</td>	Yes	226 (5.2%)	161 (5.5%)	65 (4.4%)
Practicity arteside before EUMO     361 (6.3.%)     231 (2.9.%)     133 (6.3.%)       Pre-ECMO blood gas     7.17 (0.17)     7.17 (0.17)     7.18 (0.17)       pCQ     68.86 (27.76)     68.89 (27.56)     68.79 (28.16)       pCQ     39.22 (29.00)     39.06 (29.36)     39.53 (28.29)       Pre-ECMO ventilator settings     1076 (73.6%)     2116 (72.7%)     1076 (73.6%)       MAP     16.55 (4.28)     16.5 (4.17)     16.64 (4.48)       Oxygenation index     53.38 (33.47)     53.61 (33.07)     52.92 (34.25)       Pre-ECMO rescue therapy     1000 (0.000)     1288 (88.1%)     dogamine/dobutamine/epinephrine/     0000 (0.000)       Inotropes (vasopressor/inotropic drugs/     3848 (88.0%)     2560 (87.9%)     1288 (88.1%)       dogamine/dobutamine/epinephrine/     0000 (0.000)     1205 (82.4%)     1205 (82.4%)       Nitric oxide     3355 (81.3%)     2350 (80.7%)     1208 (82.4%)       Surfactant     726 (16.6%)     480 (16.5%)     246 (16.8%)       Milmone     338 (7.7%)     226 (7.8%)     112 (7.7%)       Sildenafil     50 (1.1%)     31 (1.1%)     32 (2.2%) </td <td>Missing</td> <td>101 (2.3%)</td> <td>68 (2.3%) 221 (7.00()</td> <td>33 (2.3%)</td>	Missing	101 (2.3%)	68 (2.3%) 221 (7.00()	33 (2.3%)
pH     7.17 (0.17)     7.17 (0.17)     7.18 (0.17)       pC02     68.86 (27.76)     68.88 (27.56)     68.79 (28.16)       pO,     39.22 (29.00)     39.06 (29.36)     39.53 (28.29)       Pre-ECMO ventilator settings     1076 (73.6%)     1076 (73.6%)       MAP     16.55 (4.28)     16.5 (4.17)     16.64 (4.48)       Oxygenation index     53.38 (33.47)     53.61 (33.07)     52.92 (34.25)       Pre-ECMO rescue therapy     1076 (73.6%)     1288 (88.1%)     dogamine/dobutamine/epinephrine/       norepinephrine)     1808 (06.0%)     2560 (87.9%)     1288 (88.1%)       Bicarbonat/THAM     1441 (32.9%)     955 (32.8%)     486 (33.2%)       Nitric oxide     3556 (81.3%)     2260 (87.9%)     1205 (82.4%)       Neuromuscular blockers     2536 (68.0%)     1681 (57.7%)     855 (58.5%)       Milkinone     338 (7.7%)     226 (7.8%)     112 (7.7%)       Sildenafii     50 (1.1%)     31 (1.1%)     19 (1.3%)       Sildenafii     50 (6.3%)     107 (6.1%)     82 (5.6%)       COHD     155 (3.5%)     111 (2.7%)     52 (2.5%) <t< td=""><td>Patient arrested before ECIVIC</td><td>301 (0.3%)</td><td>231 (7.9%)</td><td>130 (8.9%)</td></t<>	Patient arrested before ECIVIC	301 (0.3%)	231 (7.9%)	130 (8.9%)
p10     p10     1.11 (0.17)     1.13 (0.17)       pC0     39.22 (29.00)     39.06 (29.36)     39.53 (28.29)       Pre-ECMO ventilator settings     1     1076 (73.6%)     1076 (73.6%)       MAP     16.55 (4.28)     16.5 (4.17)     16.64 (4.48)       Oxygenation index     53.38 (33.47)     53.61 (33.07)     52.92 (34.25)       Pre-ECMO rescue therapy     1     1076 (73.6%)     1288 (88.1%)       Inotropes (vasopressor/inotropic drugs/ dopamine/dobutamine/epinephrine/ noropinephrine)     3848 (88.0%)     2560 (87.9%)     1288 (88.1%)       Bicarbonate/THAM     1441 (32.9%)     955 (32.8%)     486 (33.2%)       Nitric oxide     3555 (81.3%)     2350 (80.7%)     1205 (82.4%)       Neuromuscular blockers     2536 (86.0%)     1881 (67.7%)     855 (88.5%)       Mitric oxide     3559 (81.3%)     226 (7.8%)     112 (7.7%)       Sidenafil     50 (11.1%)     31 (1.1%)     19 (1.3%)       Steroids     259 (5.9%)     177 (6.1%)     82 (3.7%)       CCHD     155 (3.5%)     101 (3.5%)     54 (3.7%)       MCA     14 (0.3%)     10 (0.	PIE-ECIVIO DIODU gas	7 17 (0 17)	7 17 (0 17)	7 18 (0 17)
DOC_     DOCA     DOCA <thdoca< th="">     DOCA     DOCA     <thd< td=""><td>pCO</td><td>68 86 (27 76)</td><td>68 89 (27 56)</td><td>68 79 (28 16)</td></thd<></thdoca<>	pCO	68 86 (27 76)	68 89 (27 56)	68 79 (28 16)
Pre-SchOV entilator settings     3192 (23.0%)     2116 (72.7%)     1076 (73.6%)       MAP     16.55 (4.28)     16.5 (4.17)     16.64 (4.48)       Oxygenation index     53.38 (33.47)     53.61 (33.07)     52.32 (34.25)       Pre-ECMO rescue therapy     1076 (73.6%)     1076 (73.6%)     1076 (73.6%)       Inotropes (vasopressor/inotropic drugs/ dopamine/dobutamine/epinephrine/ norepinephrine)     3848 (88.0%)     2560 (87.9%)     1286 (88.1%)       Bicarbonate/THAM     1441 (32.9%)     955 (32.8%)     486 (33.2%)       Nitric oxide     3555 (81.3%)     2350 (80.7%)     1205 (82.4%)       Neuromuscular blockers     2536 (56.0%)     1681 (57.7%)     855 (58.5%)       Milrinone     338 (7.7%)     226 (7.8%)     112 (7.7%)       Sildenafil     50 (1.1%)     31 (1.1%)     19 (1.3%)       Steroids     2595 (5.5%)     101 (3.5%)     54 (3.7%)       CCHD     155 (3.5%)     101 (3.5%)     54 (3.7%)       MCA     14 (0.3%)     10 (0.3%)     4 (0.3%)       ChTomosomal     36 (0.8%)     30 (1.0%)     6 (0.4%)       Perinatal infection     97		39.22 (29.00)	39,06 (29,36)	39 53 (28 20)
HCOV     3192 (73.0%)     2116 (72.7%)     1076 (73.6%)       MAP     16.55 (4.28)     16.5 (4.17)     16.64 (4.48)       Oxygenation index     53.38 (33.47)     53.61 (33.07)     52.92 (34.25)       Pre-ECMO rescue therapy     Inotropes (vasopressor/inotropic drugs/     3848 (88.0%)     2560 (87.9%)     1288 (88.1%)       Inotropes (vasopressor/inotropic drugs/     3848 (88.0%)     2560 (87.9%)     1288 (88.1%)       dopamine/dobutamine/epinephrine/     norepinephrine/     1205 (82.4%)     486 (16.5%)       Neuromuscular blockers     2536 (58.0%)     4861 (57.7%)     226 (7.8%)     1205 (82.4%)       Neuromuscular blockers     2536 (58.0%)     1681 (57.7%)     855 (58.5%)     112 (7.7%)       Sildenafil     50 (1.1%)     31 (1.1%)     19 (1.3%)     58 (58.5%)       Milinione     388 (7.7%)     226 (7.8%)     152 (5.6%)     66 (52.4%)       Combidity     C     259 (5.9%)     177 (6.1%)     82 (5.6%)       Chen J     155 (3.5%)     101 (3.5%)     54 (3.7%)       MCA     14 (0.3%)     10 (0.3%)     4 (0.3%)       Or Edmo	Pre-FCMO ventilator settings	33.22 (23.00)	39.00 (29.00)	39.33 (20.29)
MAD     16.55 (4.28)     16.5 (4.17)     16.64 (4.48)       Oxygenation index     53.38 (33.47)     53.61 (33.07)     52.92 (34.25)       Pre-ECMO rescue therapy     1	HEOV	3192 (73.0%)	2116 (72 7%)	1076 (73.6%)
Dividential index     53.38 (33.47)     53.31 (33.07)     52.92 (34.25)       Pre-ECMO rescue therapy     1     53.38 (33.47)     53.31 (33.07)     52.92 (34.25)       Pre-ECMO rescue therapy     1     1288 (88.1%)     1288 (88.1%)     1288 (88.1%)       Inotropes (vasopressor/inotropic drugs/ dopamine/dobutamine/epinephrine/ norepinephrine)     3848 (88.0%)     2560 (87.9%)     1288 (88.1%)       Bicarbonate/THAM     1441 (32.9%)     955 (32.8%)     486 (33.2%)       Nitric oxide     3555 (81.3%)     486 (16.5%)     246 (16.8%)       Surfactant     726 (16.6%)     480 (16.5%)     246 (16.8%)       Neuromuscular blockers     2536 (58.0%)     1681 (57.7%)     855 (58.5%)       Milinone     338 (7.7%)     226 (7.8%)     112 (7.7%)       Sildenafil     50 (1.1%)     31 (1.1%)     19 (1.3%)       Steroids     259 (5.9%)     177 (6.1%)     82 (5.6%)       Comobidity     7     7     61.0%)     40 (0.3%)       Chromosomal     36 (0.8%)     30 (1.0%)     6 (0.4%)       Perinatal infection     97 (2.2%)     65 (2.5%)     766 (52.4%)	MAP	16 55 (4 28)	16.5 (4.17)	16 64 (4 48)
Pre-ECMO rescue therapy     Construction     Construction       Inotropes (vasopressor/inotropic drugs/ dopamine/dobutamine/epinephrine/ norepinephrine)     3848 (88.0%)     2560 (87.9%)     1288 (88.1%)       Bicarbonate/THAM     1441 (32.9%)     955 (32.8%)     486 (33.2%)       Nitric oxide     3555 (81.3%)     2350 (80.7%)     1205 (82.4%)       Surfactant     726 (16.6%)     480 (16.5%)     246 (16.8%)       Neuromuscular blockers     2358 (85.9%)     1681 (57.7%)     855 (68.5%)       Milrinone     338 (7.7%)     226 (7.8%)     112 (7.7%)       Sildenafil     50 (1.1%)     31 (1.1%)     19 (1.3%)       Steroids     259 (5.9%)     177 (6.1%)     82 (5.6%)       CCHD     155 (3.5%)     101 (3.5%)     54 (3.7%)       MCA     14 (0.3%)     10 (0.3%)     4 (0.3%)       CHO     155 (3.5%)     101 (3.5%)     54 (3.7%)       MCA     14 (0.3%)     10 (0.3%)     4 (0.3%)       ChD     1528 (52.5%)     766 (52.4%)       Neuromosomal     2294 (52.4%)     1528 (52.5%)     766 (52.4%)       Netand pump type	Oxygenation index	53.38 (33.47)	53.61 (33.07)	52.92 (34.25)
Inotropes (vasopressor/inotropic drugs/ dopamine/dobutamine/ejinephrine/ norepinephrine)     3848 (88.0%)     2560 (87.9%)     1288 (88.1%)       Bicarbonate/THAM     1441 (32.9%)     955 (32.8%)     486 (33.2%)       Nitric oxide     3555 (81.3%)     2350 (80.7%)     1205 (82.4%)       Surfactant     726 (16.6%)     480 (16.5%)     246 (16.8%)       Neuromuscular blockers     2536 (58.0%)     1681 (57.7%)     855 (58.5%)       Milrinone     336 (7.7%)     226 (7.8%)     112 (7.7%)       Sidenafil     50 (1.1%)     31 (1.1%)     19 (1.3%)       Steroids     259 (5.9%)     107 (8.1%)     40.3%)       Comorbidity     C     205 (3.2%)     101 (3.5%)     54 (3.7%)       MCA     14 (0.3%)     10 (0.3%)     4 (0.3%)     26.2%)       Orhomosomal     36 (0.8%)     30 (1.0%)     6 (0.4%)     22.2%)       On ECMO     97 (2.2%)     65 (2.2%)     32 (2.2%)     01 (6.9%)       Duaptragmatic hemia fixed during ECMO     No     2294 (52.4%)     1142 (3.9.4%)     595 (40.7%)     295 (40.7%)     98 (40.7%)     98 (40.7%)     98 (40.7%)	Pre-ECMO rescue therapy			02.02 (020)
dopamine/dobutamine/epinephrine/     norepinephrine/     norepinephrine/       norepinephrine)     Bicarbonate/THAM     1441 (32.9%)     955 (32.8%)     486 (33.2%)       Nitric oxide     3555 (81.3%)     2350 (80.7%)     1205 (82.4%)       Surfactant     726 (16.6%)     480 (16.5%)     246 (16.8%)       Neuromuscular blockers     2536 (58.0%)     1681 (57.7%)     855 (58.5%)       Mitrinone     338 (7.7%)     226 (7.8%)     112 (7.7%)       Sildenafil     50 (1.1%)     31 (1.1%)     19 (1.3%)       Steroids     259 (5.9%)     177 (6.1%)     82 (5.6%)       Comorbidity     C     CCHD     155 (3.5%)     101 (3.5%)     54 (3.7%)       MCA     14 (0.3%)     10 (0.3%)     4 (0.3%)     6 (0.4%)     96 (0.4%)       Perinatal infection     97 (2.2%)     65 (2.2%)     32 (2.2%)     06 (52.4%)       No     2294 (52.4%)     1528 (52.5%)     766 (52.4%)     Yes       Yes     1742 (39.8%)     1147 (39.4%)     595 (40.7%)     01 (6.9%)       Duration of ECMO (weeks)     1.68 (1.07)     1.67 (1.05)	Inotropes (vasopressor/inotropic drugs/	3848 (88.0%)	2560 (87.9%)	1288 (88,1%)
norepinephrine)     norepinephrine)       Bicarbonate/THAM     1441 (32.9%)     955 (32.8%)     486 (33.2%)       Nitric oxide     3555 (81.3%)     2350 (80.7%)     1205 (82.4%)       Surfactant     726 (16.6%)     480 (16.5%)     246 (16.8%)       Neuromuscular blockers     2536 (58.0%)     1681 (57.7%)     855 (58.5%)       Milrinone     338 (7.7%)     226 (7.8%)     112 (7.7%)       Sildenafil     50 (1.1%)     31 (1.1%)     19 (1.3%)       Steroids     259 (5.9%)     177 (6.1%)     82 (5.6%)       Comorbidity     T     T     80 (0.8%)     30 (1.0%)     4 (0.3%)       CHD     155 (3.5%)     101 (3.5%)     54 (3.7%)     22 (2.2%)       On FCMO     150 (0.8%)     30 (1.0%)     6 (0.4%)       Perinatal infection     97 (2.2%)     65 (2.2%)     32 (2.2%)       On ECMO     128 (52.5%)     766 (52.4%)     Yes       VA     2359 (81.4%)     237 (8.1%)     101 (6.9%)       Duration of ECMO (weeks)     1.68 (1.07)     1.67 (1.05)     1.7 (1.11)       ECMO mode	dopamine/dobutamine/epinephrine/			
Bicarbonate/THAM     1441 (32.9%)     955 (32.8%)     486 (33.2%)       Nitric oxide     3555 (81.3%)     2350 (80.7%)     1205 (82.4%)       Surfactant     726 (16.6%)     440 (16.5%)     246 (16.8%)       Neuromuscular blockers     2536 (58.0%)     1681 (57.7%)     855 (58.5%)       Milrinone     338 (7.7%)     226 (7.8%)     112 (7.7%)       Sidenafil     50 (1.1%)     31 (1.1%)     19 (1.3%)       Steroids     259 (5.9%)     177 (6.1%)     82 (5.6%)       COHD     155 (3.5%)     101 (3.5%)     54 (3.7%)       MCA     14 (0.3%)     10 (0.3%)     4 (0.3%)       CHD     97 (2.2%)     65 (2.2%)     32 (2.2%)       On ECMO     97 (2.2%)     65 (2.2%)     32 (2.2%)       On ECMO     97 (2.2%)     65 (2.2%)     525 (40.7%)       Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)       Duration of ECMO (weeks)     1.68 (1.07)     1.67 (1.05)     1.7 (1.11)       ECMO mode     UN     2338 (81.8%)     1176 (80.4%)       V     815 (18.6%)     529 (18.2%	norepinephrine)			
Nitric oxide $3555 (81.3\%)$ $2350 (80.7\%)$ $1205 (82.4\%)$ Surfactant726 (16.6\%)480 (16.5\%)246 (16.8\%)Neuromuscular blockers $253 (58.0\%)$ 1681 (57.7\%)855 (58.5\%)Milrinone $338 (7.7\%)$ 226 (7.8%)112 (7.7\%)Sildenafil50 (1.1\%)31 (1.1%)19 (1.3\%)Steroids $259 (5.9\%)$ 177 (6.1%)82 (5.6%)Comorbidity $V$ $V$ $V$ $V$ CCHD155 (3.5\%)101 (3.5\%)4 (0.3\%)Chromosomal36 (0.8%)30 (1.0%)6 (0.4%)Perinatal infection97 (2.2\%)65 (2.2\%)32 (2.2\%)On ECMO $V$ $V$ $V$ $V$ No2294 (52.4\%)1528 (52.5\%)766 (52.4\%)Yes1742 (39.8%)1147 (39.4\%)595 (40.7\%)Missing338 (7.7\%)237 (8.1%)101 (6.9%)Duration of ECMO (weeks)1.68 (1.07)1.67 (1.05)1.7 (1.1)ECMO mode and pump type $V$ $815 (18.6\%)$ 529 (18.2\%)286 (19.6\%)VA3559 (81.4\%)2383 (81.8\%)1176 (80.4\%) $V$ VA3559 (81.4\%)529 (18.2\%)286 (19.6\%)Pump type $V$ 815 (18.6\%)529 (18.2\%)286 (19.6\%)Pump type $V$ 815 (18.6\%)557 (19.1\%)252 (17.2\%)Other162 (3.7\%)108 (3.7\%)1144 (78.2\%)Centrifugal809 (18.5\%)557 (19.1\%)54 (3.7\%)Other162 (3.7\%)108 (3.7\%)54 (3.7\%)Oth	Bicarbonate/THAM	1441 (32.9%)	955 (32.8%)	486 (33.2%)
Surfactant     726 (16.6%)     480 (16.5%)     246 (16.8%)       Neuromuscular blockers     2536 (58.0%)     1681 (57.7%)     855 (58.5%)       Milrinone     338 (7.7%)     226 (7.8%)     112 (7.7%)       Sildenafil     50 (1.1%)     31 (1.1%)     19 (1.3%)       Steroids     259 (5.9%)     177 (6.1%)     82 (5.6%)       Comorbidity     200 (1.1%)     31 (1.1%)     19 (1.3%)       MCA     14 (0.3%)     101 (3.5%)     54 (3.7%)       MCA     14 (0.3%)     10 (0.3%)     4 (0.3%)       Chromosomal     36 (0.8%)     30 (1.0%)     6 (0.4%)       Perinatal infection     97 (2.2%)     65 (2.2%)     32 (2.2%)       On ECMO     2294 (52.4%)     1528 (52.5%)     766 (52.4%)       Yes     1742 (39.8%)     1147 (39.4%)     595 (40.7%)       Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)       Duration of ECMO (weeks)     1.68 (1.07)     1.67 (1.05)     1.7 (1.11)       ECMO mode     VA     3559 (81.4%)     2383 (81.8%)     1176 (80.4%)       VA     3559	Nitric oxide	3555 (81.3%)	2350 (80.7%)	1205 (82.4%)
Neuromuscular blockers     2536 (58.0%)     1681 (57.7%)     855 (58.5%)       Milrinone     338 (7.7%)     226 (7.8%)     112 (7.7%)       Sildenafil     50 (1.1%)     311 (1.1%)     19 (1.3%)       Steroids     259 (5.9%)     177 (6.1%)     82 (5.6%)       Comorbidity        82 (5.6%)       CCHD     155 (3.5%)     101 (3.5%)     54 (3.7%)       MCA     14 (0.3%)     10 (0.3%)     4 (0.3%)       Chromosomal     36 (0.8%)     30 (1.0%)     6 (0.4%)       Perinatal infection     97 (2.2%)     65 (2.2%)     32 (2.2%)       On ECMO       338 (7.7%)     237 (8.1%)     101 (6.9%)       Diaphragmatic hernia fixed during ECMO      168 (1.07)     1.67 (1.05)     1.7 (1.11)       ECMO mode and pump type      259 (82.9%)     238 (81.8%)     101 (6.9%)       Duration of ECMO (weeks)     1.68 (1.07)     1.67 (1.05)     1.7 (1.11)       ECMO mode      259 (81.4%)     2383 (81.8%)     1176 (80.4%)       VV     815 (18.6%)	Surfactant	726 (16.6%)	480 (16.5%)	246 (16.8%)
Milrinone $338 (7.7\%)$ $226 (7.8\%)$ $112 (7.7\%)$ Sildenafil $50 (1.1\%)$ $31 (1.1\%)$ $19 (1.3\%)$ Steroids $259 (5.9\%)$ $177 (6.1\%)$ $82 (5.6\%)$ Comorbidity $T7 (6.1\%)$ $82 (5.6\%)$ CCHD $155 (3.5\%)$ $101 (3.5\%)$ $54 (3.7\%)$ MCA $14 (0.3\%)$ $10 (0.3\%)$ $4 (0.3\%)$ Chromosomal $36 (0.8\%)$ $30 (1.0\%)$ $6 (0.4\%)$ Perinatal infection $97 (2.2\%)$ $65 (2.2\%)$ $32 (2.2\%)$ On ECMO $T42 (39.8\%)$ $1147 (39.4\%)$ $595 (40.7\%)$ Missing $338 (7.7\%)$ $237 (8.1\%)$ $101 (6.9\%)$ Duration of ECMO (weeks) $1.68 (1.07)$ $1.67 (1.05)$ $1.7 (1.11)$ ECMO mode $VA$ $3559 (81.4\%)$ $2383 (81.8\%)$ $1176 (80.4\%)$ VV $815 (18.6\%)$ $529 (18.2\%)$ $262 (17.2\%)$ Orther $367 (77.0\%)$ $2223 (76.3\%)$ $1144 (78.2\%)$ Centrifugal $809 (18.5\%)$ $557 (19.1\%)$ $252 (17.2\%)$ Other $162 (3.7\%)$ $108 (3.7\%)$ $54 (3.7\%)$ Missing $36 (0.8\%)$ $24 (0.8\%)$ $12 (0.8\%)$ Comorbidity $F$ $F$ $F$ Pump type $F$ $F$ $F$ Roller $162 (3.7\%)$ $108 (3.7\%)$ $54 (3.7\%)$ Missing $36 (0.8\%)$ $24 (0.8\%)$ $12 (0.8\%)$ Comorbidity $F$ $F$ $F$ Perinonitis $8 (0.2\%)$ $6 (0.2\%)$ $2 (0.1\%)$ Airleak syndrome $603 (13.8\%)$ $405 (13.$	Neuromuscular blockers	2536 (58.0%)	1681 (57.7%)	855 (58.5%)
Sildenafil     50 (1.1%)     31 (1.1%)     19 (1.3%)       Steroids     259 (5.9%)     177 (6.1%)     82 (5.6%)       Comorbidity          CCHD     155 (3.5%)     101 (3.5%)     54 (3.7%)       MCA     14 (0.3%)     10 (0.3%)     4 (0.3%)       Chromosomal     36 (0.8%)     30 (1.0%)     6 (0.4%)       Perinatal infection     97 (2.2%)     65 (2.2%)     32 (2.2%)       On ECMO      97 (2.2%)     1528 (52.5%)     766 (52.4%)       No     2294 (52.4%)     1528 (52.5%)     766 (52.4%)     195 (40.7%)       Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)       Duration of ECMO (weeks)     1.68 (1.07)     1.67 (1.05)     1.7 (1.11)       ECMO mode      2383 (81.8%)     1176 (80.4%)       VV     815 (18.6%)     529 (18.2%)     286 (19.6%)       Pump type      2383 (81.8%)     1147 (78.2%)       Centrifugal     809 (18.5%)     557 (19.1%)     252 (17.2%)       Other     182 (3.7%)     108 (3.7%)	Milrinone	338 (7.7%)	226 (7.8%)	112 (7.7%)
Steroids     259 (5.9%)     177 (6.1%)     82 (5.6%)       Comorbidity	Sildenafil	50 (1.1%)	31 (1.1%)	19 (1.3%)
Comorbidity CCHD     155 (3.5%)     101 (3.5%)     54 (3.7%)       MCA     14 (0.3%)     10 (0.3%)     4 (0.3%)       Chromosomal     36 (0.8%)     30 (1.0%)     6 (0.4%)       Perinatal infection     97 (2.2%)     65 (2.2%)     32 (2.2%)       On ECMO     0     2294 (52.4%)     1528 (52.5%)     766 (52.4%)       No     2294 (52.4%)     1528 (52.5%)     766 (52.4%)       Yes     1742 (38.8%)     1147 (39.4%)     595 (40.7%)       Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)       Duration of ECMO (weeks)     1.68 (1.07)     1.67 (1.05)     1.7 (1.11)       ECMO mode and pump type     2     2383 (81.8%)     1176 (80.4%)       VA     3559 (81.4%)     2383 (81.8%)     1176 (80.4%)       VV     815 (18.6%)     529 (18.2%)     286 (19.6%)       Pump type     T     T     1144 (78.2%)       Centrifugal     809 (18.5%)     557 (19.1%)     252 (17.2%)       Other     162 (3.7%)     108 (3.7%)     54 (3.7%)       Missing     36 (0.8%) <t< td=""><td>Steroids</td><td>259 (5.9%)</td><td>177 (6.1%)</td><td>82 (5.6%)</td></t<>	Steroids	259 (5.9%)	177 (6.1%)	82 (5.6%)
CCHD     155 (3.5%)     101 (3.5%)     54 (3.7%)       MCA     14 (0.3%)     10 (0.3%)     4 (0.3%)       Chromosomal     36 (0.8%)     30 (1.0%)     6 (0.4%)       Perinatal infection     97 (2.2%)     65 (2.2%)     32 (2.2%)       On ECMO     Diaphragmatic hemia fixed during ECMO     766 (52.4%)     1528 (52.5%)     766 (52.4%)       No     2294 (52.4%)     1528 (52.5%)     766 (52.4%)     Yes       Yes     1742 (39.8%)     1147 (39.4%)     595 (40.7%)       Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)       Duration of ECMO (weeks)     1.68 (1.07)     1.67 (1.05)     1.7 (1.11)       ECMO mode and pump type     E     E     E     E       VA     3559 (81.4%)     2383 (81.8%)     1176 (80.4%)     VV       VV     815 (18.6%)     529 (18.2%)     286 (19.6%)     E       Pump type     T     E     E     E     E     E     E     223 (76.3%)     1144 (78.2%)     E     E     E     E     E     E     E	Comorbidity			
MCA     14 (0.3%)     10 (0.3%)     4 (0.3%)       Chromosomal     36 (0.8%)     30 (1.0%)     6 (0.4%)       Perinatal infection     97 (2.2%)     65 (2.2%)     32 (2.2%)       On ECMO           Diaphragmatic hernia fixed during ECMO           No     2294 (52.4%)     1528 (52.5%)     766 (52.4%)        Yes     1742 (39.8%)     1147 (39.4%)     595 (40.7%)        Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)        Duration of ECMO (weeks)     1.68 (1.07)     1.67 (1.05)     1.7 (1.11)        ECMO mode             VA     3559 (81.4%)     2383 (81.8%)     1176 (80.4%)          VV     815 (18.6%)     529 (18.2%)     286 (19.6%)          Pump type	CCHD	155 (3.5%)	101 (3.5%)	54 (3.7%)
Chromosomal     36 (0.8%)     30 (1.0%)     6 (0.4%)       Perinatal infection     97 (2.2%)     65 (2.2%)     32 (2.2%)       On ECMO     Diaphragmatic hernia fixed during ECMO         No     2294 (52.4%)     1528 (52.5%)     766 (52.4%)       Yes     1742 (39.8%)     1147 (39.4%)     595 (40.7%)       Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)       Duration of ECMO (weeks)     1.68 (1.07)     1.67 (1.05)     1.7 (1.11)       ECMO mode and pump type       2383 (81.8%)     1176 (80.4%)       VV     815 (18.6%)     529 (18.2%)     286 (19.6%)        Pump type       367 (77.0%)     2223 (76.3%)     1144 (78.2%)       Centrifugal     809 (18.5%)     557 (19.1%)     252 (17.2%)        Other     162 (3.7%)     108 (3.7%)     54 (3.7%)        Missing     36 (0.8%)     24 (0.8%)     12 (0.8%)        Comorbidity       20.1%)     148 (3.5%)     12 (0.1%) <td< td=""><td>MCA</td><td>14 (0.3%)</td><td>10 (0.3%)</td><td>4 (0.3%)</td></td<>	MCA	14 (0.3%)	10 (0.3%)	4 (0.3%)
Perinatal infection     97 (2.2%)     65 (2.2%)     32 (2.2%)       On ECMO     Diaphragmatic hernia fixed during ECMO          32 (2.2%)     32 (2.2%)     32 (2.2%)     32 (2.2%)      32 (2.2%)      32 (2.2%)      32 (2.2%)      32 (2.2%)      32 (2.2%)      32 (2.2%)        32 (2.2%)	Chromosomal	36 (0.8%)	30 (1.0%)	6 (0.4%)
On ECMO     Diaphragmatic hernia fixed during ECMO     766 (52.4%)       No     2294 (52.4%)     1528 (52.5%)     766 (52.4%)       Yes     1742 (39.8%)     1147 (39.4%)     595 (40.7%)       Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)       Duration of ECMO (weeks)     1.68 (1.07)     1.67 (1.05)     1.7 (1.11)       ECMO mode     2000     2383 (81.8%)     1176 (80.4%)       VA     3559 (81.4%)     2383 (81.8%)     1176 (80.4%)       VV     815 (18.6%)     529 (18.2%)     286 (19.6%)       Pump type     Roller     3667 (77.0%)     2223 (76.3%)     1144 (78.2%)       Centrifugal     809 (18.5%)     557 (19.1%)     252 (17.2%)       Other     162 (3.7%)     108 (3.7%)     54 (3.7%)       Missing     360 (0.8%)     24 (0.8%)     12 (0.8%)       Comorbidity     Peritonitis     8 (0.2%)     6 (0.2%)     2 (0.1%)       Airleak syndrome     603 (13.8%)     405 (13.9%)     198 (13.5%)	Perinatal infection	97 (2.2%)	65 (2.2%)	32 (2.2%)
Diaphragmatic hernia fixed during ECMO     2294 (52.4%)     1528 (52.5%)     766 (52.4%)       Yes     1742 (39.8%)     1147 (39.4%)     595 (40.7%)       Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)       Duration of ECMO (weeks)     1.68 (1.07)     1.67 (1.05)     1.7 (1.11)       ECMO mode and pump type     ECMO mode     VV     815 (18.6%)     529 (18.2%)     286 (19.6%)       VV     815 (18.6%)     529 (18.2%)     286 (19.6%)     286 (19.6%)       Pump type     Roller     3667 (77.0%)     2223 (76.3%)     1144 (78.2%)       Centrifugal     809 (18.5%)     557 (19.1%)     252 (17.2%)       Other     162 (3.7%)     108 (3.7%)     54 (3.7%)       Missing     36 (0.8%)     24 (0.8%)     12 (0.8%)       Comorbidity     Peritonitis     8 (0.2%)     6 (0.2%)     2 (0.1%)       Airleak syndrome     603 (13.8%)     405 (13.9%)     198 (13.5%)	On ECMO			
No     2294 (52.4%)     1528 (52.5%)     766 (52.4%)       Yes     1742 (39.8%)     1147 (39.4%)     595 (40.7%)       Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)       Duration of ECMO (weeks)     1.68 (1.07)     1.67 (1.05)     1.7 (1.11)       ECMO mode and pump type     ECMO mode     1176 (80.4%)     2383 (81.8%)     1176 (80.4%)       VA     3559 (81.4%)     2383 (81.8%)     1176 (80.4%)     286 (19.6%)       VV     815 (18.6%)     529 (18.2%)     286 (19.6%)       Pump type     Roller     2233 (76.3%)     1144 (78.2%)       Centrifugal     809 (18.5%)     557 (19.1%)     252 (17.2%)       Other     162 (3.7%)     108 (3.7%)     54 (3.7%)       Missing     36 (0.8%)     24 (0.8%)     12 (0.8%)       Comorbidity     Peritonitis     8 (0.2%)     6 (0.2%)     2 (0.1%)       Airleak syndrome     603 (13.8%)     405 (13.9%)     198 (13.5%)	Diaphragmatic hernia fixed during ECMO	0004 (50,484)		700 (50, 40())
res   1742 (39.8%)   1147 (39.4%)   595 (40.7%)     Missing   338 (7.7%)   237 (8.1%)   101 (6.9%)     Duration of ECMO (weeks)   1.68 (1.07)   1.67 (1.05)   1.7 (1.11)     ECMO mode and pump type   ECMO mode   1176 (80.4%)   1176 (80.4%)     VA   3559 (81.4%)   2383 (81.8%)   1176 (80.4%)     VV   815 (18.6%)   529 (18.2%)   286 (19.6%)     Pump type   Roller   2223 (76.3%)   1144 (78.2%)     Centrifugal   809 (18.5%)   557 (19.1%)   252 (17.2%)     Other   162 (3.7%)   108 (3.7%)   54 (3.7%)     Missing   36 (0.8%)   24 (0.8%)   12 (0.8%)     Comorbidity   Peritonitis   8 (0.2%)   6 (0.2%)   2 (0.1%)     Airleak syndrome   603 (13.8%)   405 (13.9%)   198 (13.5%)	NO Xaa	2294 (52.4%)	1528 (52.5%)	766 (52.4%)
Missing     338 (7.7%)     237 (8.1%)     101 (6.9%)       Duration of ECMO (weeks)     1.68 (1.07)     1.67 (1.05)     1.7 (1.11)       ECMO mode       1176 (80.4%)     1176 (80.4%)       VA     3559 (81.4%)     2383 (81.8%)     1176 (80.4%)       VV     815 (18.6%)     529 (18.2%)     286 (19.6%)       Pump type       223 (76.3%)     1144 (78.2%)       Centrifugal     809 (18.5%)     557 (19.1%)     252 (17.2%)       Other     162 (3.7%)     108 (3.7%)     54 (3.7%)       Missing     36 (0.8%)     24 (0.8%)     12 (0.8%)       Comorbidity       8 (0.2%)     6 (0.2%)     2 (0.1%)       Airleak syndrome     603 (13.8%)     405 (13.9%)     198 (13.5%)	Yes	1742 (39.8%)	1147 (39.4%)	595 (40.7%)
ECMO mode and pump type   1.08 (1.07)   1.07 (1.03)   1.7 (1.11)     ECMO mode   VA   3559 (81.4%)   2383 (81.8%)   1176 (80.4%)     VV   815 (18.6%)   529 (18.2%)   286 (19.6%)     Pump type   Roller   3367 (77.0%)   2223 (76.3%)   1144 (78.2%)     Centrifugal   809 (18.5%)   557 (19.1%)   252 (17.2%)     Other   162 (3.7%)   108 (3.7%)   54 (3.7%)     Missing   36 (0.8%)   24 (0.8%)   12 (0.8%)     Comorbidity   Peritonitis   8 (0.2%)   6 (0.2%)   2 (0.1%)     Airleak syndrome   603 (13.8%)   405 (13.9%)   198 (13.5%)	IVIISSING	330 (7.7%)	237 (0.1%)	17 (1 11)
ECMO mode   3559 (81.4%)   2383 (81.8%)   1176 (80.4%)     VA   3559 (81.4%)   529 (18.2%)   286 (19.6%)     VV   815 (18.6%)   529 (18.2%)   286 (19.6%)     Pump type	ECMO made and nump tune	1.08 (1.07)	1.67 (1.05)	1.7 (1.11)
VA   3559 (81.4%)   2383 (81.8%)   1176 (80.4%)     VV   815 (18.6%)   529 (18.2%)   286 (19.6%)     Pump type        Roller   3367 (77.0%)   2223 (76.3%)   1144 (78.2%)     Centrifugal   809 (18.5%)   557 (19.1%)   252 (17.2%)     Other   162 (3.7%)   108 (3.7%)   54 (3.7%)     Missing   36 (0.8%)   24 (0.8%)   12 (0.8%)     Comorbidity        Peritonitis   8 (0.2%)   6 (0.2%)   2 (0.1%)     Airleak syndrome   603 (13.8%)   405 (13.9%)   198 (13.5%)	ECMO mode			
VX   8359 (81.4%)   2363 (81.8%)   1176 (60.4%)     VV   815 (18.6%)   529 (18.2%)   286 (19.6%)     Pump type		2550 (81 404)	0282 (81 804)	1176 (20 404)
Pump type     3367 (77.0%)     2223 (76.3%)     1144 (78.2%)       Roller     3367 (77.0%)     2223 (76.3%)     1144 (78.2%)       Centrifugal     809 (18.5%)     557 (19.1%)     252 (17.2%)       Other     162 (3.7%)     108 (3.7%)     54 (3.7%)       Missing     36 (0.8%)     24 (0.8%)     12 (0.8%)       Comorbidity     Peritonitis     8 (0.2%)     6 (0.2%)     2 (0.1%)       Airleak syndrome     603 (13.8%)     405 (13.9%)     198 (13.5%)		815 (18 60/)	520 (18 204)	286 (10.6%)
Roller   3367 (77.0%)   2223 (76.3%)   1144 (78.2%)     Centrifugal   809 (18.5%)   557 (19.1%)   252 (17.2%)     Other   162 (3.7%)   108 (3.7%)   54 (3.7%)     Missing   36 (0.8%)   24 (0.8%)   12 (0.8%)     Comorbidity   Peritonitis   8 (0.2%)   6 (0.2%)   2 (0.1%)     Airleak syndrome   603 (13.8%)   405 (13.9%)   198 (13.5%)	Pump type	010 (10.070)	020 (10.270)	200 (13.070)
Centrifugal     800 (11.5%)     522 (10.5%)     1144 (10.2%)       Centrifugal     809 (18.5%)     557 (19.1%)     252 (17.2%)       Other     162 (3.7%)     108 (3.7%)     54 (3.7%)       Missing     36 (0.8%)     24 (0.8%)     12 (0.8%)       Comorbidity     Peritonitis     8 (0.2%)     6 (0.2%)     2 (0.1%)       Airleak syndrome     603 (13.8%)     405 (13.9%)     198 (13.5%)	Roller	3367 (77 0%)	2223 (76.3%)	1144 (78 2%)
Other     162 (3.7%)     108 (3.7%)     54 (3.7%)       Missing     36 (0.8%)     24 (0.8%)     12 (0.8%)       Comorbidity     Peritonitis     8 (0.2%)     6 (0.2%)     2 (0.1%)       Airleak syndrome     603 (13.8%)     405 (13.9%)     198 (13.5%)	Centrifugal	809 (18 5%)	557 (19.1%)	252 (17 2%)
Missing     36 (0.8%)     24 (0.8%)     12 (0.8%)       Comorbidity     9     10	Other	162 (3 7%)	108 (3 7%)	54 (3 7%)
Comorbidity     8 (0.2%)     6 (0.2%)     2 (0.0%)       Airleak syndrome     603 (13.8%)     405 (13.9%)     198 (13.5%)	Missing	36 (0.8%)	24 (0.8%)	12 (0.8%)
Peritonitis8 (0.2%)6 (0.2%)2 (0.1%)Airleak syndrome603 (13.8%)405 (13.9%)198 (13.5%)	Comorbidity		2 (0.070)	12 (0.070)
Airleak syndrome 603 (13.8%) 405 (13.9%) 198 (13.5%)	Peritonitis	8 (0.2%)	6 (0.2%)	2 (0.1%)
	Airleak syndrome	603 (13.8%)	405 (13.9%)	198 (13.5%)

Table 1. (Continued)

Recipients' Characteristics	Entire Cohort (n=4,374), Mean (SD)/Count (%)	Development Set (N=2,912), Mean (SD)/Count (%)	Validation Set (N=1,462), Mean (SD)/Count (%)
Complications			
Mechanical complications	2408 (55.1%)	1571 (53.9%)	837 (57.3%)
Hemorrhagic complications			
Pulmonary hemorrhage	405 (9.3%)	266 (9.1%)	139 (9.5%)
Other hemorrhagic complications	1724 (39.4%)	1145 (39.3%)	579 (39.6%)
Neurologic complications			
Seizures	286 (6.5%)	189 (6.5%)	97 (6.6%)
Severe neurologic complication	637 (14.6%)	431 (14.8%)	206 (14.1%)
Renal complications			
Elevated creatinine	258 (5.9%)	150 (5.2%)	108 (7.4%)
Dialysis	1340 (30.6%)	871 (29.9%)	469 (32.1%)
Cardiac complications			
STUN	154 (3.5%)	105 (3.6%)	49 (3.4%)
Tamponade	103 (2.4%)	70 (2.4%)	33 (2.3%)
CPR required	124 (2.8%)	87 (3.0%)	37 (2.5%)
Infectious complications/sepsis	353 (8.1%)	244 (8.4%)	109 (7.5%)
Metabolic complications			
Glucose < 40	132 (3.0%)	88 (3.0%)	44 (3.0%)
Glucose > 240	235 (5.4%)	146 (5.0%)	89 (6.1%)

ICD9 Code: CCHD, 746.01/745/745.1/745.2/745.31/745.32/745.33/746.1/746.11/746.2/747.41/747.1/746.7; MCA, 759.7; Chromosomal syndrome, 759.7/758.0/758.5/758.39/758/758.8; Perinatal infection, 771.8; Peritonitis, 568.89/567.8; Pulmonary hemorrhage, 770.3 and as coded by ELSO complication codes; Airleak syndrome: Pneumothorax (512/512.0/770.2 or having pneumothorax as coded in ELSO complication codes).

CCHD, critical congenital heart disease; ECMO, extracorporeal membrane oxygenation; ELSO, Extracorporeal Life Support Organization; MAP, mean airway pressure; MCA, multiple congenital anomalies; THAM, tromethamine; HFOV, high-frequency oscillatory ventilation; VA, Venoarterial; VV, Venovenous; CPR, Cardiopulmonary Resuscitation; STUN, Cardiac Stun.

comorbidities, along with ECMO modality and pump type and ECMO comorbidities/complications, are detailed in **Table 1**.

#### Development of the Prediction Models

We developed two mortality prediction models/scores: pre- and on-ECMO for CDH. The coefficient estimates for the pre-ECMO model are shown in **Table 2**. Lower weight, Apgar score, pH, MAP, bilateral diaphragmatic hernia, repair on-ECMO, prenatal diagnosis, handbagging, pre-ECMO arrest, HFOV, concomitant CCHD, and presence of perinatal infection were associated with increased odds of mortality. Rightsided hernia was associated with decreased odds of mortality. Table 3 depicts the final prediction model coefficients for the on-ECMO model. In addition to the above significant predictors in the pre-ECMO model, we found that longer ECMO duration, use of inhaled nitric oxide, the presence of multiple congenital anomalies or airleak syndrome, other hemorrhagic complications, severe neurologic complications, tamponade, infectious complications, elevated creatinine/dialysis, and CPR were also associated with increased mortality risk.

#### Internal Validation

Model predictive discrimination was assessed on the validation dataset (n=1,462). For the pre-ECMO model, *C* statistic was 0.65 (95% confidence interval [CI], 0.62–0.68). Applying the development data set used in this study, the Neo-RESCUERS equation discrimination was lower (C = 0.59, 95% CI, 0.56– 0.62). Note that, the 95% CIs only overlap at the end point of 0.62 (upper limit for Neo-RESCUERS and lower limit for our pre-ECMO score). Thus, there is substantial improvement relative to the Neo-RESCUERS score. The results suggest that the pre-ECMO score of our study discriminates better as it specifically focuses on the CDH population. Revalidation of the PIPER equation in our CDH-specific training data set resulted in *C* statistic (C = 0.60; 95% Cl, 0.57–0.63). Similarly, compared to the PIPER score there is little overlap in the Cls (upper limit of 0.63 for PIPER and lower limit of 0.62 our pre-ECMO score).

For the on-ECMO model, improved performance to discriminate mortality was observed, given a higher C statistic of 0.73 (95% CI, 0.71-0.76). Based on the final variables selected by the model, complications during the ECMO procedure as well as some ECMO-related variables played a significant role in predicting mortality, resulting in a higher C-statistic score compared with pre-ECMO model, as expected. When revalidated using the same development data set for this study, the C statistic for the Haricharan model was 0.67 (95% Cl, 0.68-0.71). Again, note that CI overlap is only at the end point (0.71 is upper limit for Haricharan, and it is the lower upper limit for our on-ECMO model), thus demonstrating better discrimination with our model. Similarly, when PIPER+ was revalidated in our development data set and had decreased discrimination accuracy (C = 0.70, 95% Cl, 0.67–0.73). There was only a slight overlap in the CIs (upper limit of 0.73 for PIPER+ and lower limit of 0.71 for our on-ECMO score).

A Hosmer–Lemeshow test was used to test the calibration: the  $\chi^2$  goodness-of-fit statistic was 5.85 (p = 0.67) for the pre-ECMO model and 6.26 (p = 0.62) for the on-ECMO model, indicating that both prediction models fit (p < 0.05). The shrinkage factor  $\gamma$  based on 2000 bootstraps is 0.89 (95% CI, 0.79–1.00) in the pre-ECMO and 0.90 (95% CI, 0.83–0.99) in the on-ECMO model, which was used to adjust the final prediction models. **Figure 1** shows the predicted mortality as a function of (A) pre-ECMO and (B) on-ECMO RSs (smooth curve) along with the actual observed mortality rate by decile of the RS in the development and validation data sets. The close agreement between observed and predicted mortality in **Figure 1** provide additional validation of the goodness-of-fit of the prediction models.

#### CDH ECMO RISK SCORE

able 2. Fie-EGINO MOUELIUL FIEULCUIU MULUI	able 2.	Pre-ECMO	Model for	Predicting	Mortalit
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		32	(95% Confidence Interval)	р
Demographics				
Weight (pre-ECMO)	-0.6147	0.0773	0.54 (0.46-0.63)	~0.0001
Angar at 5 min	_0.1459	0.0214	0.86 (0.83_0.90)	<0.0001
Side of bernia	-0.1435	0.0214	0.00 (0.00 0.00)	<0.0001
Loft			1 00 (Reference)	
Bight	_0.2022	0.0984		0 0025
Both	-0.2972	0.0904	1.50 (0.86, 2.62)	0.0023
Missing	-0.4070	0.2041	1.30 (0.80-2.02)	0.1313
Propatal diagnosis	-0.3337	0.2455	1.43 (0.00-2.31)	0.1474
No			1 00 (Poforonoo)	
Yee	0.4200	0.0975	1 55 (1 21 1 94)	<0.0001
Handbagging (before ECMO)	0.4390	0.0675	1.55 (1.51–1.64)	<0.0001
			1.00 (Deference)	
NO	0.5300	0 1020		0.0010
tes Missing	0.5729	0.1039	1.01 (0.77, 0.01)	0.0010
Missing	0.2673	0.2681	1.31 (0.77–2.21)	0.3187
Patient arrested before EGNIO			1.00 (Deferrer e e)	
NO Xa a	0.0580	0 1 5 7 7		0 1014
Yes	0.2583	0.1577	1.29 (0.95–1.76)	0.1014
It diaphragmatic nernia was fixed (before	ECIMO)		1.00 (Deferrer e e)	
NO Xa a	0.0500	0.1.400		0 7040
Yes	0.0538	0.1420	1.06 (0.80–1.39)	0.7049
Missing	0.5546	0.1572	1.74 (1.28–2.37)	0.0004
Pre-ECMO blood gas	4 0 4 0 0	0.0470		0 0004
	-1.6422	0.2478	0.19 (0.12–0.31)	<0.0001
Pre-ECMO ventilator settings				
HFOV				
No	0.4040	0.00.11	1.00 (Reference)	0 0001
Yes	0.4919	0.0941	1.64 (1.36–1.97)	< 0.0001
MAP	0.0517	0.0101	1.05 (1.03–1.07)	<0.0001
Comorbidity				
CCHD				
No			1.00 (Reference)	
Yes	0.6029	0.2477	1.83 (1.12–2.97)	0.0149
Perinatal infection				
No			1.00 (Reference)	
Yes	0.3900	0.2712	1.48 (0.87–2.51)	0.1504

CCHD, critical congenital heart disease; ECMO, extracorporeal membrane oxygenation; MAP, mean airway pressure; HFOV, high-frequency oscillatory ventilation.

To assess the robustness of these models to missing data, we refitted the models using only complete data, as well as multiple imputation using 10 imputed data sets. The estimates of coefficients were quite similar for the models in both sensitivity analyses (results not shown). For the pre-ECMO model, the *C* statistic was 0.65 (95% CI, 0.62–0.68) on complete data analysis and 0.64 (95% CI, 0.61–0.68) on multiple imputation analysis. For the on-ECMO model, *C* statistics were both 0.73 (95% CI, 0.70–0.76), which matched the main results presented above based on mean imputation.

#### Exploration of Clinical RGs and Patient Features Within RGs

We examined predicted mortality in five clinical RGs, defined a priori based on percentiles of the RS, as (1) lowest 5%, (2) 5%–25%, (3) 25%–75%, (4) 75%–95%, and (5) highest 5% of the RS for both pre- and on-ECMO models. In pre- and on-ECMO data sets, RSs detected 2–4 fold differences in mortality. For the pre-ECMO model, groups 1–5 corresponded to RS  $\leq$  –0.9, (0.9, –0.3), (–0.3, 0.5), (0.5, 1.2) and RS > 1.2, respectively (**Figure 2A**). The observed mortality rates in validation data set for groups 1–5 were 38%, 35%, 51%, 66%, and 75%, respectively (**Figure 2A**); thus, mortality for

neonates with RS in the 5th to 25th percentile appeared to be the same as those in the lowest 5% of the RS, while mortality increased for those with RS greater than the 25th percentile. This suggested combining groups 1 and 2 into a single lower RG. Similarly, we defined the RGs for on-ECMO model based on the same percentile groups as the pre-ECMO model above; here the five groups corresponded to on-ECMO RS  $\leq$  -1.4, (1.4, -0.6), (--.6, 0.8), (0.8, 2.0), and > 2.0 (**Figure 2B**). The observed mortality rates in the validation set corresponding to the five RGs were 26%, 24%, 53%, 74%, and 86%, respectively (**Figure 2B**).

Finally, we illustrate how the models predict pre-ECMO and on-ECMO mortality for several "new" (potential) neonates. **Table 4** shows the predicted probability of death for 3 distinct neonates (patients 1A–1C) pre-ECMO and on-ECMO (patients 2A–2C) with the RGs depicted. Overall, these demonstrate how the models estimate mortality based on each patient characteristics within the ELSO Registry data elements.

#### DISCUSSION

The primary objective of our study was to develop and validate mortality risk prediction models specifically for the

Table 3.	On-ECMO	Model	for Predicting	Mortality
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Predictors	Parameter	SE	Odds Ratio (95% Confidence Interval)	p
Demographics				
Pre-ECMO weight	-0.6288	0.0823	0.53 (0.45–0.63)	<0.0001
Apgar at 5 min	-0.1288	0.0227	0.88 (0.84–0.92)	<0.0001
Side of hernia			1.00 (Deferrer ec)	
Len Bight	0.2400	0 1052		0.0010
Right	-0.3409	0.1052	0.71 (0.30-0.67)	0.0012
Dolli	0.0040	0.3009	1.34 (1.00-3.31)	0.0272
Prenatal diagnosis	0.5557	0.2337	1.71(1.05-2.85)	0.0370
No			1 00 (Beference)	
Yes	0.3368	0.0934	1.40 (1.17–1.68)	0.0003
If diaphragmatic hernia was fixed	during FCMO	0.0001		0.0000
No			1.00 (Reference)	
Yes	-0.1450	0.0947	0.87 (0.72–1.04)	0.1259
Missing	0.5263	0.1702	1.69 (1.21–2.36)	0.0020
Handbagging (before ECMO)				
No			1.00 (Reference)	
Yes	0.5265	0.1962	1.69 (1.15–2.49)	0.0073
Missing	0.2155	0.2914	1.24 (0.70–2.20)	0.4597
Length of ECMO (weeks)	0.3522	0.0477	1.42 (1.30–1.56)	< 0.0001
Pre-ECMO blood gas				
рН	-1.2850	0.2618	0.28 (0.17–0.46)	< 0.0001
Pre-ECMO ventilator settings				
HFOV				
No			1.00 (Reference)	
Yes	0.4323	0.1070	1.54 (1.25–1.90)	< 0.0001
MAP	0.0421	0.0108	1.04 (1.02–1.07)	<0.0001
ECMO settings				
Pump type				
Centrifugal			1.00 (Reference)	
Roller	-0.1097	0.1106	0.90 (0.72–1.11)	0.3209
Other	0.4327	0.2444	1.54 (0.95–2.49)	0.0766
Missing	-0.6517	0.4982	0.52 (0.20–1.38)	0.1908
Pre-ECMO rescue therapy				
Nitric oxide				
No	0.0111	0.4400		0.0700
Yes	-0.2144	0.1186	0.81 (0.64–1.02)	0.0706
Comorbidity				
			1 00 (Deference)	
NO	0.9160	0.0600		0 0000
MCA	0.0109	0.2002	2.20 (1.34-3.63)	0.0023
No			1 00 (Poforonco)	
Ves	1 387	0 8303		0.00/8
Airleak syndrome	1.007	0.0000	4.00 (0.75 20.00)	0.0040
No			1 00 (Beference)	
Yes	0 2987	0 1263	1.35 (1.05–1.73)	0.0180
Complications	0.2001	0.1200		0.0100
Hemorrhagic other				
No			1.00 (Reference)	
Yes	0.6204	0.0899	1.86 (1.56-2.22)	< 0.0001
Severe neurologic complication				
No			1.00 (Reference)	
Yes	1.0612	0.1285	2.89 (2.25–3.72)	<0.0001
Elevated creatinine				
No			1.00 (Reference)	
Yes	0.4782	0.2172	1.61 (1.05–2.47)	0.0277
Dialysis				
No			1.00 (Reference)	
Yes	0.5023	0.0978	1.65 (1.36–2.00)	<0.0001
Tamponade				
No			1.00 (Reference)	
Yes	0.5144	0.3064	1.67 (0.92–3.05)	0.0931
CPR required			1.00 (D-fame)	
INO Mar	0.0047	0.0000		0.000
Yes	0.9217	0.3003	2.51 (1.40–4.53)	0.0021
Intectious complications/sepsis			1.00 (Deference)	
	0.0000	0 1001		0.0400
res	0.3830	0.1021	1.47 (1.07-2.02)	0.0182

CCHD, critical congenital heart disease; ECMO, extracorporeal membrane oxygenation; MAP, mean airway pressure; MCA, multiple congenital anomalies; HFOV, high-frequency oscillatory ventilation; CPR, Cardiopulmonary Resuscitation.



**Figure 1.** Predicted probability of mortality for pre-ECMO model (**A**) and on-ECMO (**B**) as a function of risk score. Red and blue dots represent observed mortality in groups based on decile of the risk score in development and validation set, respectively. Vertical dashed lines indicate the cutoff for five defined risk groups. ECMO, extracorporeal membrane oxygenation.

CDH-ECMO population. We have noted that prior<sup>1,9</sup> pre-ECMO risk models can overestimate mortality if the presence or absence of on ECMO complications are not considered. And, we wanted to be able to compare initial mortality risk to risk during ECMO to allow for assessment of quality of ECMO care provided. This was the reason for choosing to develop two independent models to estimate mortality risk for the CDH-ECMO population. Our models were divided into distinct clinical time points where this information could be most useful: pre- and on-ECMO. We believe that the risk models presented in our study use clinically relevant predictor variables and enable clinicians to ask questions such as: "What is the mortality risk of a low BW infant with a right-sided diaphragmatic defect if were to be treated with ECMO?" and "How does the mortality risk change after 2 weeks of ECMO with severe intraventricular hemorrhage and/or other complications?".

The most suitable application of these models is to properly risk-stratify infants, retrospectively, accounting for all available clinical data for research and quality improvement.

Parallels exist between the pre-ECMO model developed in this study and previous risk models developed for the general CDH population, which combined ECMO and non-ECMO data. The CDH Study Group (CDHSG) score was based on 5 min Apgar and BW<sup>3</sup>. The Wilford Hall/Santa Rosa prediction equation (WHSR = highest PaO<sub>2</sub> – highest PCO<sub>2</sub>) was developed next.<sup>4</sup> Hoffman *et al.*<sup>5</sup> later showed that neither of these scores were adequately discriminatory when specifically revalidated within the ECMO population. More recently, Brindle *et al.*<sup>6</sup> developed a simple CDH scoring equation based on low BW (<1.5 kg), Apgar scores, severe pulmonary hypertension, critical congenital heart disease, and chromosomal anomalies. Unfortunately, the Brindle score is not applicable to the



**Figure 2.** Observed rate of mortality in the validation cohort according to the five risk score groups; n = number of patients in each of the five risk groups ((1) lowest 5%, (2) 5%–25%, (3) 25%–75%, (4) 75%–95%, and (5) highest 5% of the RS for both pre- and on-ECMO models). Error bar is the 95% confidence interval of death rate. ECMO, extracorporeal membrane oxygenation. A: Depicts risk groups per the pre-ECMO risk score. B: Depicts the risk groups per the On-ECMO risk score.

Table 4. Predicted Pre- and On-ECMO Probability of Death (%) for Potential Neonatal Characteristics

	F	Pre-ECMO			(	On-ECMO	
	Risk Score	Risk Group	Predicted Mortality Percent (95% CI)		Risk Score	Risk Group	Predicted Mortality Percent (95% CI)
Patient 1A	-0.12	3	47.1 (43.5–50.7)	Patient 2A	-0.34	3	41.6 (37.6–45.7)
Patient 1B	0.27	3	56.8 (54.2–59.5)	Patient 2B	1.18	4	76. 6 (71.7–81.5)
Patient 1C	0.81	4	69.3 (59.7–78.8)	Patient 2C	1.77	4	85.5 (81.1–89.8)

Patient 1A: A typical neonate with a left sided CDH with all average characteristics (using mean for continuous variables and majority category for categorical variables), pre-ECMO weight is 3.1 kg, 5 min Apgar score = 6, CDH was not diagnosed prenatally, pre-ECMO ventilator type was HFOV with an MAP of 17 cm of H<sub>2</sub>O, and pH before cannulation was 7.2. Handbagging was not needed before ECMO, did not arrest before ECMO. CDH was not fixed before ECMO There was no history of a perinatal infection. There was no evidence of CCHD.

Patient 1B: A neonate with the same characteristics as Patient 1A, except that CDH was diagnosed prenatally.

Patient 1C: A neonate with the same characteristics as Patient 1A, except that Patient 1C has CCHD diagnosed.

Patient 2A: A typical neonate with a left sided CDH (no comorbidities) with all average characteristics but absence of any complication while on ECMO. pre-ECMO weight is 3.1 kg, Apgar score = 6, CDH was prenatally diagnosed, handbagging was not needed before ECMO, iNO was used before ECMO, pre-ECMO ventilator type was HFOV, MAP = 17 cm of H<sub>2</sub>O, pH before cannulation was 7.2, roller pump was used for ECMO. Diaphragm was not repaired on-ECMO. Current ECMO duration is 1.7 weeks.

Patient 2B: A neonate with the same conditions as Patient 2A but with two on-ECMO complications: hemorrhagic and severe neurologic complications.

Patient 2C: A neonate with the same characteristics as Patient 2B, except ECMO 1 week longer (2.7 weeks) and has Airleak syndrome (pneumothorax).

CCHD, critical congenital heart disease; CHD, congenital heart disease; ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide; MAP, mean airway pressure; MCA, multiple congenital anomalies; HFOV, high-frequency oscillatory ventilation; CPR, Cardiopulmonary Resuscitation.

ECMO population as BW < 1.5 kg is not feasible for ECMO. Kays *et al.*<sup>7</sup> also reported a CDH mortality prediction model, derived from a single institution experience (n = 172), based on CDHSG score, 1 min Apgar, and first pH. Revalidation of the Kays equation with our data set is not possible as first pH is not coded as a variable within ELSO registry data. We revalidated and compared the Neo-RESCUERs and PIPER equations in our data set; based on *C* statistic, our pre-ECMO risk model provided improved prediction.

We next compared the on-ECMO model to previously developed mortality risk models. The first study for comparison is by Seetharamaiah et al.,14 who determined from CDHSG data (1995-2005) predictors associated with survival in the CDH-ECMO population that underwent CDH repair. Seetharamaiah et al.14 identified GA, BW, prenatal diagnosis, length of ECMO, and patch repair as survival indicators. We cannot comparatively revalidate the Seetharamaiah predictors with ELSO data, as the ELSO Registry does not record whether repair with patch was used. Our on-ECMO score can be directly compared with the Haricharan's equation. When revalidated using the same development data set for this study, the C statistic for the Haricharan model and PIPER+ had lower discrimination accuracy, thus, demonstrating better discrimination with our model. This improved discrimination can be attributed to expanded data points and model selection methods used in this study.<sup>20</sup>

We made several observations after examination of the RGs for the pre- and on-ECMO models. For both models, analysis of RG distributions in the two lowest RGs (1 and 2) does not differ significantly with similar neonatal characteristics. Also, the pattern of increasing mortality as a function of increasing RGs is similar for both models. Several subtle differences exist between the two models in the distribution of RGs. First, for the pre-ECMO model, mortality estimate is greater by about 10% for groups 1 and 2 (low risk) compared with the same RGs of the on-ECMO model. Second, the two highest RGs of the on-ECMO model have observed mortality about 10% higher than the corresponding RGs for the pre-ECMO model. This improved discrimination of mortality between lower and higher RGs is attributed to additional information (predictor variables) for the on-ECMO model. It is also critical to point out that the pre-ECMO model demonstrated here and by previous studies can overestimate risk in absence of length of ECMO and on-ECMO complications. This point becomes important as CDH patients represent the largest group of neonatal respiratory failure patients experiencing prolonged ECMO courses.<sup>23</sup> Therefore, the pre-ECMO model provides an average risk of mortality assuming some patients will develop certain complications and have prolonged ECMO runs. This can be helpful as the interplay between the RSs provide a means to address, pinpoint, and improve ECMO care. The on-ECMO model, therefore, is a better prediction tool to estimate mortality risk, assuming those clinical parameters are known.

Clinicians should be very cautious in the application of this or other RSs at the bedside. We specifically discourage clinicians from withholding ECMO for neonates based on high RSs, as survival in the highest RG is 35% and the RS should never come before clinical acumen. Including on-ECMO data may help teams and families understand why support is continuing or occasionally with explaining why discontinuation of support is being considered. Although ideally clinical risk indexes can be used at the bedside, the RSs developed in this study, as well as all other ECMO mortality RSs mentioned above, are best suited for analyzing groups of patients as opposed to the individual neonate. The ECMO risk equations can be used similar to the pediatric American College of Surgeons National Surgical Quality Improvement Program risk equation to provide risk-stratified outcome information to institutions on a periodic basis on CDH infants requiring ECMO.<sup>24</sup> Furthermore, the scores can be used to analyze patients for quality improvement purposes within the same organization. Future iterations of the risk equation may include local institutional adjustments, as predicted outcomes may be different, for instance, at ECMO centers of excellence or high volume centers, which can only be identified with proper

risk adjustment methods, and we believe that the mortality risk equations developed in this study provide the statistically most accurate means to provide such information for the CDH population. Finally, the risk equations can be used for multiple research questions and comparative analyses.

Although our findings add to existing data on CDH-ECMO risk prediction, limitations exist. Similar to most retrospective studies, our study may include potential coding errors and/or missing data. Precise indications for employing ECMO are not standardized across institutions, neither are ECMO care protocols. There are variations in treatment of CDH before ECMO and during ECMO and timing of diaphragm repair across institutions. The clinical variability introduces unmeasurable heterogeneity and randomness, which may affect outcomes. Another limitation was the inability to know the contribution of ECMO to mortality, as the ELSO Registry only includes data for ECMO patients. Therefore, the pre-ECMO risk model should only be calculated in infants who will be treated with ECMO or where ECMO is strongly considered. As is inherent in many databases, the general issue of selection bias is a major limitation, and for the ELSO Registry, there is a selection bias in that it contains patients for whom ECMO has been selected as therapy. Thus, ELSO data reflect the outcomes of patients with CDH for whom ECMO was chosen. Therefore, our prediction model is not a general prediction model of outcome for all CDH patients to be used to decide whether to select ECMO as a therapy or not. Finally, we note that potential candidate predictor variables are limited by what is available in ELSO.

The models developed in this study account for whether or not prenatal diagnosis was established. Important potential information on prenatal prognosticators including lung-head ratio, MRI lung volumes and liver up or down were not available as data elements in the ELSO Registry. Had they been available, these could have potentially improved prediction performance, only in those patients who are prenatally diagnosed. Given, however, prenatal measurements such as lung-head ratio or MRI lung volumes are highly variable on GA, as well as center, and standardization is lacking such that these could be reported to a central registry with accuracy, that is, different centers measure slightly different versions of these anatomic indexes at different gestation ages and not all reports were observed to expected values.<sup>25</sup> Furthermore, there are more centers who provide ECMO than centers who have established fetal centers. Future studies could be aimed at standardizing fetal prognostication and comparatively validating prenatal risk assessment to postnatal risk assessment methods.

In conclusion, we have developed risk models for CDH that allow mortality risk prediction just before and during ECMO using data reported to the ELSO Registry. The equations developed in this study improve upon previous efforts to define risk in the CDH-ECMO population with increased statistical accuracy. At present, our scores can serve as excellent research tools and for benchmarking outcomes amongst different centers. The ability to assess outcome risk systematically and objectively may allow for a greater patient-centered decision making process and improve the care of these high RGs of neonates. Online calculators for both pre- and on-ECMO models are freely accessible at www.choc.org/ecmocalc, where the predicted mortality, confidence interval, and RG can be calculated rapidly and efficiently.

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