Published in final edited form as:

J Pediatr Surg. 2017 December ; 52(12): 2018–2025. doi:10.1016/j.jpedsurg.2017.08.037.

Cannulating the Contraindicated: Effect of Low Birth Weight on Mortality in Neonates with Congenital Diaphragmatic Hernia on Extracorporeal Membrane Oxygenation

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Abstract

Background/Purpose—Restrictions for ECMO in neonates include birth weight less than 2 kg (BW<2kg) and/or gestational age less than 34 weeks (GA<34 weeks). We sought to describe their relationship on mortality.

Methods—Neonates with a primary diagnosis code of CDH were identified in the Extracorporeal Life Support Organization (ELSO) registry, and logistic regression models were used to examine the effect of BW<2kg and GA<34 weeks on mortality.

Results—We identified 7,564 neonates with CDH. The overall mortality was 50%. There was a significantly higher risk of death with unadjusted odds ratio (OR) 2.39 (95% confidence interval [CI]: 1.53 – 3.74; $P < 0.01$) for BW<2kg neonates. The adjusted OR of death for BW<2kg neonates remained significantly high with over two-fold increase in the odds of mortality for BW<2kg neonates when adjusted for potential confounding variables (OR 2.11, 95% CI: 1.30–3.43; $P < 0.01$). However, no difference in mortality was observed in neonates with GA<34weeks.

Conclusions—While mortality among CDH neonates with a BW<2kg was substantially increased, GA<34weeks was not significantly associated with mortality. Effort should be made to

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identify the best candidates for ECMO in this high-risk group and develop treatment strategies to optimize their survival.

Keywords

CDH; ECMO; low birthweight; low gestation

1. INTRODUCTION

The recommended lower limits of neonatal ECMO are weight of 2kg and post-gestational age of 34 weeks. The weight and GA restrictions have been suggested to maximize the benefits of ECMO. The pre-ECMO weight of less than 2kg was suggested in light of the findings by Revenis et al. in 1992, who reported lower weight infants (2 to 2.5 kg) to have higher rates of mortality and intracranial hemorrhage compared to higher weight infants [1]. Similarly, Hardart et al. showed a linear relationship between post-conceptual age and incidence of intracranial hemorrhage, ranging from 22% at less than 32 weeks to 12% by 36 weeks [2]. There has not been a CDH specific report on the outcomes of infants treated with ECMO whose pre-ECMO weight was less than 2kg and/or post-gestational age less than 34 weeks.

Pioneers in the field of congenital heart surgery advocate for and perform primary repair of congenital heart defects in extremely low birth weight (<1500g) neonates [3, 4]. Reddy et al., reported excellent outcomes in extremely low birth weight neonates where cardiopulmonary bypass was utilized during congenital heart surgery [3]. In parallel, Rozmiarek et al. demonstrated potentially acceptable mortality rates in infants down to a weight of 1.6 kg, for neonatal respiratory ECMO [5]. With the advances in gentle ventilation strategies, and improved anticoagulation techniques, it may be possible that infants with CDH may benefit from ECMO even if they weigh less than 2kg or are less than 34 weeks in GA, assuming cannulation is possible and risks of anticoagulation are potentially minimized. While the weight and gestational age guidelines have remained relatively consistent to maximize the efficacy of ECMO, the traditionally held belief that CDH babies should be limited to a 2-week course of ECMO has also come into question, signifying that ECMO indications and contraindications remain moving targets [6].

However, understanding the precise effect of low birth weight (BW<2kg) and low gestational age (GA<34 weeks) on mortality will require a large study cohort because of the few cases of BW<2kg or GA<34 weeks CDH-neonates treated with ECMO (less than 2%). Thus, our current study utilizes a large cohort from the ELSO registry data to address this knowledge gap.

2. METHODS

2.1 Data Source and Cohort

The ELSO Registry collects clinical information for adults and children with cardiorespiratory failure treated with ECMO [7]. The dataset used in this study was provided by the ELSO Registry for the years from 1988 to 2015. The study population consisted of

neonates whose primary diagnosis was CDH. Every subject in the dataset was treated with ECMO. Infants whose birth weights were less than 2kg (BW<2kg) and/or were born with low gestational age of less than 34 weeks (GA<34 weeks) were identified within the study population strictly based on the numerical confines of birth weight or gestational age at those limits. The first ECMO run was used for each neonate. We utilized pertinent secondary ICD-9 diagnosis codes to establish dichotomous variables to identify presence of comorbidities. We excluded patients with missing sex and ECMO mode (72 patients) and the final cohort included n = 7,564 infants with CDH who were treated with ECMO.

2.2 Outcome and Main Exposure Variables

The primary outcome was patient mortality (mortality at discharge) and the main exposure was BW<2kg. The secondary exposure, GA<34 weeks, was based on the estimated gestational age at birth. We considered three nested models to examine the effect of the exposure variables (BW<2kg and GA<34 weeks) on outcomes: 1) *Unadjusted model (M1)* included only BW<2kg/GA<34 weeks; 2) *Partially adjusted model (M2)* adjusted for patients' demographics, disease characteristics, and treatment variables; and 3) *Fully adjusted model (M3)* adjusted for comorbidities and complications in addition to covariates in model M2. A nested model was selected so that effect of gestational age and birth weight on mortality could be examined initially from a disease-specific severity standpoint and then further examined while adjusting for comorbid conditions and complications associated with treatment.

