ARTICLE

Comparison of early postnatal prediction models for survival in congenital diaphragmatic hernia

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Abstract

Objective To compare the PF-PCO$_2$ equation—partial pressure of arterial oxygen (PaO$_2$)/fraction of inspired oxygen (FiO$_2$) minus partial pressure of carbon dioxide (PCO$_2$)—to three other tools for postnatal prediction of survival in infants with congenital diaphragmatic hernia (CDH).
Study design A retrospective analysis of 203 infants with CDH from 1 January 2003 to 30 June 2018. Area under the curve (AUC) analysis was performed for survival and secondary outcomes of survival without extracorporeal membrane oxygenation support (ECMO) and death despite ECMO. Predictive scores were calculated to determine cutoff for PF-PCO$_2$ score.
Results The PF-PCO$_2$ tool had the highest AUC (0.84 for survival, 0.92 for survival without ECMO, and 0.83 for death despite ECMO). PF-PCO$_2$ best predicted survival when >-60 and survival without ECMO when $>+80$. There was no optimal cutoff score for death despite ECMO.
Conclusion The PF-PCO$_2$ tool best predicted postnatal survival in infants with CDH.

Introduction

Congenital diaphragmatic hernia (CDH) occurs in ~1 in 3000 live births and has a mortality rate between 20–40% [1–4]. Prenatal predictors of survival, based on ultrasound and magnetic resonance imaging findings [5, 6], can aid in prenatal counselling of families regarding survival and prognosis. Ultimately, the severity of pulmonary hypoplasia and ability to oxygenate and ventilate determines survival in these patients [2, 7–10].

Several postnatal models for predicting survival of infants with CDH have been developed and tested in both local populations and the Congenital Diaphragmatic Hernia Study Group (CDHSG) registry, which includes infants with CDH from North America, Europe, and Australia. These include tools created specifically for infants with CDH, such as the CDHSG Probability of Survival Equation (CDHSG-PS) [1], Wilford Hall Santa Rosa Prediction Formula (WHSRpf) [8], and Brindle tool [11], as well as predictors of morbidity and mortality in general neonatal and pediatric populations [12, 13]. No postnatal prediction tool is applied consistently across institutions caring for infants with CDH. Furthermore, problems with existing tools include poor generalizability and difficulty in calculating a score at the patient's bedside.

Of the tools developed specifically for the CDH population, the WHSRpf tool includes measures of oxygenation and ventilation. This equation is the difference between the best partial pressure of arterial oxygen (PaO$_2$) and partial pressure of carbon dioxide (PaCO$_2$) in the first 24 h of life [8]. However, PaO$_2$ alone is a poor measure of hypoxemia. Thus, we modified the WHSRpf equation to include the PaO$_2$/fraction of inspired oxygen (FiO$_2$) (PF) ratio to better account for the degree of hypoxemia in infants with CDH [14, 15]. The final equation we refer to as the PF-PCO$_2$ tool, or the difference between the PF ratio and PCO$_2$, where PaO$_2$ and PaCO$_2$ are the best values (not necessarily from the same blood gas) obtained in the first 24 h of life and FiO$_2$, is the FiO$_2$ recorded at the same time as the PaO$_2$. Chandrasekharan et al. have also described this equation in a brief letter to the editor [16].

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Table 1 Models for postnatal prediction of survival in CDH

Model	Formula	Cutoff
CDHSG-PS	$1 - [1/(1 + e^{-x})]$ $-x = 5.0240 + 0.9165(\text{birth weight}) + 0.4512(5 \text{ min Apgar})$	Low risk mortality = 0–33% Moderate risk mortality = 34–66% High risk mortality = 67–100%
WHSRpf	$PaO_2 - PCO_2$	≥0 = low risk of mortality
Brindle tool	1 point each for: low birth weight (<1500 g), low Apgar score (<7), and major cardiac anomaly[a] 2 points each for: missing Apgar and severe pulmonary hypertension[b]	0 = low risk of death (<10%) 1–2 = Intermediate risk of death (25%) ≥3 = high risk of death (50%)

[a]Major cardiac anomaly—all anomalies other than patent ductus arteriosus and patent foramen ovale

[b]Severe pulmonary hypertension—right to left shunting across a patent ductus arteriosus or estimates of pulmonary pressures

Given the importance of a clinical prediction tool in guiding therapy and postnatal counseling, we performed a retrospective review comparing the equation, PF-PCO_2, with three other published tools (CDHSG-PS, WHSRpf, and Brindle score) to predict survival in our local population of CDH infants. We also determined the predictive ability of this equation for the secondary outcomes of survival without extracorporeal membrane oxygenation support (ECMO) and death despite ECMO. Our hypothesis was that the PF-PCO_2 tool will be most predictive of survival, survival without ECMO, and death despite ECMO.

Methods

Eligible infants were identified retrospectively from an internal database of infants with CDH admitted to the University of Utah or Primary Children's Hospital Neonatal Intensive Care Units (NICU's) from 1 January 2003 to 30 June 2018. This database contains prospectively captured data on each infant, including need for ECMO and measures of ventilation and oxygenation, including blood gas (PaO_2 and $PaCO_2$) and ventilator support data (FiO_2 and mean airway pressure) at various time points. Infants admitted to the University of Utah or Primary Children's NICU's pre-repair were eligible for this study. Exclusion criteria were diagnosis of CDH after 24 h of life, gestational age less than $34^{0/7}$ weeks, birth weight less than 1800 g, and presence of other major anomalies or chromosomal disorders. All infants were repaired at our center. Major cardiac anomalies were defined as all cardiac anomalies except for patent foramen ovale, patent ductus arteriosus, ventricular septal defect, or atrial septal defect.

CDHSG-PS, WHSRpf, and Brindle scores were calculated for all eligible infants based on previously published formulae (Table 1).(1,8,11) PF-PCO_2 was calculated for all eligible infants per the formula—[PaO_2/FiO_2]-$PaCO_2$—

where PaO_2 and $PaCO_2$ are the highest and lowest values, respectively, from post-ductal arterial blood gases obtained in the first 24 h of life. The FiO_2 is the value recorded at the time of the PaO_2. Institutional review board approval and a waiver of informed consent due to retrospective nature of the study were obtained from the University of Utah and Primary Children's Hospital.

The primary outcome was the ability of each tool to predict survival. Secondary outcomes included: ability of the PF-PCO_2 tool to predict survival without ECMO and death despite ECMO; and defining cutoff values that best predict all outcomes for the PF-PCO_2 tool. To determine these cutoff points, positive (PPV) and negative predictive values (NPV) were calculated for the PF-PCO_2 tool at intervals of 20 from −80 to +80.

The primary outcome and other categorical measures were analyzed by Chi-square or Fisher's Exact test. Student's t-test was used for analysis of normally distributed continuous data and Mann–Whitney U test was applied for ordinal data or continuous data that was not normally distributed. Two-sided P-values less than 0.05 were considered statistically significant and no adjustment was made for multiple comparisons. Area under the curve analysis was performed. SPSS (version 24, IBM, Armonk NY) was used for statistical analysis.

Results

Figure 1 shows the patient flowchart. After exclusion of 70 infants, the final study group of 203 included 165 infants who survived and 38 infants who died. Within each group, missing data precluded WHSRpf and PF-PCO_2 score calculation for seven infants. Of the 19 infants diagnosed with CDH after 24 h of life, two (11%) were born at <34 weeks GA and <1800 g and three (16%) had a severe anomaly. The remaining 14 infants diagnosed after 24 h of life underwent primary repair of their defect and survived without ECMO. Missing data precluded
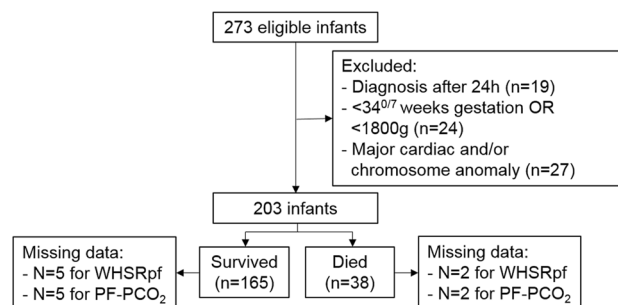
Fig. 1 Patient flowchart. *WHSRpf* Wilford Hall Santa Rosa Prediction Formula, *PF-PCO$_2$* (PaO$_2$/FiO$_2$)-PCO$_2$ equation

PF-PCO$_2$ calculation for these infants. Patient characteristics are shown in Table 2. Infants who survived had a higher birth weight, but this was not statistically significant. They were also less likely to have pulmonary hypertension pre-repair, liver in the thorax, and to undergo ECMO. There was a significant difference in type of repair, with surviving infants more likely to undergo primary repair ($p < 0.001$). There were no differences in survival ($p = 0.119$) or ECMO use ($p = 0.322$) when infants were divided into 5-year epochs corresponding to their birth year (1 = 2003–2007, 2 = 2008–2012, and 3 = 2013–2018). This was also true on regression analysis, where birth epoch did not influence survival ($p = 0.057$ for epoch 1 versus 3; $p = 0.079$ for epoch 2 versus 3). For the PF-PCO$_2$ and WHSRpf equations, the median age of the highest PaO$_2$ and lowest PaCO$_2$ values was 7 h (interquartile range 3–14 h) and 6 h (4–14 h), respectively. There was a significant difference in the median predictive score for each tool between groups (Table 2).

As seen in Fig. 2, the PF-PCO$_2$ tool best predicted survival, with an AUC of 0.84 (95% confidence interval (CI) 0.77–0.91), versus 0.80 (95% CI 0.72–0.88) for WHSRpf, 0.77 (95% CI 0.69–0.86) for CDHSG-PS. The AUC's for the Brindle score are not included in the figure as they are inversely related to the other scores. The AUC for survival by the Brindle tool was the lowest among the predictive scores tested at 0.74 (95% CI 0.65–0.83). For survival without ECMO, PF-PCO$_2$ outperformed the other tools with an AUC of 0.92 (95% CI 0.87–0.96) versus 0.87 (95% CI 0.81–0.93) for WHSRpf, 0.72 (95% CI 0.65–0.80) for CDHSG-PS, and 0.75 (95% CI 0.68–0.82) for the Brindle tool. Finally, for death despite ECMO, PF-PCO$_2$ had the highest AUC at 0.83 (95% CI 0.76–0.91) versus 0.82 (95% CI 0.75–0.89) for WHSRpf, 0.75 (95% CI 0.65–0.85) for CDHSG-PS, and 0.77 (95% CI 0.67–0.88) for the Brindle tool.

The scatterplot diagram in Fig. 3 shows the distribution of PF-PCO$_2$ scores for the outcomes of survival, survival without ECMO, and death despite ECMO. A PF-PCO$_2$ score >−60 was most predictive of survival and >+80 was

Table 2 Baseline characteristics of patients in each group

	Survived $N = 165$	Died $N = 38$	P
Birth weight, g (mean, SD)	3138 (455)	2995 (637)	0.109
Gestational age, weeks (mean, SD)	38 (1)	38 (2)	0.079
Inborn	96 (58%)	25 (66%)	0.389
Male sex	103 (62%)	26 (68%)	0.489
Race			0.891
Caucasian	134 (81%)	31 (82%)	
Hispanic	21 (13%)	5 (13%)	
African American	2 (1%)	1 (3%)	
Other	8 (5%)	1 (3%)	
Apgar (median, 25–75%)			
1 min	5 (3 to 7)	2 (1 to 3)	<0.001
5 min	7 (6 to 8)	6 (4 to 7)	<0.001
Fetal diagnosis	99 (60%)	27 (71%)	0.206
Pulmonary hypertension (pre-repair)	142 (86%)	38 (100%)	0.015
Left sided hernia	148 (90%)	32 (84%)	0.336
Liver in thorax	59 (36%)	19 (50%)	<0.001
Repair type			<0.001
Primary	113 (68%)	5 (13%)	
Muscle flap	41 (25%)	7 (18%)	
Patch	11 (7%)	7 (18%)	
None	0 (0%)	19 (50%)	
ECMO	44 (27%)	22 (58%)	<0.001
Birth epoch			0.119
1 (2003–2007)	53 (32%)	16 (42%)	
2 (2008–2012)	53 (32%)	15 (39%)	
3 (2013–2018)	59 (36%)	7 (18%)	
Predictive score (median, 25–75%)			<0.001
PF-PCO$_2$	182 (66 to 264)	−7 (−36 to +14)	
WHSRpf	58 (-4 to +142)	−34 (−55 to −10)	
CDHSG-PS	77 (63 to 84)	51 (30 to 66)	
Brindle	0 (0 to 2)	2 (1 to 3)	

Data as mean (SD) or number (%), unless otherwise specified in the table

ECMO extracorporeal membrane oxygenation, *IQR* interquartile range, *PF-PCO$_2$* (PaO$_2$/FiO$_2$)-PCO$_2$ equation, *WHSRpf* Wilford Hall Santa Rosa Prediction Formula, *CDHSG-PS* Congenital Diaphragmatic Hernia Study Group Probability of Survival Equation

most predictive of survival without ECMO (Table 3). More subjects with a PF-PCO2 score >−60 survived (97%, $p < 0.001$) and score >+80 survived without ECMO (93%, $p < 0.001$). The PF-PCO$_2$ score had poor predictive ability for the outcome of death despite ECMO.
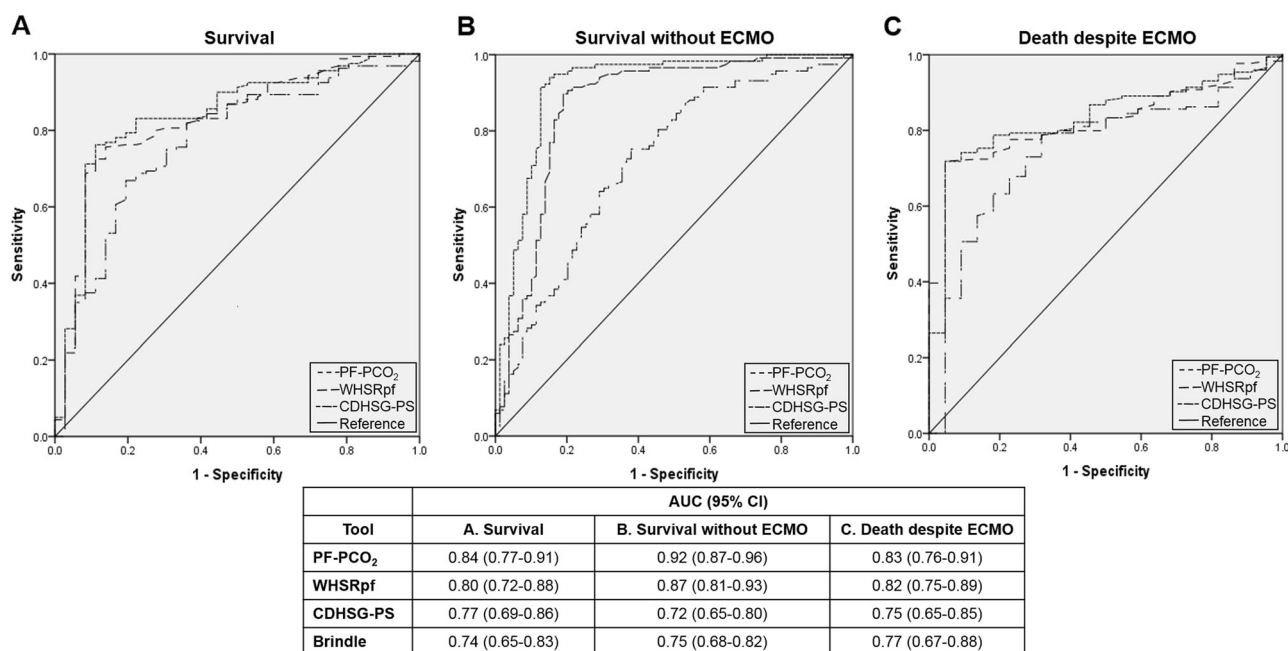
	AUC (95% CI)		
Tool	**A. Survival**	**B. Survival without ECMO**	**C. Death despite ECMO**
PF-PCO$_2$	0.84 (0.77-0.91)	0.92 (0.87-0.96)	0.83 (0.76-0.91)
WHSRpf	0.80 (0.72-0.88)	0.87 (0.81-0.93)	0.82 (0.75-0.89)
CDHSG-PS	0.77 (0.69-0.86)	0.72 (0.65-0.80)	0.75 (0.65-0.85)
Brindle	0.74 (0.65-0.83)	0.75 (0.68-0.82)	0.77 (0.67-0.88)

Fig. 2 AUC curves for each predictive tool. Brindle curves are not shown due to low AUC and opposite test direction compared to the other scores. *ECMO* extracorporeal membrane oxygenation, *CDHSG-* *PS* Congenital Diaphragmatic Hernia Study Group Probability of Survival Equation, *WHSRpf* Wilford Hall Santa Rosa Prediction Formula, *PF-PCO$_2$* (PaO$_2$/FiO$_2$)-PCO$_2$ equation

Discussion

This retrospective review showed that, in our single center experience, the PF-PCO$_2$ tool was superior to the CDHSG-PS, