UNIVERSITY OF CALIFORNIA
IRVINE

Development and Validation of ECMO Mortality-Risk Models for Congenital Diaphragmatic Hernia

THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in Biological and Translational Sciences

by

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2017

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ABSTRACT OF THE THESIS

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Master of Science in Biological and Translational Sciences

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Rationale: There are no validated bedside tools that can predict mortality risk of a neonate with CDH prior to initiation of ECMO and during the course of ECMO.

Objectives: To develop ECMO specific mortality risk prediction models for CDH.

Methods: The Extracorporeal Life Support Organization (ELSO) registry (2000-2015) was used to develop mortality prediction scores for CDH relative to timing of ECMO. Prediction models were developed using multivariable logistic regression models. Observed mortalities for the pre- and on-ECMO were further examined by five clinical risk groups defined by percentiles of the risk score.

Results: 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% CI: 0.62-0.68). Within the highest risk group, based on the pre-ECMO risk score, mortality was with 87% (144 neonates) and 75% (92 neonates), in the training and validation datasets, respectively. The pre-ECMO risk score included pre-ECMO ventilator settings, pH, prior DH repair, critical congenital heart disease, perinatal infection, and demographics. For the on-ECMO model, mortality prediction improved substantially: C = 0.73 (95% CI: 0.71-0.76) with the addition of on-ECMO associated complications and comorbidities. Within the highest risk group, defined by the on-ECMO risk score, mortality was 90% (147 neonates) and 86% (77 neonates) in the training and validation datasets, respectively. The post-ECMO mortality prediction model which accounted for the timing of CDH repair post-ECMO had the best predictive discrimination with C = 0.80 (95% CI: 0.78-0.82).

Conclusion: Mortality among neonates with CDH needing ECMO can be reliably predicted with validated clinical variables identified in this study relative to timing of ECMO.

CHAPTER 1. INTRODUCTION

BACKGROUND

What is the problem. Congenital diaphragmatic hernia (CDH) is a condition in which the natural barrier between the abdomen and thorax is missing. Although the cause of CDH is uncertain, it is a developmental defect, an embryopathy, that starts very early during pregnancy. In an affected fetus, abdominal organs are shifted to the thoracic cavity and diminish the volume of intra-thoracic space. The resulting pulmonary parenchymal compression affects formation of both lungs, at the structural level, during fetal development. As a result, infants with CDH are born with a varying range of of hypoplastic and poorly developed lungs. In utero, there is minimal consequence for the developing fetus as placental and fetal circulation allow for normal levels of gas exchange. After birth, immature lungs are not able to meet the demands of adult type circulation. This leads to hypoxia, which further exacerbates and leads to high levels of pulmonary vascular resistance and causes progressive, respiratory failure[1]. If not treated with mechanical ventilation, this is a lethal problem for a newborn.

Extra-corporeal membrane oxygenation (ECMO) is a rescue therapy that maintains cardiac and respiratory function during recovery from a reversible respiratory problem. As noted, CDH is associated with varying degrees of reversible pulmonary hypertension, and in the severest cases, infants require ECMO to support cardiopulmonary function. Up to 20% of neonates with CDH require ECMO, also referred to as extra-corporeal life support (ECLS)[2,3]. Placing an infant on ECMO requires placement of large cannulas within the great vessels and circulating the patient's blood outside the body through an artificial lung, also known as membrane oxygenator. The artificial lung then removes carbon dioxide and replenishes oxygen within the red blood cells and pumps the oxygenated blood back to the central circulation.

ECMO is extremely invasive to both initiate and to maintain, therefore clinicians must critically consider how much of it will benefit the patient. Even, the procedure of placing ECMO cannulas to initiate ECMO in a neonate could result in dire consequences given the small size and fragility of the neck vessels. Providing cardiopulmonary support to a patient more then a few hours requires the use of anticoagulants. Infants have very a delicate brain microvasculature, and use of anticoagulants in neonates during ECMO increases the risk of intra-ventricular hemorrhage. There are many other ECMO related complications too numerous to list. Yet, it is clear to most clinicians that ECMO can save lives, when done on patients who are able to benefit.

As reported by the ELSO Registry, the incidence of CDH treated with ECMO is 250-300 infants per year[4]. Roughly half of these infants do not survive[4]. The remaining survivors have a high degree of long-term morbidity such as poor neurodevelopmental outcomes[5,6]. Research efforts, therefore, must be directed to understand the factors that lead to poor outcomes in this high-risk population. There are currently no risk stratification models that allow a population of infants with CDH who require ECMO to be risk stratified. *The purpose of this study was to develop and validate mortality risk models for infants with CDH who require ECMO. The future goal of having a validated risk score is the ability to study and subsequently improve current treatment paradigms for this high-risk group.*

Pertinent research questions. Clinicians have been looking for risk stratification tools to decide who is and who isn't a good candidate for ECMO since the early days of extra-corporeal life support (ECLS)[7]. There are many occasions when deciding to go on ECMO may not be clear-cut. Indications for ECMO may be difficult to justify compared to its inherent risks as well as inappropriate use of expensive resources. ECMO requires the use of blood products, expensive

monitors and circuitry as well as significant number of additional man hours to provide it. In fact, in many countries, this is not a feasible treatment to offer, given its cost and escalation of resources required to provide it. The current recommended contraindications for ECMO in neonates are weight <2kg, gestational age >34 weeks, absence of severe intracranial hemorrhage and chromosomal abnormalities[8]. Beyond that, clinicians are often left with a spectrum of clinical scenarios and the urgency to make decision to initiate ECMO, and continue to provide it once on ECMO.

Why CDH specific ECMO risk prediction models are needed? There are wide variations in institutional practice patterns that surround CDH and ECMO. There are no standardized guidelines to help clinicians make such difficult decisions about which neonate should or should not be placed on ECMO. Many institutions have different criteria to decide when to proceed to ECMO, and then how to manage ECMO and how to repair the diaphragmatic hernia relative to ECMO[1,9,10]. Outcomes can hypothetically vary vastly at each step, outlined in Figure 1. Most research studies comparing various treatment choices are done without proper risk stratification. Although there are multiple risk prediction models for the general CDH population[11-13], there are no models specifically applicable to the ECMO population. A key question is who are the neonates with CDH that will do poorly on ECMO? Or more precisely, is there a severity of illness score specific for ECMO? Second, is it possible to determine disease severity prior to and during ECMO? There is a significant need to use existing data to develop risk models designed to understand the CDH-ECMO predictors of mortality. Another question is, within the reaches of the exclusion criteria, are there neonates who may benefit from ECMO? ECMO itself may generate complex clinical conditions and change the disease severity from low risk to high risk, such a question can only be answered with the use of an accurate risk prediction model. And

third, is it possible improve quality of care based on use of improved risk stratification tools available at the bedside? And finally, can having a risk score allow for researchers to be able to design better studies to compare various medical or surgical treatment options inherent to CDH?

Why is CDH different than other neonatal conditions requiring respiratory ECMO? Given the poor the outcomes associated with CDH, the decision to initiate ECMO, and to continue to provide ECMO is even more complex compared to other neonatal conditions. As depicted on Figure 1A, when a neonate requires ECMO for reasons other than CDH, the timeline is not complicated with timing of CDH repair relative to ECMO. In other words, a usual neonate, with respiratory failure treated with ECMO, does not require surgery during ECMO. The only relative events are going on ECMO and being eventually liberated from ECMO (Fig 1A), when the cardiorespiratory failure has resolved. Whereas for CDH, one has to repair the diaphragmatic hernia either Pre-, On-, or Post-ECMO (Fig 1B). This adds a significant complexity to outcomes associated with CDH and ECMO. And therefore, requires a unique and specific risk model to estimate risk of mortality on each of those various timelines, to be helpful at the bed side, and/or for QI or research projects. *Therefore, it is imperative to attempt to identify risk factors that favor survival and provide ECMO to the best candidates.* Furthermore, it is also imperative to understand, amongst the highest risk patients, what are the factors that favor survival, so care won't be limited due to subjective opinions and preconceptions that an infant with CDH is likely to do poorly on ECMO.

For example, one could estimate the risk of mortality at the bedside prior to ECMO, and decide whether that particular neonate with could benefit from ECMO, this would be done using a pre-ECMO risk model, which would include variables known to ECMO providers before ECMO. Then again, an ECMO provider may want to know how long to continue ECMO and estimate risk of mortality on different hours, days of ECMO, to see if that neonates is likely to benefit from ECMO, with or without the development of various on-ECMO complications. This would require knowing length of ECMO, and absence or presence of such complications to estimate mortality, on-ECMO. Finally, if an infant was liberated from ECMO, and the CDH was not yet repaired, a clinician could estimate whether an infant would benefit from CDH repair after ECMO based on mortality estimation, post-ECMO. Another use of a post-ECMO score would be retrospective risk stratification of infants at one institution vs. another, knowing details about events surrounding use of ECMO and timing of CDH repair. Currently, there are no accurate risk models that can provide clinicians with this type of detail to estimate risk of mortality associated with ECMO and CDH.

***How does this study move science along*?** 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 [11-15]. Additional risk stratification methods are needed such that the likelihood of survival of a given neonate with CDH can be estimated. Because of the nature of ECMO, two separate models would optimize usefulness to the ECMO providers: 1) immediately prior to initiation of ECMO, and 2) during the course of ECMO (Figure 1). No previously developed risk model can address these two very specific questions independently. There are no

available bedside tools that can risk stratify neonates with CDH prior to going on ECMO or during an ECMO run.

***Directional hypothesis*.** Having the ability to determine disease severity prior to and during an ECMO run for CDH will improve risk stratification methods available and eventually improve the outcomes of infants with CDH by improved patient selection, improved ability to conduct research based on risk stratification and as well as improve parent physician interactions by ability provide more precise information.

***Where are you headed*.** Bedside interpretation of data will allow for clinicians to immediately risk stratify their patients and inform families of expected survival rates. Such bedside calculation of risk estimation specific for CDH and ECMO can be accomplished with the risk scores developed in this study. However, further discussions within ECMO and CDH communities will need to be held to decide if leaders in the field will recommend the use of the scores developed in this study, at the bedside. Overall, accurate estimation of mortality risk may allow for families to better participate in the process of complex clinical decision making. Furthermore, an improved risk stratification tool will allow for institution level comparison of outcomes and allow for areas where care can be improved within organizations. **Ultimately, lives can be saved if better care can be appropriately delivered.**

CHAPTER 2. BACKGROUND

Epidemiology. CDH affects 1 in every 2000-3000 live births in the United States[16], which is roughly about 1000-1500 infants per year. Although CDH is commonly an isolated finding, incidence of associated anomalies have been reported to range from 10-50% in variety of series, most common defects are skeletal and cardiac[17]. There is an additional 1/3rd more affected fetuses that are not represented in the live birth statistics as they are stillborn. According to a most up-to-date epidemiologic study, commonly associated other anomalies include cardiac defects seen in 14% of infants followed by chromosomal defects seen in up to 10% of infants with CDH[17]. Association of other anomalies increase risk of mortality and morbidity[12,17,18]. In fact, most of the stillbirths are a result of other severe anomalies that affect the fetuses, not the presence of CDH.

Anatomy & Embryology. The embryologic development of the diaphragm is poorly understood. Failure of muscular fusion of the diaphragm leaflets is believed to lead to weakening of the area and herniation of bowel contents into the chest cavity. Resulting compression leads to pulmonary maldevelopment and hypoplasia at the alveolar level of both lungs, as previously explained. In some cases, the defect is small, and in others it may be complete agenesis of the diaphragm. In 80% of the cases, the diaphragmatic defect is on the left side and remainder of the cases it is on the right side. Extremely rarely, infants can have bilateral defects, which is more likely a form of eventration of the diaphragm as opposed to a true defect[2,4]. Studies have demonstrated that the size of the defect directly correlates with poorer outcomes[2].

ECMO use for CDH. ECMO supports cardiorespiratory functions when either one or both are failing. That being said, ECMO only leads to survival if the conditions its being used for is reversible. The persistent pulmonary hypertension associated with CDH is a reversible condition

and can be treated with ECMO. Most infants with severe CDH require ECMO for 1-2 weeks, after which the pulmonary hypertension resolves, pulmonary function improves and adequately to provide gas exchange, leading to survival in ideal circumstances. There are several clinical situations that can occur relative to ECMO (Figure 1). The simplest option is when ECMO is not utilized, and patient's condition is treated with all other available conventional therapies, this doesn't always work, and ECMO is required in 20% of cases. If the neonate is a candidate for ECMO, either before or after the diaphragmatic hernia is repaired, ECMO can be initiated. If the infant stabilizes, and then alternatively, diaphragmatic hernia can be repaired during ECMO, and if able ECMO can be stopped. Alternatively, ECMO can be continued and stopped before repairing the diaphragm, and the diaphragm repair can performed at a later time when the infant is stable. Many institutions have their own preferences regarding these treatment patterns, and in expert hands all are probably equally safe. Given the lack of a risk severity index, it is not possible to compare any of these treatment choices to each other.

History of ECMO for CDH. ECLS originated during the 1970s at the UC Irvine Medical Center and Children's Hospital of Orange County (CHOC) under the leadership of Dr. Robert Bartlett. In fact, the first description of use of ECMO for neonatal respiratory failure was described by Dr. Bartlett at CHOC and UC Irvine. With regards to CDH, the first use of ECMO was described by German et al,[1]. A critical contributions from our institution by Dr. German also included the description and understanding of the pathophysiology of pulmonary hypertension as the culprit of cardiorespiratory failure in CDH[1]. This early report was also the first description of of repair of CDH during ECMO (Figure 1). In this first cases series of 4 infants with CDH treated with ECMO, there was only 1 survivor[1].

A series of randomized trials followed; The first prospective randomized trial of ECMO in neonatal respiratory failure was conducted by Dr. Bartlett and colleagues. This trial involved an adaptive design using the randomized play-the winner method. The trial only had one control patient who died in the control arm and all the survivors were in the ECMO group[19]. There were significant commentaries that followed which criticized the technology of ECMO and the trial itself, given there was only a single control patient. A second trial was undertaken at the Boston Children's Hospital, which showed 28/29 survival in the ECMO group and 6/10 survival in the conventional medical therapy, control group[20]. Both trials were criticized for either exposing critically ill infants to high risks of ECMO or conversely, denying ECMO to patients in the control group. The UK collaborative conducted a larger trial and showed further benefit towards ECMO in neonates demonstrated by greater survival and lesser degrees of neurodevelopmental disability at 1 year of age[21]. Clinicians globally soon realized that ECMO regularly results in survival in neonatal respiratory failure and surviving neonates for the most part, grow up to be healthy, which therefore led to wide adoption of ECMO. Over the last 3 decades, the use of ECMO has expanded and has become common place in most tertiary medical centers.

Specific to CDH, there has never been a randomized trial conducted to determine whether the use of ECMO in CDH is beneficial. This is of particular interest, as CDH carries the greatest mortality of all neonatal conditions requiring respiratory ECMO. The UK collaborative trial had the largest number of infants with CDH, where 14/18 in the ECMO group died, and 17/17 in the conventional arm died[21]. Mortality among infants with primary diagnosis other than CDH was 21% in the same study[21]. Now, this study was conducted in the late 1980s and survival rates have improved since then, and hypothetically a similar trial today would show far superior survival in infants with CDH requiring ECMO. According to the Extra-Corporeal Life Support Organization

(ELSO) there are over 7500 neonates who have been treated with ECMO, that have been submitted to the Registry. The overall mortality rate for these infants has remained near 50% with very little change since the early 1990s[4,22]. There has never been a risk adjusted analysis of the mortality over time to determine whether sicker infants are being placed on ECMO, as indications for ECMO have changed significantly with improvements in critical care and ventilation strategies.

A recent report from Children's Hospital of Philadelphia showed survival rates of 67% if CDH was repaired prior to ECMO, 44% if repair while on-ECMO and 100% if repaired after ECMO[10]. And according to a report per Seetharamaiah et al., report from the Congenital Diaphragmatic Hernia Study Group (CDHSG), from the years 1995-2004, the survival rate for those receiving ECMO was 67% overall and 61% if CDH repair was attempted at all[23]. What is clear is that depending on the subgroup analyzed, there is a wide variation in the survival rate of the CDH-ECMO cohort, ranging from 50% to 100%. That being said, it is unclear, if every center has the same criteria to initiate ECMO, as in some centers may be more selective in initiating ECMO and hence their patient population may have greater degree of burden of illness. Whereas, other centers may be very liberal on early use of ECMO and their patient's may be less sick and have greater survival. There is no current method to risk stratify infants with CDH who require ECMO to tease out these details and compare results cross institutions.

ECMO Risk Models. Given issues raised above, accurate discrimination of disease severity in the CDH-ECMO population is required to test and improve current treatment preferences. Furthermore, there is a need to have a bedside tool that gives ECMO providers the ability to compare/contrast the predicted outcomes of an infant with CDH requiring ECMO, and

potentially guide ongoing intervention on an individual basis. To that end, there has been a persistent effort to develop mortality risk prediction tools for ECMO. Dr. Bartlett's neonatal pulmonary insufficiency index (NPII) was a function of pH and FiO_2[7]. An alternative method included alveolar-arterial oxygen gradient measurements over 6-12h to predict outcomes[7]. However, since the development of these predictors, management patterns have evolved and become significantly more complex. As compared to oxygenation based risk prediction, Bohn et. al. suggested severe CO_2 retention and significant preductal shunting unresponsive to hyperventilation, was more predictive of poor outcomes[24]. Treatment patterns continued to evolve and become significantly more complex requiring use of additional risk models.

CDH Risk Models. The development of Congenital Diaphragmatic Hernia Study Group (CDHSG) and ELSO registries allowed for larger datasets to be available for development of risk prediction models. The CDHSG's score was developed to risk stratify all infants born with CDH, with the purpose of estimating disease severity in the first 5 minutes of life [13]. The CDHSG risk equation was based on birth weight (BW) and Apgar score at 5m. Wilford Hall/Santa Rosa CDH survival prediction equation (WHSR= highest PaO_2-Highest PCO_2) was next developed and externally validated from the CDHSG data [14]. In a follow up study, Hoffman et. al., showed that neither the CDHSG, nor the WHSR scores were able to discriminate survivors from non-survivors within in the CDH-ECMO population [15]. More recently, Brindle and coworkers reported a modified version of the CDHSG score [12]. The Brindle's score is made up of integer scores assigned to presence of low birth weight (BW), missing Apgar scores, severe pulmonary hypertension, major cardiac anomaly, chromosomal anomaly. Although the Brindle score is very valuable, it is not specific nor able to discriminate the ECMO population into risk groups. Kays

et. al., reported a CDH mortality risk prediction model derived from single institution experience of 172 neonates with CDH, in this model risk of mortality was defined by CDHSG score predicted mortality plus Apgar score at 1min and first pH [11]. Kays score included Bohn's hypothesis that pH and pCO_2 are predictive of mortality and combined these with CDHSG score. Survival was 50% or greater in the most severe 10% as defined by their score. An external validation of the Kay score for the CDH-ECMO population has not been reported.

CDH ECMO Risk Models. In 2008, Haricharan et. al. reported a CDH specific ECMO mortality prediction score using ELSO registry data [25]. The Haricharan score includes demographic variables, other pre-ECMO/on-ECMO variables and bypass duration>15d were modeled together [25]. There were only 24 patients in the high-risk category, making the power of predictive model small [25]. All the variables within the model are dichotomous and does not include ranges. Furthermore, the candidate variables were not chosen based on an unbiased criterion selection method. A decade's worth of data has since been collected in the ELSO registry to develop a more robust risk model that predicts mortality separately before ECMO, during ECMO relative to duration of ECMO and takes into account pre-ECMO rescue therapies and associated on-ECMO complications.

More recently, Barbaro et. al., developed the Neo-RESCUERS risk prediction model for all neonates receiving respiratory ECMO [26]. This model combined once again demographics along with pre-ECMO/on-ECMO variables to predict mortality risk in all neonates, and their data included neonates with CDH as well as all other causes of respiratory neonatal respiratory ECMO. The neonates with CDH were the sickest cohort in this risk prediction model, making it it difficult to further risk stratify neonates with CDH into their specific risk groups. Furthermore,

the Neo-RESCUERS model does not include unique key variables such as timing or repair for CDH (depicted on Figure 1) or side of CDH.

A similar score was developed for all neonates requiring ECMO, the Pittsburgh Index for Pre-ECMO Risk (PIPER) specific for venoarterial (VA) ECMO[27]. There are two modalities for establishing ECMO, VA and venovenous (VV). For all conditions other than CDH, VV is often the preferred ECMO modality for pure respiratory failure. Specific to CDH, in a prior study, we demonstrated that mode of ECMO does not predict mortality, even after accounting for initial severity of illness by a multivariable model and using center as a random effect[4]. PIPER overall is very similar to the Haricharan score, as it is based on multiple dichotomous variables, and does not include an unbiased candidate variable selection method. And more specifically, does not include parameters that are specific to infants with CDH, such as prenatal diagnosis of CDH, side of CDH, timing of CDH repair (Figure 1).

Purpose of study. The purpose of this study was to develop separate mortality risk models before ECMO and on-ECMO for CDH. Lastly, to address the need to determine risk or mortality knowing all events relative to CDH repair and ECMO, we sought to develop a post-ECMO risk model specific for CDH. This is specifically needed for CDH to guide ECMO providers to assess initial severity of illness and predict mortality while on ECMO, in an effort to either prolong or stop ECMO. The novel risk models developed in this study give ECMO providers the ability to risk stratify neonates based on initial severity of illness and on-ECMO severity of illness models relative to duration of ECMO. Finally, a post-ECMO model can be used to determine risk of survival after CDH repair following liberation from ECMO, or prospective risk stratification to compare outcomes across institutions, since all events prior to discharge are included in a post-ECMO risk model.

CHAPTER 3. METHODS

Data Source and Cohort.

The Children's Hospital Orange County institutional review board approved this study (#150969) as exempt status. We queried the ELSO registry data for neonates whose primary diagnosis was CDH from 2000 to 2015. We omitted data from prior to 2000 to limit the data to the most current treatment practices. ELSO registry data are organized such that each patient has a primary diagnosis, for this study CDH was the primary diagnosis. In addition, every patient has up to 25 other secondary diagnoses. We exhaustively searched ELSO Registry for all secondary ICD-9 diagnoses codes to establish dichotomous variables to identify presence of complications/comorbidities. Candidate predictors evaluated for pre and on-ECMO models were selected based on clinical considerations and/or previous studies [4,7,11-13,23-25,28-30].

Candidate Variables

For the pre-ECMO model, we considered the following demographic variables including gender, pre-ECMO weight, race, gestational age (GA), post-gestational age, 5-min Apgar, side of CDH, prenatal diagnosis of CDH, CDH repair prior to ECMO, hand-bagging and pre-ECMO arrest; blood gas/ventilator variables included pH, pCO_2 and pO_2, mean airway pressure (MAP), oxygenation index (OI); pre-ECMO rescue therapies included inotropes, bicarbonate/THAM, iNO, surfactant, neuromuscular blockers, milrinone, sildenafil and steroids; comorbidity variables included pre-ECMO renal failure[26], critical congenital heart disease (CCHD)[31,32], multiple congenital anomalies (MCA), chromosomal anomalies and perinatal infection.

For the on-ECMO model, we identified additional variables including repair of diaphragmatic hernia on-ECMO and ECMO duration, ECMO mode (venoarterial and venovenous) [4] 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 CPR), in addition we considered PDA R to L and PDA bidirection per echocardiogram findings during ECMO, infectious (positive cultures and WBC < 1500), and endocrine complications (glucose < 40 and > 240) were grouped. Neurologic complications were divided into seizures and severe neurologic complications [CNS hemorrhage, infarct, intraventricular hemorrhage (IVH) grade 3&4]; renal complications were separated into two elevated creatinine groups (1.5 - 3 and >3), and dialysis (hemofiltration, CAVHD).

For the post-ECMO model we included all above variables from the pre and on-ECMO variables as described above. In addition, we accounted for CDH repair post-ECLS or no repair as additional candidate variables. Post-ECMO CDH repair included the categories: no repair, repaired before, during, or after ECMO and missing.

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 Apgar, pCO_2, pO_2, oxygenation index 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 non-missing weight with birth weight (BW) and age (days) as independent variables. Similarly, missing values in gestational age (4.5%) were imputed based on decile groups of BW. The Henderson-Hasselbalch equation was used to calculate missing pH (3.5%) given known HCO3 and pCO_2. MAP (10.2%) was imputed based

on a clinical formula as a function of peak inspiratory pressure (PIP), respiratory rate and positive end expiratory pressure (PEEP), (i-time = 0.5 seconds). Oxygenation index was calculated as OI = [(fio2*MAP)/po2)] and missing values (10.2 %) were obtained using mean imputation.

Statistical Methods

The outcome of the prediction models was inpatient mortality during or following 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 one-third 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 (AIC)[33,34]. We estimated a linear shrinkage factor (γ) using the bootstrap method (with 2000 bootstrap replications) applied to the development dataset to assess potential model overfitting (optimism) [33,35-37]. The shrinkage factor γ 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 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, $RS = \gamma X\beta$, where X represents patient variables, β are the final model coefficients, and γ is the shrinkage factor. The predicted probability for a new patient was $1/(1+e^{-RS})$. Furthermore, we explored five clinical risk groups based on percentiles of

the risk score (lowest 5%, 5-25%, 25-75%, 75-95% and highest 5%). The observed mortality in each of five risk groups was assessed in the validation set. Finally, we examined summary statistics of the predictor variables in the five clinical risk groups to further understand and identify salient features of patients in each risk group. Analyses were performed in R version 3.22 using library RMS and SAS version 9.3.

CHAPTER 4. RESULTS

Baseline characteristics

Baseline characteristics of the cohort are provided in **Table 1**. Briefly, the majority were male and white race. The mean pre-ECMO weight was 3.07 ± 0.52 kg and gestational age was 38.1 ± 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, 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 and post-ECMO for CDH (Figure 2). 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 CCDH and presence of perinatal infection were associated with increased 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 length, use of iNO, having diagnosis of MCA 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% CI: 0.62-0.68) (**Table 4**). 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) (**Table 4A**). 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 on predicting mortality, resulting in a higher C-statistic score compared to pre-ECMO model, as expected. A Hosmer-Lemeshow test was used to test the calibration: the χ^2 (Chi-square) 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 (**Table 4A**), indicating that both prediction models fit (P < 0.05). The shrinkage factor γ 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 (**Table 4A**), which was used to adjust the final prediction models. **Figure 2** shows the predicted mortality as a function of (A) pre-ECMO and (B) on-ECMO risk scores (smooth curve) along with the actual observed mortality rate by decile of the risk scores (RS) in the development and validation datasets. The close agreement between observed and predicted mortality in **Figure 2** provide additional validation of the goodness-of-fit of the prediction models. We further compared performance of previously published CDH or neonatal ECMO risk scores (table 4B). This calculation was based on previously published risk scores (by points) and/or β-coefficients if available. As demonstrated, the scores validated in the current study, which are CDH/ECMO specific, all perform superior to previously published scores (table 4B).

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 datasets. 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.

Lastly, we examined mortality risk prediction post-ECMO to account for repair of diaphragmatic hernia repair subsequent to an ECMO run. For this, we included post-ECMO information on the timing of CDH repair variable and whether repair was made. Specifically, the revised CHD repair predictor variable, incorporating post-ECMO repair information included the categories: no repair, repaired before, during, or after ECMO and missing. Post-ECMO prediction of mortality improved: C-statistic 0.80 (95% CI: 0.78-0.82).

Exploration of clinical risk groups (RG) and patient features within risk groups

We examined predicted mortality in five clinical risk groups, 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. For 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 3A**). The observed mortality rates in validation dataset for groups 1-5 were 38%, 35%, 51%, 66% and 75%, respectively (**Figure 3A**); thus, mortality for neonates with RS in the 5-25th percentile appeared to be the same as those in the lowest 5% of the RS while mortality increased for those with RS greater the 25th percentile. This suggested combining groups 1 and 2 into a single lower risk group. Similarly, we defined the risk groups 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], (-0.6, 0.8], (0.8, 2.0] and > 2.0 (**Figure 3B**). The observed

mortality rates in the validation set corresponding to the five risk groups were 26%, 24%, 53%, 74% and 86%, respectively (**Figure 3B**). We next examined the characteristics (predictor variables) of neonates in each risk groups. Supplemental **Table S1** (pre-ECMO) and **S2** (on-ECMO) showed patient characteristics (predictors) in each risk groups in development dataset. The predictor profiles were quite similar in groups 1 and 2. For the on-ECMO risk score the typical predictor profiles (**Table S2**) included higher pre-ECMO weight and Apgar score; fewer CDH diagnosed prenatally; lower rate of handbagging and shorter ECMO runs; higher rate of diaphragmatic hernia fixed during ECMO; more roller pumps were employed; lower rate of pre-ECMO HFOV; on average, higher pH and lower MAP; lower rate of comorbidities (CCHD, airleak syndrome); and fewer complications (hemorrhagic, severe neurologic complication, elevated creatinine, dialysis, tamponade, CPR and sepsis/infection).

Finally, we illustrate how the model predicts pre-ECMO and on-ECMO mortality for several "new" (potential) neonates. **Table 5** shows the predicted probability of death for 3 distinct neonates (1A-1C) pre-ECMO and on-ECMO (2A-2C) with the risk groups depicted. Overall these demonstrate how the models estimate mortality based on each patient characteristics within the ELSO registry data elements.

CHAPTER 5. DISCUSSION

The objective of our study was to develop mortality risk prediction models specifically for the CDH-ECMO population. Although, previous work evaluated models for CDH patients in general or neonates receiving respiratory ECMO, these models represent the most robust analyses that have focused specifically on the CDH-ECMO cohort. Our models were divided into two distinct clinical time points where this information can 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 birth weight infant with a right sided diaphragmatic defect before ECMO?" and "How does the mortality risk change after 2 weeks of ECMO with severe intra-ventricular hemorrhage and/or other complications?" Lastly, the purpose of the post-ECMO model was properly to risk stratify infants, retrospectively, accounting for all available clinical data.

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[13]. The Wilford Hall/Santa Rosa prediction equation (WHSR = highest PaO_2 - highest PCO_2) was developed next [14]. Hoffman et al. later showed that neither of these scores were adequately discriminatory when specifically revalidated within the ECMO population [15]. More recently, Brindle et al. developed a simple CDH scoring equation based on low BW (<1.5kg), Apgar scores, severe pulmonary hypertension, CCHD, and chromosomal anomalies [12]. Unfortunately, the Brindle score is not applicable to the ECMO population as BW<1.5kg is not feasible for ECMO. Kays et al. also reported a CDH mortality prediction model, derived from a single institution experience (n=172), based on CDHSG score, 1min Apgar and first-pH [11]. Survival was 50% or greater in the

most severe 10%, similar to our CDH-ECMO population. Revalidation of the Kays equation with our dataset is not possible as first-pH is not coded as a variable within ELSO registry data.

A direct comparison of our pre-ECMO model to the Neo-RESCUERs score (a pre-ECMO mortality prediction score developed for all neonates receiving respiratory ECMO) is possible [26]. Applying the development dataset used in this study, the Neo-RESCUERS equation discrimination drops significantly (C = 0.59, 95% CI 0.56-0.62), demonstrating that the pre-ECMO score of our study discriminates better as it specifically focuses on the CDH population. PIPER is another score that can be compared to our pre-ECMO score and its performance based on C-statistic is inferior, and it is not solely derived from CDH specific ECMO population and is only meant for risk stratification during VA-ECMO.

Likewise, the on-ECMO model developed in this study can be compared to previously developed risk models. The first study for comparison is by Seetharamaiah and coworkers, who determined from CDHSG data (1995-2005) predictors associated with survival in the CDH-ECMO population that underwent CDH repair[23]. Seetharamaiah et al. identified high GA, high BW, lack of prenatal diagnosis, shorter length of ECMO, and patch repair as indicators for survival. Despite similarities between our model and the variables identified by Seetharamaiah, we can not revalidate the Seetramaiah predictors in the ELSO registry, as the ELSO registry does not record data on whether or not primary or patch repair was performed.

Our on-ECMO score can also be directly compared to the Haricharan score which was developed using ELSO data from 1997-2007 [25]. The Haricharan model included only 24 patients in the high-risk category, severely limiting reliability and generalizability of that model. The authors did not list a C-statistic. When re-validated using the same development dataset for this study, the C-statistic for the Haricharan model was 0.67 (95% CI 0.68-.071) compared to our

score of 0.73 (95% CI 0.70-0.75), thus demonstrating better discrimination with our model. This improved discrimination can be attributed to expanded datapoints, including CDH repair, pump-type, additional pre-ECMO rescue therapies, comorbidities, and additional complications. In addition, we included length of ECMO as a continuous variable, making it possible to calculate mortality risk precisely in the first two weeks and beyond.

PIPER+ is another score that can be compared to our on-ECMO model, but as stated previously it is not CDH specific and it is a VA-ECMO only score. When compared to the on-ECMO score of this study, PIPER+'s discrimination is lower. PIPER+ also uses all on-ECMO complications per systems, which minimizes the affect of severe complications compared to ones that are less likely to affect outcomes. For example, severe neurologic complications and seizures are all grouped as neurologic complications. This is true for all additional systems of on-ECMO complications within PIPER+. We therefore believe that the on-ECMO score of our study is theoretically better designed, and lacks "noise" that may interfere with better performance of our risk score. Finally, the selection method (AIC criterion) used in our study is also devoid of bias, where as other's have solely depended on forward/backward selection methods based on p-value.

Compared to previous studies[11,25], the clinical risk groups described in this study have greater power, potentially increasing their reliability. We made several observations after examination of the risk groups for the pre-and on-ECMO models. For both models, analysis of risk group distributions in the two lowest risk groups (1 and 2) do not differ significantly with similar neonatal characteristics. Also, the pattern of increasing mortality as a function of increasing RGs are 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 to the same RGs of the on-ECMO model. Second, the two highest risk groups of the on-ECMO model have observed mortality about 10% higher than the corresponding risk groups for the pre-ECMO model. This improved discrimination of mortality between lower and higher risk groups is attributed to additional information (predictor variables) for the on-ECMO model.

While our findings add to existing data on CDH-ECMO risk prediction, there were limitations. One limitation was that every neonate was subjected to ECMO, and it is impossible to know the contribution of ECMO to mortality, specifically relevant for the pre-ECMO model. Therefore, the pre-ECMO risk model should only be applied/calculated in infants who are candidates for ECMO. Further validation must occur to use the pre-ECMO model within the at-risk population of infants for ECMO. Other limitations include potential coding errors and/or missing data common to all retrospective studies. Furthermore, precise indications for employing ECMO are not standardized across institutions. A comparative study of different risk equations solely with ELSO data is also not possible as additional variables present in smaller series or the CDHSG are not always coded in ELSO. Overall, we urge caution when applying these models to clinical practice until future studies externally revalidate our findings.

In conclusion, we have developed risk models for CDH that allow mortality risk prediction just prior to, during and after ECMO. The equations developed in this study add to the 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 risk groups of neonates. Online mortality risk calculators for both pre- and on-ECMO models are

freely accessible at the http://www1.icts.uci.edu/berd/cdhecmoscore.html, where the predicted mortality, confidence interval and risk group can be calculated rapidly and efficiently (Fig 4).

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CHAPTER 6. FUTURE DIRECTIONS

Future Research Question/Goal I: Comparative validation of previously established CDH risk-scores for ECMO. We have recently developed and validated mortality risk models for neonates with CDH requiring ECMO. We hypothesize that the risk models developed specifically for the CDH-ECMO population will perform superior to previously established risk scores. We aim to test this hypothesis by revalidating all previously established CDH mortality risk models using data from the Extra-Corporeal Life Support Organization (ELSO) and the Congenital Diaphragmatic Hernia Study Group (CDHSG) registries. In addition, we will rigorously test the performance of above mentioned risk scores via external validation by using an external sample of neonates with CDH treated at CHOC over the last decade.

Future Research Question/Goal II: Utilizing CDH-ECMO risk scores—risk adjusted outcomes. The estimated mean survival for infants with CDH treated with ECMO is reported as ~50%. It is believed that this rate has been unchanged for the last 2-3 decades. We hypothesize that neonates with CDH treated with ECMO are sicker prior to being candidates for ECMO in the current era compared to the last 2 decades. We will test this hypothesis by studying observed mortality rates as a function of risk scores and risk groups per year ECMO. In a second separate study, we aim to compare ECMO related complications grouped as preventable vs. those related disease process. We hypothesize that select group of low risk patient's convert to medium or high risk as a result of ECMO related preventable complications. Both these observational studies will demonstrate the research utility of CDH-ECMO risk scores, as previously such questions had not been studied by risk adjusting with validated risk-scores specific to timing of ECMO.

How the future study questions/goals will improve scientific knowledge? An example of questions one may ask as an ECMO provider or an ECMO includes the following: Who are the neonates with CDH that will do poorly on ECMO? Is it possible to determine disease severity prior to and during ECMO precise enough that ECMO can be avoided if futile for a neonate with CDH? Or, are there cases where a physician misjudged disease severity and withheld ECMO for CDH? Within the reaches of the exclusion criteria are there patient's who may benefit from ECMO? Is it ECMO or the initial disease process that is responsible for poor outcomes while on ECMO? Is it possible to improve the quality of care based on use of improved risk stratification tools available at the bedside? Can having an ECMO specific risk score for CDH allow for researchers to be able to design better studies to compare various medical or surgical treatment options inherent to CDH? With the currently developed risk scoring systems, the ability to provide satisfactory studies to answer above questions is limited.

To that end, clinicians have been looking for risk stratification tools to decide who is and who isn't a good candidate for ECMO since the early days of extra-corporeal life support[7]. There are many occasions when deciding to go on ECMO may not be clear-cut. Indications for ECMO may be difficult to justify compared to its inherent risks as well as inappropriate use of expensive resources. ECMO requires the use of blood products, expensive monitors and circuitry as well as significant number of additional person hours to administer. The recommended contraindications for ECMO in neonates are weight <2kg, gestational age >34 weeks, absence of severe intracranial hemorrhage and chromosomal abnormalities[8]. Beyond that, clinicians are often left with a spectrum of clinical scenarios and the urgency to make decision to initiate ECMO, and continue to provide it once on ECMO. Given the poor the outcomes associated with CDH, the decision to initiate ECMO, and to continue to provide ECMO is even more complex compared to

other neonatal conditions. *Therefore, it is imperative to attempt to identify risk factors that favor survival and provide ECMO to the best candidates.* Furthermore, it is also imperative to understand, amongst the highest risk patients, what are the factors that favor survival, so care won't be limited due to preconceptions that infant is likely to do poorly on ECMO. Our risk models do provide such information, however, they require additional effort to improve their accuracy, such that they can be adopted for use at the bedside, on an individual patient.

Ultimately, there are wide variations in institutional practice patterns that surround CDH and ECMO. There are no standardized guidelines to help clinicians make such difficult decisions about which neonate should or should not be placed on ECMO. Many institutions have different criteria to decide when to proceed to ECMO, and then how to manage ECMO and how to repair the diaphragmatic hernia relative to ECMO[1,9,10]. Outcomes can hypothetically vary vastly at each step outlined in Figure 1. Most research studies comparing various treatment choices are done without proper risk stratification, and could potentially lead to erroneous conclusions. The purpose of the proposed future studies are to provide additional validation for the mortality risk models for CDH developed by our group. This is specifically needed for CDH to guide ECMO providers to assess initial severity of illness and predict mortality while on ECMO at the individual level, such that it can be used at the bedside to aid clinical decision making. Furthermore, we seek to demonstrate the utility of the risk scores as research tools with additional studies to address some of the questions raised in this thesis.

What will the future study questions ultimately add to our science. Our results will contribute to the literature on CDH ECMO outcomes and provide further evidence for which risk factors contribute to mortality. In the absence of randomized clinical trials, precise risk assessment may allow for improved study design. Having proper risk model, that are thoroughly

validated could lead to adoption of these risk models to be used at the bedside tools to aid clinical decision making and improve accuracy of information provided to families.

Experimental Design of Future Studies

Data Source: ELSO Registry, CDHSG Registry and internal data from CHOC.

Question Ia: Revalidation of previously established ECMO risk models for the CDH-ECMO population Data: There are several historical indexes including oxygenation index, ventilation index, Dr. Bartlett's index (NPII)[7] and Bohn's criteria[24]. We will study the ability of these indexes to predict mortality both from the ELSO registry and CDHSG. C-statistic and Hosmer-Lemenshow goodness-of-fit will be compared. Unlike the ELSO Registry, CDHSG includes the at risk population of infants who were not treated with ECMO and provides a greater spectrum of possible clinical avenues.

Question Ib: Validation of previously established CDH risk models for the ECMO population

Although some data is equally present in both registries, ELSO contains no data on infants who do not require ECMO. Therefore, the greatest advantage of using both the ELSO and CDHSG data will be to compare our pre-ECMO score and it's ability to predict risk of mortality in the general CDH population. There are additional variables in CDHSG such as size of diaphragmatic hernia, prenatal diagnostic measures, which may allow us to improve the prediction ability of the pre-ECMO score. We will also compare our pre-ECMO score to the CDHSG's score, WHSR, Brindle Score and Neo-RESCUERS. Furthermore, we will compare the on-ECMO score to the Haricharan score.

Question Ic: External validation of pre- and on-ECMO scores with CHOC data. We will create a retrospective database to include all data elements represented in the CDHSG and ELSO registries. There are roughly about 10-12 neonates with CDH that are treated at CHOC each year

and we treat 2/year with ECMO. For the last decade we are anticipating have about 60-75 patient's in total. Next we will calculate risk scores and risk groups of our past experience and calculate risk adjusted mortality to benchmark across the median mortality rate from ELSO and CDHSG registries.

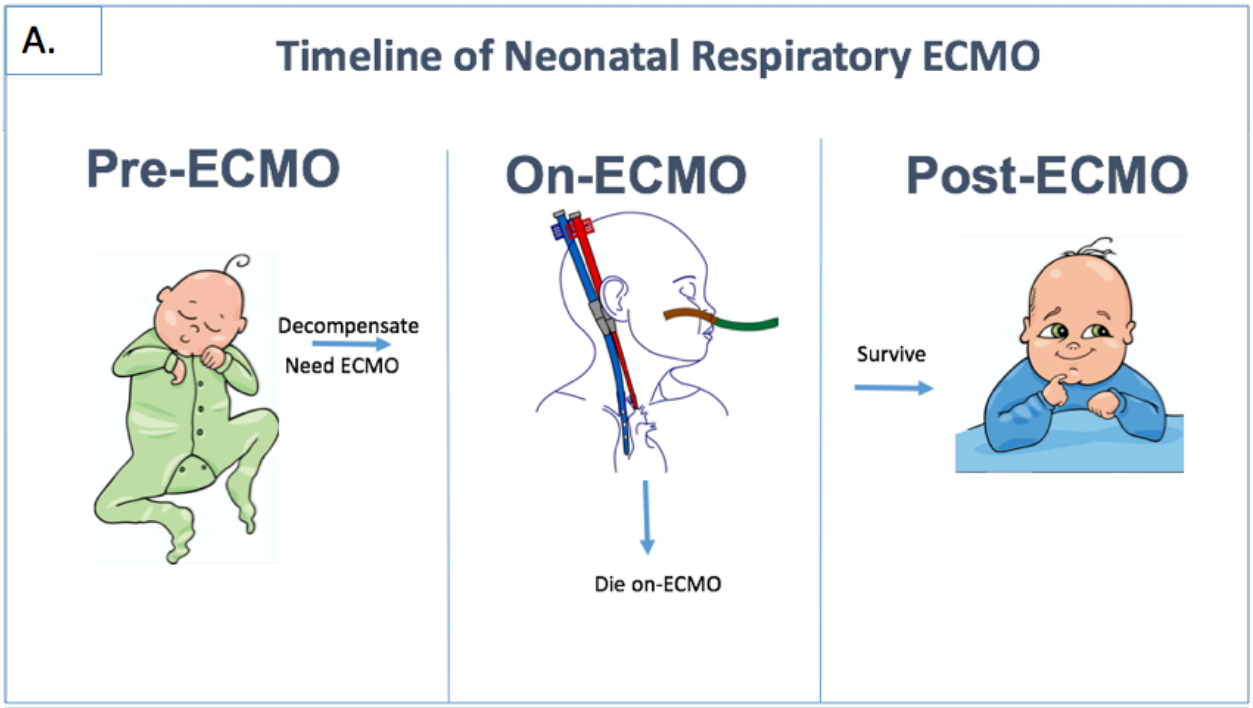
Question IIa: Risk adjusted comparison of CDH mortality from 1990-Current: It is reported that mortality rates are 50%/year for CDH treated with ECMO and this rate has minimally changed since the 1990s. However, it is unknown whether this is secondary to patient's getting sicker or treatment plans having minimal affect. There have been significant advances in neonatal critical care medicine, and there are more medical treatment options that are available before offering ECMO. It is therefore plausible that in the current era infants with CDH are sicker prior to being placed on ECMO, if they need ECMO. To test this hypothesis, we will study the distribution of risk scores and risk groups of the pre- and on-ECMO scores/year and see if there is a correlation with mortality. We are anticipating that the lack of change in mortality is secondary to infants getting sicker over time.

Question IIb: Preventable complications contribute to ECMO related mortality of infants with CDH: The contribution of ECMO to mortality in CDH is unknown. To test this, we will determine number of patients in low risk groups per the pre- and on-ECMO scores and determine which ones cross from low risk to medium/high risk during ECMO, as a result of on-ECMO complications. We will dichotomize on-ECMO complications to preventable and disease process (patient complications) and determine if these contribute to the mortality of low risk infants who

have mortality. (Preventable Complications = Oxygenator failure, raceway rupture, other tubing rupture, pump malfunction, heat exchanger malfunction, clots (oxygenator, bridge, bladder, other), Air in circuit, cracks in pigtail connectors, cannula problems, cannulation site bleeding, surgical site bleeding, hemolysis, culture proven infection).

FIGURES

Figure 1. (A) Expected timeline of neonatal respiratory ECMO (in neonates who require ECMO for reasons other than CDH) compared to (B) expected potential relationship of CDH repair relative to ECMO.



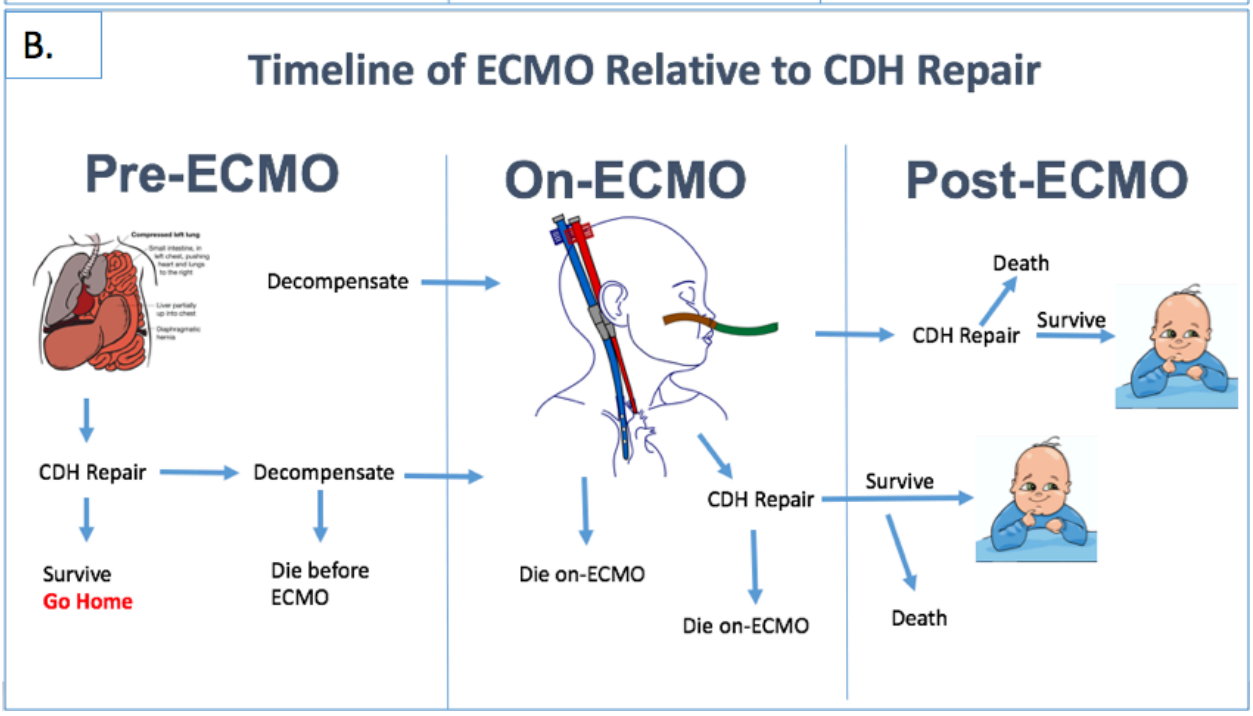


Figure 2. Predicted probability of mortality for pre-ECMO model (Panel A) and on-ECMO (Panel B) as a function of risk score. Red and blue dots represent observed mortality in groups based on decile of the risk score in development and validation set, respectively. Vertical dashed lines indicate the cutoff for five defined risk groups.

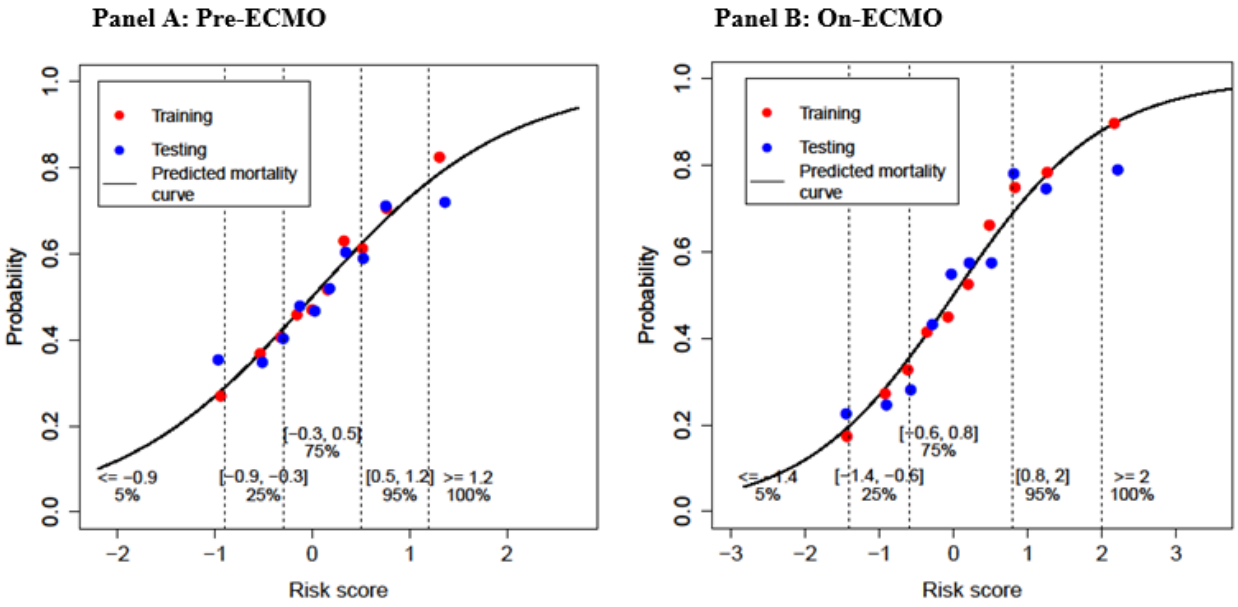


Figure 3. Observed rate of mortality in the validation cohort according to the five risk score groups; n = number of patients in each of the five groups. Error bar is the 95% confidence interval of death rate.

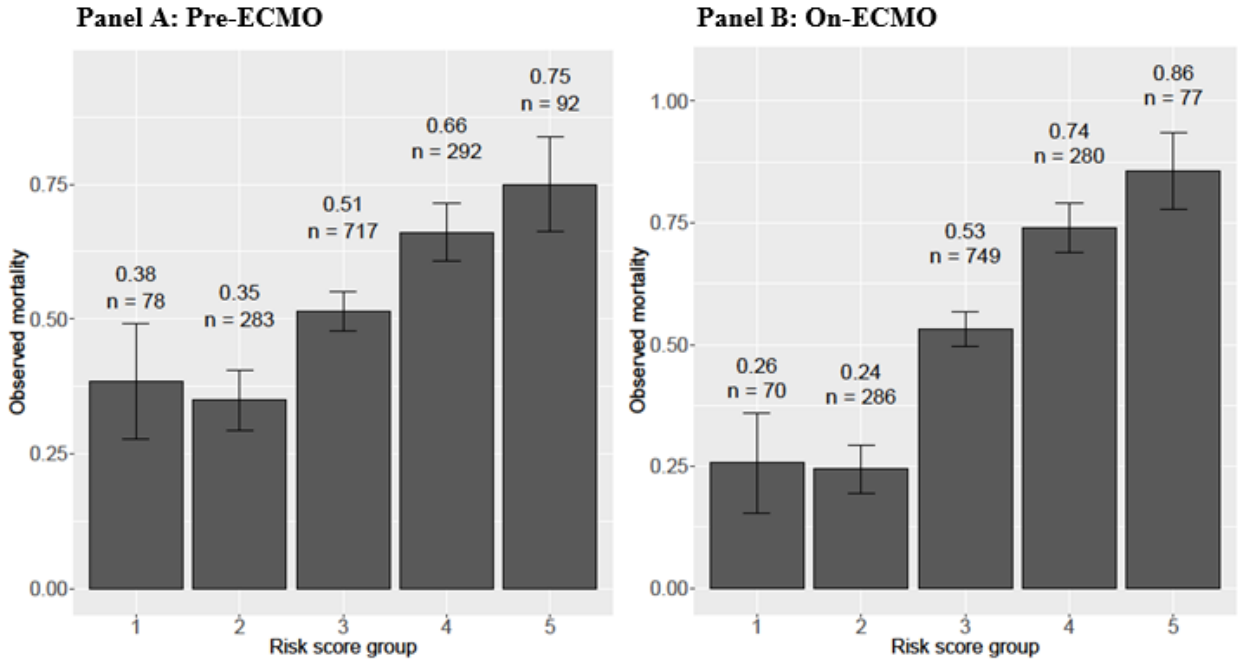
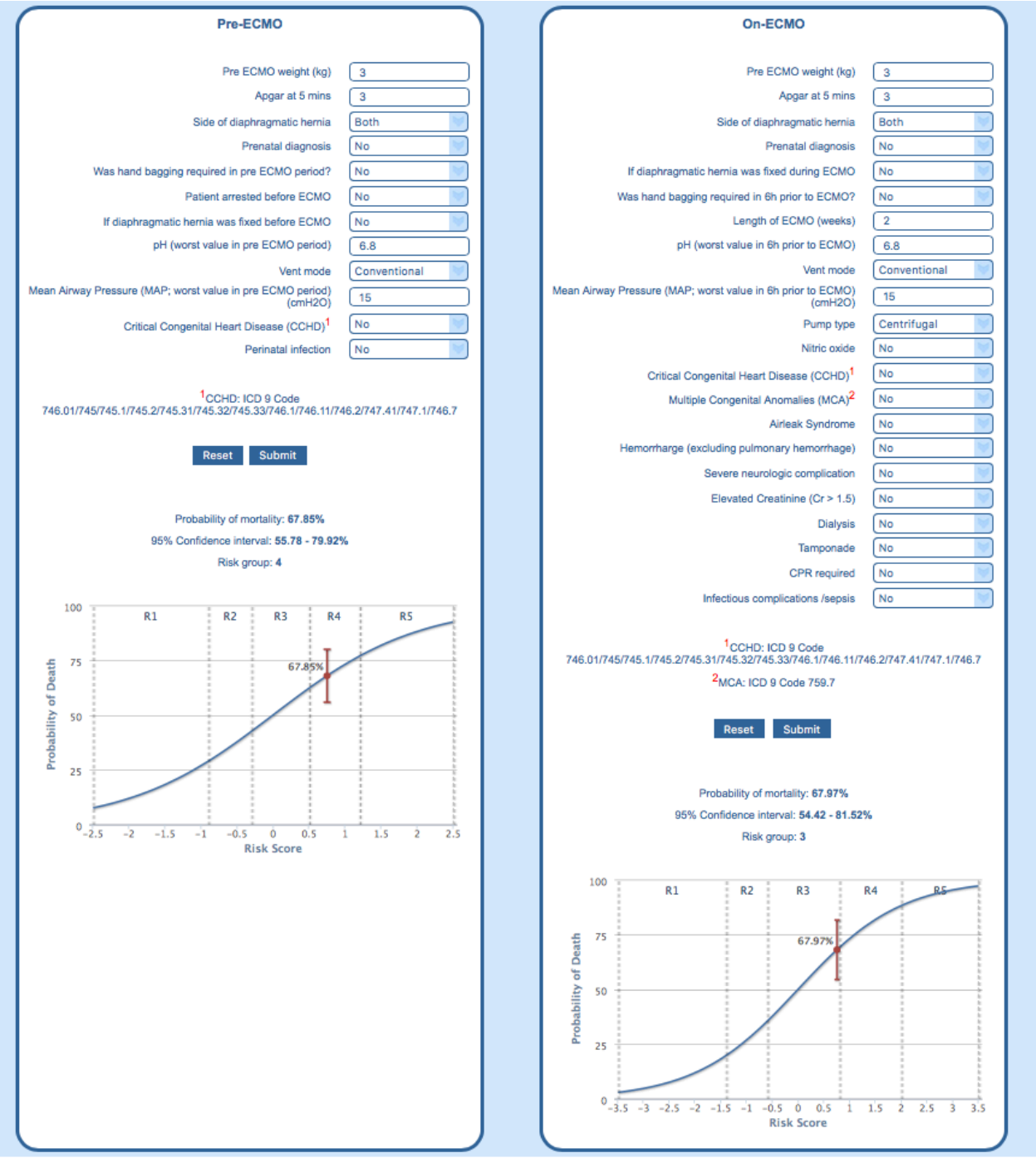


Figure 4. Demonstrates an example risk calculation from pre and on-ECMO risk equations



TABLES

Table 1. Predictor variables, including baseline patient characteristics

Recipients' characteristics	**Entire cohort (n=4,374)**	**Development set (N=2,912)**	**Validation set (N=1,462)**
Pre ECMO			
	Mean (SD)/ Count (Percent)	Mean (SD)/ Count (Percent)	Mean (SD)/ Count (Percent)
Demographics			
Gender (% male)	2522 (57.7%)	1688 (58.0%)	834 (57.0%)
Weight (pre-ECMO)	3.07 (0.52)	3.07 (0.52)	3.05 (0.51)
Race/ethnicity, %			
White	2660 (60.8%)	1778 (61.1%)	882 (60.3%)
Hispanic	757 (17.3%)	511 (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	38.1 (1.71)	38.1 (1.72)	38.09 (1.69)
Apgar at 5 mins	6.22 (1.98)	6.23 (1.97)	6.19 (2.01)
Post gestational Age (days)	2.38 (3.88)	2.37 (3.97)	2.41 (3.67)
Side of hernia			
Left	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%)	37 (2.5%)
Missing	143 (3.3%)	93 (3.2%)	50 (3.4%)
Prenatal Diagnosis	2887 (66.0%)	1909 (65.6%)	978 (66.9%)
Diaphragmatic hernia fixed before ECMO			
No	3623 (82.8%)	2405 (82.6%)	1218 (83.3%)
Yes	413 (9.4%)	270 (9.3%)	143 (9.8%)
Missing	338 (7.7%)	237 (8.1%)	101 (6.9%)
Handbagging			
No	4047 (92.5%)	2683 (92.1%)	1364 (93.3%)
Yes	226 (5.2%)	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%)
Pre-ECMO blood gas			
pH	7.17 (0.17)	7.17 (0.17)	7.18 (0.17)
PCO_2	68.86 (27.76)	68.89 (27.56)	68.79 (28.16)
PO_2	39.22 (29.00)	39.06 (29.36)	39.53 (28.29)
Pre-ECMO ventilator settings			
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			

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	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			
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 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			
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%)
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)

Table 2. Pre-ECMO model for predicting mortality

Predictors	Parameter	S.E	Odds Ratio (95% Confidence Interval)	P-value
Demographics				
Weight (pre-ECMO)	-0.6147	0.0773	0.54 (0.46-0.63)	<0.0001
Apgar at 5 mins	-0.1459	0.0214	0.86 (0.83-0.90)	<0.0001
Side of hernia				
Left			1.00 (Reference)	
Right	-0.2972	0.0984	0.74 (0.61-0.90)	0.0025
Both	-0.4076	0.2841	1.50 (0.86-2.62)	0.1513
Missing	-0.3557	0.2455	1.43 (0.88-2.31)	0.1474
Prenatal Diagnosis				
No			1.00 (Reference)	
Yes	0.4390	0.0875	1.55 (1.31-1.84)	<0.0001
Handbagging (prior to ECMO)				
No			1.00 (Reference)	
Yes	0.5729	0.1839	1.77 (1.24-2.54)	0.0018
Missing	0.2673	0.2681	1.31 (0.77-2.21)	0.3187
Patient arrested before ECMO				
No			1.00 (Reference)	
Yes	0.2583	0.1577	1.29 (0.95-1.76)	0.1014
If diaphragmatic hernia was fixed (before ECMO)				
No			1.00 (Reference)	
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				
pH	-1.6422	0.2478	0.19 (0.12-0.31)	<0.0001
Pre-ECMO ventilator settings				
HFOV				
No			1.00 (Reference)	
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

Table 3. On-ECMO model for predicting mortality

Predictors	Parameter	S.E	Odds Ratio (95% Confidence Interval)	P-value
Demographics				
Pre-ECMO weight	-0.6288	0.0823	0.53 (0.45-0.63)	<0.0001
Apgar at 5 mins	-0.1288	0.0227	0.88 (0.84-0.92)	<0.0001
Side of hernia				
Left			1.00 (Reference)	
Right	-0.3409	0.1052	0.71 (0.58-0.87)	0.0012
Both	0.6645	0.3009	1.94 (1.08-3.51)	0.0272
Missing	0.5357	0.2557	1.71(1.03-2.83)	0.0376
Prenatal Diagnosis				
No			1.00 (Reference)	
Yes	0.3368	0.0934	1.40 (1.17-1.68)	0.0003
If diaphragmatic hernia was fixed during ECMO				
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 (prior to 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				
pH	-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			1.00 (Reference)	
Yes	-0.2144	0.1186	0.81 (0.64-1.02)	0.0706
Comorbidity				
CCHD				
No			1.00 (Reference)	
Yes	0.8169	0.2682	2.26 (1.34-3.83)	0.0023
MCA				
No			1.00 (Reference)	

Yes	1.387	0.8303	4.00 (0.79-20.38)	0.0948
Airleak Syndrome				
No			1.00 (Reference)	
Yes	0.2987	0.1263	1.35 (1.05-1.73)	0.0180
Complications				
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				
No			1.00 (Reference)	
Yes	0.9217	0.3003	2.51 (1.40-4.53)	0.0021
Infectious complications /sepsis				
No			1.00 (Reference)	
Yes	0.3830	0.1621	1.47 (1.07-2.02)	0.0182

Table 4. (A) Discrimination C-statistics, Hosmer-Lemeshow test statistics and shrinkage factor for pre and on-ECMO prediction models (B) Comparison to previously published CDH or neonatal ECMO risk scores.

Table 4A

	Discrimination C (95% Confidence Interval)	**Hosmer-Lemeshow test: χ^2 (P-value)**	**Shrinkage factor (95% Confidence Interval)**
Pre-ECMO	0.65 (0.62-0.68)	5.85 (0.6643)	0.89 (0.79-1.00)
On-ECMO	0.73 (0.71-0.76)	6.26 (0.6181)	0.90 (0.83-0.99)

Table 4B

Risk Model Name	**Model Type**	**Validated using published coefficients/points on testing data**	
		Points	**Original coefficients**
Kays	Pre-ECMO	-	0.61 (0.58, 0.63)
Brindle	Pre-ECMO	0.57 (0.54, 0.59)	0.57 (0.54, 0.59)
PIPER	Pre-ECMO	0.59 (0.56, 0.63)	-
Neo-RESCUERs	Pre-ECMO	-	0.59 (0.56, 0.62)
CDH pre-ECMO	Pre-ECMO	-	0.65 (0.62-0.68)
Hari	On-ECMO	0.69 (0.66, 0.71)	0.69 (0.66, 0.71)
PIPER+	On-ECMO	0.71 (0.67, 0.73)	-
CDH on-ECMO	On-ECMO	-	0.73 (0.71-0.76)
CDH post-ECMO	Post-ECMO	-	0.80 (0.78-0.82)

Table 5. Predicted pre-and on-ECMO probability of death (%) for potential neonatal characteristics.

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)

Pre-ECMO Model:
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 3.1kg, 5min Apgar score = 6, CDH was not diagnosed prenatally, pre-ECMO ventilator type was HFOV with a MAP of 17cm of H_2O and pH prior to cannulation was 7.2. Handbagging was not needed prior to 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.
On-ECMO Model:
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 3.1kg, Apgar score = 6, CDH was prenatally diagnosed, handbagging was not needed prior to ECMO, iNO was used prior to ECMO, pre-ECMO ventilator type was HFOV, MAP = 17 cm of H_2O, pH prior to cannulation was 7.2, roller pump was used for ECMO. Diaphragm was not repaired on-ECMO. Current ECMO duration is1.7 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 (2.7weeks) and has Airleak syndrome (pneumothorax).

9. ACKNOWLEDGEMENTS

This work was supported fully by CHOC/Pediatric Surgical 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. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. We would also like to acknowledge the co-authors whom are listed below, and are on the finalized manuscript, submitted Annals of Surgery and is in peer-review.

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