2.3 Covariates

We considered risk factors that may confound the association between BW<2kg and mortality. Demographics and baseline covariates included gender, race, post-gestational age, 5 minute Apgar, side of CDH, prenatal diagnosis of CDH, hand-bagging before ECMO, and pre-ECMO arrest. Disease characteristics and treatment factors included blood gas variables (pH, pCO₂ and pO₂). Ventilator settings included mean airway pressure (MAP). For oxygenation, we examined oxygenation index (OI). Ventilator type included high frequency oscillatory ventilation (HFOV) and conventional ventilator. Pre-ECMO rescue therapies included inotropes, bicarbonate/THAM, iNO, surfactant, neuromuscular blockers, milrinone, sildenafil, and steroids. ECMO specific variables included duration of ECMO, ECMO mode (venoarterial (VA) or venovenous (VV)) [8], pump type (roller or centrifugal), and cannulation type (central or peripheral). Comorbidity and complication variables included critical congenital heart disease (CCHD) [9], multiple congenital anomalies (MCA), chromosomal anomalies, perinatal infection, peritonitis, and airleak syndrome (pneumothorax), which were all defined by appropriate ICD-9 codes per secondary diagnoses. Mechanical complications were grouped together; hemorrhagic complications were grouped together; neurologic complications were divided into seizures and severe neurologic complications (CNS hemorrhage, infarct, intraventricular hemorrhage (IVH) grades 3 or 4); renal complications were separated into elevated creatinine (>1.5) and renal replacement therapy (dialysis, hemofiltration, CAVHD); cardiac complications included STUN, tamponade, and need for CPR; infectious complications included positive cultures and elevated WBC; and endocrine complications included glucose < 40 mg/dL and > 240 mg/dL.

2.4 Statistical Analysis

The summary of the patient characteristics by birth weight group and gestational age group were provided as means $\pm$ standard deviation (SD) for continuous variables or proportions for categorical variables. For continuous variables, t-test was used to test the difference between groups. Categorical variables were examined by Fisher exact test. Logistic regression models were used to estimate adjusted odds ratio and 95% confidence interval (CI). To ensure the robustness of these models to missing data, we reported results based on multiple imputation using 10 imputed datasets to address missing values for the following variables: 5 min Apgar, pCO₂, pO₂, pH, oxygenation index, and duration of ECMO. MAP was missing in 12.0% of the entire cohort and we imputed missing values based on a clinical formula as a function of peak inspiratory pressure (PIP), respiratory rate, and positive end expiratory pressure (PEEP). Oxygenation index was calculated as $OI = ((FiO_2 * MAP) / pO_2)$ and missing values (10.9 %) were obtained using mean imputation. Results were similar based on simple mean imputation (not shown). Analyses were performed using SAS version 9.3.

3. RESULTS

3.1 Baseline characteristics

The analysis included $n = 7,564$ neonates with CDH, all of whom were treated with ECMO. There were 100 neonates with BW < 2kg (Table 1). The summary of the patients' baseline characteristics by BW < 2kg and GA < 34 weeks are provided in Table 1 and Table 2, respectively. Table 3 is a frequency table showing reasons for discontinuation of ECMO in infants with BW < 2 kg and GA < 34 weeks who failed to survive. The prevalence of neonates with BW < 2kg was similar over time: 36 from the 1990's, 35 from the 2000's and 26 from 2010–2015. Out of the 100 neonates with BW < 2kg (ranging from 1.28–1.99 kg), only 13 had pre-ECMO weight ≥ 2 kg (mean pre-ECMO weight of these 13 patients was 2.3 kg). Furthermore, there were 3 infants with a birth weight less than 1.5kg and two of them survived. Of these 3 infants, one was 1.28kg at birth and was cannulated after 21 days of life with a weight of 2.2kg, second patient was 1.35kg at birth and cannulated at 16 days of life with a weight of 1.7kg, and last patient was 1.43kg at birth and was cannulated at 6 days of life with a weight of 1.43kg. We identified 109 neonates with GA < 34 weeks (Table 2), whose mean BW and pre-ECMO weight were both 2.3 kg. There were 45 neonates in 1990's, 33 in the 2000's, and 29 in 2010–2015, respectively, with GA < 34 weeks. There were 28 infants with both BW < 2kg and GA < 34 weeks. Overall mortality was 50% for the entire cohort, 71% for the BW < 2kg group, and 56.3% for the GA < 34 weeks group. The mean GA of the < 2kg cohort was 35.1 weeks, and mean BW of the GA < 34 weeks group was 2.3 kg.

We compared rates of severe neurologic complications in both the primary and secondary exposure groups. Overall for the < 2kg group, there was no difference in rates of severe neurological complications during ECMO (Table 1). Furthermore, after examining only the survivors—as a subgroup, there was no significant difference in the rate of severe neurologic complications between infants with BW < 2kg and ≥ 2 kg (4 out of 29 in survivors with BW < 2kg and 289 out of 3317 for BW ≥ 2 kg; $P = 0.93$). For infants born with GA < 34 weeks,

there was a significant difference in rates of severe neurological events during ECMO (Table 2). This difference persisted among the survivors (rate of severe neurologic complications among survivors with GA < 34 weeks and ≥ 34 weeks were 13.64% and 8.06%).

Peripheral cannulation was the predominant cannulation method for both the <2kg and <34week groups, although in a small subset central cannulation was noted (Table 1 and Table 2). We further examined peripheral cannulation possibilities for the <2kg patients. In 88/100 infants with BW<2kg, information on cannula preference was available in the ELSO Registry. The most common VA cannulation option was Biomedicus 8F for the artery and 10F for the vein (28.4%, 25 out of 88), alternatively equally common cannula options was Biomedicus 8F for both the artery and vein (28.4%, 25 out of 88). Other cannulation choices included Biomedicus 8F for the artery and 12F for the vein (10.2%, 9 out of 88) and Biomedicus 10F (artery) and 12F for vein (5.7%, 5 out of 88). We also looked at the < 34 weeks group and there was no significant difference in cannula choices. In a small subset of infants (n=5) VV cannulation was possible where 12F Origen cannula was utilized in both study populations. One out of these five infants that were initially cannulated for VV was converted back to VA ECMO with the addition of a Biomedicus 8F arterial cannula. We did not compare this to the >2kg and >34wk groups due to wide range of choices available in that population.

3.2 Low birth weight and gestational age on mortality

3.2.1 Unadjusted analysis—In the “unadjusted” model (M1), BW<2kg neonates had significantly higher risk of death compared to non-BW<2kg neonates: odds ratio (OR) of 2.39 (95% CI: 1.53 – 3.74; P < 0.01; see Table 4). The effect of GA<34 weeks was not significantly associated with mortality, OR = 1.23 (P = 0.33).

3.2.2 Partially adjusted analysis for demographics, and disease and treatment characteristics—The effect of BW<2kg on mortality was based on a logistic regression model (M2), adjusted for patients’ demographics, disease characteristics variables and treatment variables. Results are shown in Table 4. The adjusted odds (likelihood) of death for BW<2kg neonates was more than doubled compared to non-BW<2kg neonates (adjusted OR, aOR = 2.17, 95% CI: 1.35–3.49; P < 0.01). The effect of GA<34 weeks was not significantly associated with mortality (aOR: 1.35; P = 0.18). Among patients’ demographics variables, lower Apgar score at 5 min, prenatal diagnosed with CDH, Blacks race, having bilateral diaphragmatic hernia, and pre-ECMO arrest were associated with increased mortality risk. Specifically, infants who were diagnosed prenatally have a 53% higher odds of death (95% CI: 1.37 – 1.71; P < 0.01). Black infants have an increased risk of mortality with aOR = 1.33 relative to Whites (95% CI: 1.13 – 1.56; P < 0.01). Neonates with right sided hernia have 24% lower odds of mortality compared to neonates with left side hernia (95% CI: 0.67 – 0.87; P < 0.01). Presence of pre-ECMO arrest was associated with a 59% increase in the odds of mortality (95% CI: 1.34 – 1.89; P < 0.01). Among disease characteristic variables, the longer duration of ECMO, lower pH, HFOV, higher oxygenation index, and not using nitric oxide were associated with a higher risk of death. A one-week increase in the duration of ECMO treatment was associated with a 64% increase in the odds of mortality (95% CI: 1.55 – 1.74; P < 0.01). One standard deviation increase in pH was

associated with a 22% decrease of odds of death (95% CI: 0.71 – 0.86; $P < 0.01$). Adjusted OR of mortality in neonates on HFOV compared to conventional ventilator was 1.36 (95% CI: 1.20 – 1.54; $P < 0.01$).

3.2.3 Fully adjusted analysis: Further adjustment for comorbidities and complications—We next examined the extent to which the significant effect of BW<2kg on mortality may be attenuated after accounting for comorbidities and complications. Thus, Model 3 included comorbidity and complication factors in addition to covariates in Model 2. Results are summarized in Table 5. The aOR of death for BW<2kg neonates relative to non-BW<2kg neonates remained significantly high: aOR = 2.11 (95% CI: 1.30–3.43; $P = 0.0024$). Similarly, the effect of GA<34 weeks was not significantly associated with mortality (OR: 1.16; $P = 0.5286$). The effects of patients' demographics, and disease and treatment characteristics on mortality were similar to Model 2 in terms of direction, magnitude and significance level. Among comorbidity variables, presence of CCHD and airleak syndrome were associated with 49% (95% CI: 1.02 – 2.17; $P = 0.04$) and 22% (95% CI: 1.03 – 1.44; $P = 0.02$) increased odds of death, respectively. As expected, most complications were found to be significantly associated with mortality, including hemorrhagic complications, severe neurologic complication, elevated creatinine, having dialysis, cardiac complications, and infectious complications/sepsis. See Table 5 for details.

In summary, the significant adverse effect of BW<2kg on mortality, specifically a two-fold increase in likelihood of death, was consistent and robust to varying level of covariate adjustments (models M1-M3; Figure 1). For GA<34 weeks, although there was an observed increased likelihood of mortality for infants with GA<34 weeks compared to non-GA<34 weeks infants (point estimates of 15% to 35% increased odds of death), this was not statistically significant in all models examined (Figure 2).

4. DISCUSSION

Clinicians often face unpredictable circumstances where data may be lacking to make clinical decisions. An infant with CDH who is <2kg in weight and is failing conventional therapy is one such circumstance, and most would not consider ECMO. Conventional wisdom and common sense dictate that such infants won't survive ECMO, and even if they do, there may be significant morbidities. On the other hand, it may be possible to provide care to these infants today in a way that was not previously thought possible. Perhaps low birth weight infants, during the process of growing and maturing, may improve lung volume if lungs are not injured with barotrauma. Parallels can be drawn here to extremely low birth weight infants who undergo primary repair of congenital heart defects on cardiopulmonary bypass with excellent outcomes. In this study, we hypothesized that low birth weight was associated with increased risk of mortality in CDH-neonates, and sought to identify additional factors that predict increased mortality risk. To that end, we reviewed the ELSO Registry data to compile the largest cohort of infants with CDH on ECMO. Because the prevalence of BW<2kg neonates on ECMO is low (less than 2%), a large cohort is necessary to rigorously determine the effect of BW<2kg on mortality. Our overall results demonstrate that risk of mortality is substantial in BW<2kg neonates on ECMO.

Our analyses demonstrated that BW<2kg infants had a 2-fold increased risk of mortality when compared with infants ≥2kg at birth. This difference remained consistent even when adjusting for other variables. GA<34 weeks however is not associated with increased risk of death after adjusting for weight. This is consistent with previous studies looking at the effect of birth weight on mortality in the ECMO population. Revenis et al. investigated the increased risk of death for neonatal ECMO, not specifically the CDH-ECMO population, and found an OR for mortality of 3.5, which is cited in the ELSO guidelines to make birth weight less than 2kg a cut off for ECMO. In contrast, the OR of mortality in the CDH-ECMO population of this study was lower at 2.1. This result is similar to a more recent study by Rozmiarek et al. looking at all neonatal ECMO patients in the ELSO Registry. The effect of GA<34 weeks on mortality trended towards increased mortality (OR: 1.16; P = 0.53), but was not statistically different. Failing to show a difference in mortality between GA<34 weeks and gestational age ≥34 weeks contrasts with previous studies on ECMO and non-ECMO neonates with CDH [10, 11].

Although this study is not able to address long term neurodevelopmental outcomes, we compared rates of severe neurologic complications (acute neurologic events). Like all neonates placed on ECMO, there is a persistent risk of severe neurologic complications during ECMO for BW<2kg infants, however there was no statistically significant difference between infants <2kg and those that were ≥2kg. When we looked at the subgroup of survivors, there was still no difference in rates of such neurologic events. This contrasts with previously published associations of birth weight and IVH [12]. This was unanticipated considering that severe neurologic complications are a significant cause of death among neonates on ECMO. Although a description of long term neurologic outcomes is not within the realm of this study, these facts infer that survivors for either the primary exposure (BW <2kg) or secondary exposure (GA<34 weeks) groups should be regarded at high risk for neurologic impairment.

Some of the baseline characteristics varied in a predictable manner between the ≥2kg and <2kg weight groups. The <2kg infants were slightly older as measured by post-gestational age prior to being placed on ECMO. Neonates who were <2kg were predominantly placed on VA-ECMO (likely because of smaller cannula availability). In addition, although rare, there were twice as many infants who were centrally cannulated in the <2kg category. There were also similar differences between the GA<34 weeks group and the ≥34 weeks' gestational age group which included increased post-gestational age prior to being placed on ECMO, increased likelihood of VA-ECMO, and increased use of surfactant, indicating that in the CDH-ECMO population, both birth weight and gestational age have predictive properties in dictating treatment choices. However, when mortality at discharge is the primary outcome, most of this is driven by weight and not gestational age.

When feasible, for low birth weight infants with congenital heart disease, cardiac surgeons have the capacity to wait-and-grow to avoid the risks of cardiopulmonary bypass. Wait-and-grow is not a treatment style that can be applied to unstable infants with CDH that acutely need ECMO. Data in this study supports this observation that most of the infants were cannulated soon after birth, most likely due to urgent need to provide ECMO support. Most infants were cannulated three to four days after birth and only 13 out of the 100 infants with

BW < 2kg had a pre-ECMO weight that was greater than 2kg. The fact that cannulation for ECMO was provided based on physiologic need is further substantiated by the fact that within the nested models, post-gestational age, which is age at which ECMO cannulation, does not have an effect on mortality.

There were a number of limitations with this study. This was a retrospective study with data inclusion as far back as 1988 in order to increase the number of neonates with CDH who were placed on ECMO that are below the current recommendations for weight and GA. This likely introduces confounding variables as standard medical therapy has changed over this time period and neonates throughout the study period were likely subjected to significantly different medical therapies. While severe neurologic events were included, this study is not able to assess neurodevelopmental outcomes. Typical of retrospective studies, miscoding errors with the original data entry may be present. The limited number of patients in the main exposure groups may have selection bias and potential effect of center experience on survival. Method and timing for surgical repair of CDH was also not accounted for in this analysis. Unfortunately, the ELSO database only includes infants that have already undergone treatment with ECMO. It does not include data for infants that could have been placed on ECMO or infants that were treated with alternative therapies, so it cannot be inferred whether or not ECMO provides a survival benefit in the BW<2kg and GA<34 weeks groups. Further research would need to be done to compare other treatment modalities to ECMO in these specific patient populations.

In conclusion, our study showed that survival is possible if BW<2kg infants with CDH are placed on ECMO but we would like to emphasize that these infants should be regarded as a population at high risk of death and neurologic impairment. Central cannulation or VA-peripheral cannulation were the preferred methods to initiate ECMO in this high-risk group. Future studies should be directed to improving anticoagulation strategies and minimizing risk of ECMO related complication to favor survival of high risk premature and low birth weight CDH infants. Current weight and GA cut-offs may be extended in some circumstances for offering ECMO in the CDH population, as some of these infants will survive without severe neurologic complications. An organized effort should be made to identify the best candidates for ECMO in this high-risk group and develop treatment strategies to optimize their survival.

Acknowledgments

This work was supported by CHOC/Pediatric Surgical Faculty (PSF) Tithe Award and 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.

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Figure 1.

Association between BW<2kg and mortality across all models.

Figure 2.
Association with mortality and GA < 34 weeks across all models.

Table 1

Baseline patient characteristics by birth weight groups

Recipients' characteristics	< 2kg (N = 100)	2kg (N = 7111)	
	Mean (SD)/Count (Percent)	Mean (SD)/Count (Percent)	P-value
Demographics			
<i>Gestational Age</i>	35.06 (2.16)	38.30 (1.82)	<0.0001
<i>Gender (% male)</i>	48 (48.0%)	4073 (57.3%)	0.0672
<i>Race/ethnicity, %</i>			0.2951
Whites	58 (58.0%)	4272 (60.7%)	
Hispanics	10 (10.0%)	1050 (14.8%)	
Blacks	15 (15.0%)	891 (12.5%)	
Others	17 (17.0%)	898 (12.6%)	
<i>Apgar at 5 mins</i>	5.69 (1.97)	6.05 (2.11)	0.1047
<i>Age (days) before ECMO</i>	3.65 (5.26)	1.92 (3.23)	0.0015
<i>Side of hernia</i>			0.0330
Left	74 (74.0%)	5028 (70.7%)	
Right	14 (14.0%)	1395 (19.6%)	
Both	5 (5.0%)	100 (1.4%)	
Missing	7 (7.0%)	588 (8.3%)	
<i>Prenatal Diagnosis</i>	71 (71.0%)	3968 (55.8%)	0.0023
<i>Handbagging</i>			0.5454
No	87 (87.0%)	6381 (89.7%)	
Yes	10 (10.0%)	561 (7.9%)	
Missing	3 (3.0%)	169 (2.4%)	
<i>Patient arrested before ECMO</i>	20 (20.0%)	763 (10.7%)	0.0056
<i>Site of cannulation</i>			0.0781
Central	8 (8.6%)	290 (4.6%)	
Peripheral	85 (91.4%)	6029 (95.4%)	
Pre-ECMO blood gas			
<i>pH</i>	7.21 (0.21)	7.24 (0.2)	0.1244
<i>PCO₂</i>	63.69 (28.15)	60.84 (27.77)	0.3171
<i>PO₂</i>	45.24 (39.97)	39.07 (30.52)	0.1327
Pre-ECMO ventilator settings			
<i>HFOV</i>	54 (54%)	4059 (57.1%)	0.5432
<i>MAP</i>	17.12 (6.97)	18.41 (7.24)	0.1030
<i>Oxygenation index</i>	49.67 (27.85)	61.66 (51.35)	0.0002
ECMO mode, duration and pump type			
<i>ECMO mode</i>			

Recipients' characteristics	< 2kg (N = 100)	2kg (N = 7111)	
	Mean (SD)/Count (Percent)	Mean (SD)/Count (Percent)	P-value
VA	95 (95.0%)	5971 (84.0%)	0.0013
VV	5 (5.0%)	1140 (16.0%)	
<i>Duration of ECMO (weeks)</i>	1.66 (1.73)	1.54 (0.98)	0.4943
<i>Pump type</i>			0.6818
Roller	77 (77.0%)	5380 (75.7%)	
Centrifugal	15 (15.0%)	907 (12.8%)	
Other	2 (2.0%)	165 (2.3%)	
Missing	6 (6.0%)	659 (9.3%)	
Pre-ECMO rescue therapy			
<i>Inotropes (Vasopressor/inotropic drugs/Dopamine/Dobutamine/Epinephrine/Norepinephrine)</i>	83 (83.0%)	5831 (82.0%)	0.8959
<i>Bicarbonate/THAM</i>	43 (43%)	2670 (37.6%)	0.2985
<i>Nitric oxide</i>	55 (55%)	3794 (53.4%)	0.7630
<i>Surfactant</i>	24 (24%)	1091 (15.3%)	0.0247
<i>Neuromuscular blockers</i>	53 (53%)	4019 (56.5%)	0.4794
<i>Milrinone</i>	3 (3.0%)	328 (4.6%)	0.6297
<i>Sildenafil</i>	3 (3.0%)	47 (0.7%)	0.0317
<i>Steroids</i>	4 (4.0%)	254 (3.6%)	0.7827
Comorbidity			
<i>CCHD</i>	7 (7.0%)	165 (2.3%)	0.0097
<i>MCA</i>	0 (0.0%)	13 (0.2%)	1.0000
<i>Chromosomal</i>	1 (1.0%)	43 (0.6%)	0.4601
<i>Perinatal infection</i>	3 (3.0%)	107 (1.5%)	0.1958
<i>Peritonitis</i>	0 (0.0%)	8 (0.1%)	1.0000
<i>Airleak Syndrome</i>	4 (4.0%)	861 (12.1%)	0.0082
Complications			
<i>Mechanical complications</i>	66 (66.0%)	3966 (55.8%)	0.0427
<i>Hemorrhagic Complications</i>			
<i>Pulmonary hemorrhage</i>	4 (4.0%)	157 (2.2%)	0.2872
<i>Other Hemorrhagic Complications</i>	44 (44.0%)	2893 (40.7%)	0.5390
<i>Neurologic Complications</i>			
<i>Seizures</i>	5 (5.0%)	630 (8.9%)	0.2139
<i>Severe neurologic complication</i>	18 (18.0%)	1067 (15.0%)	0.3981
<i>Renal Complications</i>			
<i>Elevated Creatinine</i>	12 (12.0%)	583 (8.2%)	0.1957
<i>Dialysis</i>	30 (30.0%)	1944 (27.3%)	0.5725
<i>Cardiac Complications</i>			
<i>STUN</i>	9 (9.0%)	463 (6.5%)	0.3058

Recipients' characteristics	< 2kg (N = 100)	2kg (N = 7111)	
	Mean (SD)/Count (Percent)	Mean (SD)/Count (Percent)	P-value
<i>Tamponade</i>	0 (0.0%)	116 (1.6%)	0.4126
<i>CPR required</i>	4 (4.0%)	189 (2.7%)	0.3443
<i>Infectious complications/sepsis</i>	10 (10.0%)	573 (8.1%)	0.4583
<i>Metabolic Complications</i>			
<i>Glucose < 40</i>	3 (3.0%)	220 (3.1%)	1.0000
<i>Glucose > 240</i>	6 (6.0%)	382 (5.4%)	0.6585

Table 2

Baseline patient characteristics by gestational age groups

Recipients' characteristics	< 34 w (N = 109)	34 w (N = 7160)	
	Mean (SD)/Count (Percent)	Mean (SD)/Count (Percent)	P Value
Demographics			
<i>Birthweight</i>	2.27 (0.48)	3.07 (0.51)	<0.0001
<i>Pre-ECMO weight</i>	2.30 (0.49)	3.10 (0.53)	<0.0001
<i>Gender (% male)</i>	71 (65.1%)	4097 (57.2%)	0.1181
<i>Race/ethnicity, %</i>			0.3595
Whites	70 (64.2%)	4321 (60.3%)	
Hispanics	13 (11.9%)	1059 (14.8%)	
Blacks	17 (15.6%)	886 (12.4%)	
Others	9 (8.3%)	894 (12.5%)	
<i>Apgar at 5 mins</i>	5.92 (1.77)	6.04 (2.11)	0.4904
<i>Age (days) before ECMO</i>	3.02 (4.97)	1.94 (3.27)	0.0253
<i>Side of hernia</i>			0.5907
Left	73 (67.0%)	5076 (70.9%)	
Right	27 (24.8%)	1394 (19.5%)	
Both	1 (0.9%)	104 (1.5%)	
Missing	8 (7.3%)	586 (8.2%)	
<i>Prenatal Diagnosis</i>	65 (59.6%)	4000 (55.9%)	0.4964
<i>Handbagging</i>			0.2020
No	95 (87.2%)	6445 (9.0%)	
Yes	13 (11.9%)	550 (7.7%)	
Missing	1 (0.9%)	165 (2.3%)	
<i>Patient arrested before ECMO</i>	12 (11.0%)	786 (11.0%)	1.0000
<i>Site of cannulation</i>			0.6290
Central	3 (3.0%)	291 (4.6%)	
Peripheral	97 (97.0%)	6085 (95.4%)	
Pre-ECMO blood gas			
<i>pH</i>	7.21 (0.17)	7.24 (0.2)	0.1730
<i>PCO₂</i>	63.05 (22.84)	60.96 (27.84)	0.3531
<i>PO₂</i>	41.65 (40.74)	39.01 (30.19)	0.5060
Pre-ECMO ventilator settings			
<i>HFOV</i>	64 (58.7%)	4114 (57.5%)	0.8455
<i>MAP</i>	18.03 (6.66)	18.35 (7.17)	0.6609
<i>Oxygenation index</i>	57.46 (40.61)	61.49 (51.24)	0.3344
ECMO mode, duration and pump type			

Recipients' characteristics	< 34 w (N = 109)	34 w (N = 7160)	
	Mean (SD)/Count (Percent)	Mean (SD)/Count (Percent)	P Value
<i>ECMO mode</i>			
VA	99 (90.8%)	5998 (83.8%)	0.0484
VV	10 (9.2%)	1162 (16.2%)	
<i>Duration of ECMO (weeks)</i>	1.56 (1.66)	1.54 (0.97)	0.8749
<i>Pump type</i>			0.7765
Roller	85 (78.0%)	5439 (76.0%)	
Centrifugal	14 (12.8%)	900 (12.6%)	
Other	3 (2.8%)	167 (2.3%)	
Missing	7 (6.4%)	654 (9.1%)	
Pre-ECMO rescue therapy			
<i>Inotropes (Vasopressor/inotropic drugs/Dopamine/Dobutamine/Epinephrine/Norepinephrine)</i>	89 (81.7%)	5887 (82.2%)	0.8995
<i>Bicarbonate/THAM</i>	49 (45.0%)	2709 (37.8%)	0.1362
<i>Nitric oxide</i>	58 (53.2%)	3873 (54.1%)	0.9229
<i>Surfactant</i>	39 (35.8%)	1101 (15.4%)	<0.0001
<i>Neuromuscular blockers</i>	64 (58.7%)	4066 (56.8%)	0.6983
<i>Milrinone</i>	4 (3.7%)	317 (4.4%)	1.0000
<i>Sildenafil</i>	2 (1.8%)	46 (0.6%)	0.1616
<i>Steroids</i>	3 (2.8%)	247 (3.4%)	1.0000
Comorbidity			
<i>CCHD</i>	2 (1.8%)	175 (2.4%)	1.0000
<i>MCA</i>	0 (0.0%)	14 (0.2%)	1.0000
<i>Chromosomal</i>	0 (0.0%)	45 (0.6%)	1.0000
<i>Perinatal infection</i>	2 (1.8%)	109 (1.5%)	0.6833
<i>Peritonitis</i>	0 (0.0%)	8 (0.1%)	1.0000
<i>Airleak Syndrome</i>	13 (11.9%)	866 (12.1%)	1.0000
Complications			
<i>Mechanical complications</i>	67 (61.5%)	4008 (56.0%)	0.2850
<i>Hemorrhagic Complications</i>			
<i>Pulmonary hemorrhage</i>	1 (0.9%)	163 (2.3%)	0.5215
<i>Other Hemorrhagic Complications</i>	40 (36.7%)	2917 (40.7%)	0.4325
<i>Neurologic Complications</i>			
<i>Seizures</i>	8 (7.3%)	628 (8.8%)	0.7331
<i>Severe neurologic complication</i>	34 (31.2%)	1061 (14.8%)	<0.0001
<i>Renal Complications</i>			
<i>Elevated Creatinine</i>	14 (12.8%)	590 (8.2%)	0.1116
<i>Dialysis</i>	28 (25.7%)	1971 (27.5%)	0.7461
<i>Cardiac Complications</i>			

Recipients' characteristics	< 34 w (N = 109)	34 w (N = 7160)	
	Mean (SD)/Count (Percent)	Mean (SD)/Count (Percent)	P Value
<i>STUN</i>	4 (3.7%)	470 (6.6%)	0.3246
<i>Tamponade</i>	2 (1.8%)	117 (1.6%)	0.6994
<i>CPR required</i>	2 (1.8%)	199 (2.8%)	0.7711
<i>Infectious complications/sepsis</i>	4 (3.7%)	585 (8.2%)	0.1086
<i>Metabolic Complications</i>			
<i>Glucose < 40</i>	1 (0.9%)	221 (3.1%)	0.2646
<i>Glucose > 240</i>	3 (2.8%)	390 (5.4%)	0.2859

Table 3

Frequency table for ECMO discontinuation in infants with BW < 2kg and GA < 34 week who failed to survive.

	BW < 2 kg		GA < 34 week	
Discontinuation	N	Percent	N	Percent
Lung Recovery	32	45.71	28	43.08
Died - Family Request	5	7.14	7	10.77
Died - Hemorrhage	6	8.57	8	12.31
Died - Dx incompatible with life	9	12.86	9	13.85
Died - Organ failure	14	20	10	15.38
Died - Reason not specified	4	5.71	3	4.62
Total	70	100	65	100

Table 4

Association with mortality in partially adjusted model

Parameter	Category	OR	95% Confidence Interval	P-value
Demographics				
Gestational age group	34 weeks		1.00 (Reference)	
	< 34 weeks	1.350	(0.875 – 2.083)	0.1752
Birth weight group	2kg		1.00 (Reference)	
	<2kg	2.173	(1.354 – 3.488)	0.0013
Apgar at 5 mins		0.878	(0.854 – 0.902)	<0.0001
Prenatal diagnosis		1.534	(1.372 – 1.714)	<0.0001
Sex	Male		1.00 (Reference)	
	Female	1.030	(0.931 – 1.141)	0.5636
Race	Whites		1.00 (Reference)	
	Hispanics	1.014	(0.876 – 1.175)	0.8494
	Blacks	1.328	(1.134 – 1.556)	0.0004
	Others	1.241	(1.050 – 1.465)	0.0111
Side of diaphragmatic hernia	Left		1.00 (Reference)	
	Right	0.761	(0.668 – 0.868)	<0.0001
	Both	2.417	(1.544 – 3.784)	0.0001
	Missing	1.145	(0.881 – 1.487)	0.3114
Hand bagging	No		1.00 (Reference)	
	Yes	1.126	(0.924 – 1.371)	0.2399
	Missing	1.174	(0.826 – 1.668)	0.3713
Patient arrested before ECMO		1.589	(1.338 – 1.887)	<0.0001
Post gestational age (days)		0.997	(0.981 – 1.013)	0.7132
ECMO mode, duration and pump type				
Duration of ECMO (weeks)		1.638	(1.545 – 1.738)	<0.0001
ECMO mode	VA		1.00 (Reference)	
	VV	0.880	(0.765 – 1.011)	0.0706
Pump type	Roller		1.00 (Reference)	
	Centrifugal	1.175	(1.003 – 1.376)	0.0456
	Other	1.250	(0.884 – 1.766)	0.2070
	Missing	0.734	(0.555 – 0.970)	0.0300
Pre-ECMO blood gas				
pco2		1.001	(0.998 – 1.004)	0.6482
po2		0.999	(0.997 – 1.001)	0.2902
pH		0.289	(0.181 – 0.462)	<0.0001
Pre-ECMO ventilator settings				
HFOV		1.362	(1.202 – 1.542)	<0.0001

Parameter	Category	OR	95% Confidence Interval	P-value
MAP		1.011	(1.000 – 1.022)	0.0424
Oxygenation index		1.002	(1.000 – 1.003)	0.0327
Pre-ECMO rescue therapy				
Inotropes		0.972	(0.825 – 1.145)	0.7360
Bicarbonate/THAM		1.080	(0.963 – 1.212)	0.1886
Nitric oxide		0.828	(0.728 – 0.941)	0.0038
Surfactant		1.023	(0.886 – 1.181)	0.7565
Neuromuscular blockers		0.970	(0.865 – 1.088)	0.5999
Milrinone		1.045	(0.805 – 1.357)	0.7414
Sildenafil		0.543	(0.290 – 1.017)	0.0564
Steroids		0.866	(0.650 – 1.154)	0.3276

Table 5

Association with mortality in fully adjusted model

Parameter	Category	OR	95% Confidence Interval	P Value
Demographics				
Gestational age group	34 weeks		1.00 (Reference)	
	< 34 weeks	1.155	(0.738 – 1.806)	0.5286
Birth weight group	2kg		1.00 (Reference)	
	< 2kg	2.114	(1.303 – 3.430)	0.0024
Apgar at 5 mins		0.884	(0.859 – 0.909)	<0.0001
Prenatal diagnosis		1.474	(1.312 – 1.655)	<0.0001
Sex	Male		1.00 (Reference)	
	Female	1.034	(0.930 – 1.150)	0.5372
Race	Whites		1.00 (Reference)	
	Hispanics	1.026	(0.880 – 1.197)	0.7395
	Blacks	1.401	(1.188 – 1.652)	0.0001
	Others	1.213	(1.019 – 1.445)	0.0298
Side of diaphragmatic hernia	Left		1.00 (Reference)	
	Right	0.761	(0.663 – 0.873)	0.0001
	Both	2.105	(1.295 – 3.421)	0.0027
	Missing	1.073	(0.816 – 1.410)	0.6149
Hand bagging	No		1.00 (Reference)	
	Yes	1.028	(0.836 – 1.264)	0.7915
	Missing	1.153	(0.802 – 1.656)	0.4422
Patient arrested before ECMO		1.408	(1.176 – 1.685)	0.0002
Age (days) before ECMO		0.999	(0.982 – 1.017)	0.9316
ECMO mode, duration and pump type				
Duration of ECMO (weeks)		1.472	(1.379 – 1.571)	<0.0001
ECMO mode	VA		1.00 (Reference)	
	VV	0.833	(0.719 – 0.965)	0.0150
Pump type	Roller		1.00 (Reference)	
	Centrifugal	1.057	(0.894 – 1.249)	0.5183
	Other	1.324	(0.928 – 1.889)	0.1216
	Missing	0.710	(0.530 – 0.951)	0.0218
Pre-ECMO blood gas				
pco2		1.001	(0.998 – 1.004)	0.5654
po2		0.999	(0.997 – 1.001)	0.2632
pH		0.327	(0.201 – 0.532)	<0.0001
Pre-ECMO ventilator settings				
HFOV		1.330	(1.167 – 1.515)	<0.0001

Parameter	Category	OR	95% Confidence Interval	P Value
MAP		1.006	(0.995 – 1.017)	0.2779
Oxygenation index		1.002	(1.000 – 1.004)	0.0362
Pre-ECMO rescue therapy				
Inotropes		0.946	(0.798 – 1.122)	0.5241
Bicarbonate/THAM		1.016	(0.901 – 1.147)	0.7924
Nitric oxide		0.836	(0.731 – 0.957)	0.0092
Surfactant		0.971	(0.836 – 1.128)	0.7010
Neuromuscular blockers		0.940	(0.833 – 1.060)	0.3131
Milrinone		0.992	(0.755 – 1.304)	0.9558
Sildenafil		0.523	(0.271 – 1.009)	0.0534
Steroids		0.799	(0.589 – 1.083)	0.1482
Comorbidity				
CCHD		1.487	(1.020 – 2.170)	0.0393
Chromosomal		1.877	(0.839 – 4.198)	0.1254
MCA		1.745	(0.348 – 8.739)	0.4981
Perinatal infection		1.357	(0.881 – 2.089)	0.1659
Peritonitis		6.596	(0.754 – 57.716)	0.0883
Airleak Syndrome		1.221	(1.034 – 1.442)	0.0188
Complications				
Mechanical complications		1.065	(0.952 – 1.191)	0.2698
Pulmonary hemorrhage		1.172	(0.961 – 1.430)	0.1165
Other Hemorrhagic		1.381	(1.229 – 1.552)	<0.0001
Seizures		0.954	(0.784 – 1.161)	0.6373
Severe neurologic complication		3.119	(2.657 – 3.661)	<0.0001
Elevated Creatinine		1.969	(1.585 – 2.446)	<0.0001
Dialysis		1.758	(1.550 – 1.994)	<0.0001
STUN		1.326	(1.064 – 1.653)	0.0121
Tamponade		1.778	(1.110 – 2.848)	0.0167
CPR required		2.579	(1.771 – 3.754)	<0.0001
Infectious complications/sepsis		1.372	(1.120 – 1.682)	0.0023
Glucose > 240		1.157	(0.906 – 1.478)	0.2423
Glucose < 40		0.946	(0.692 – 1.295)	0.7304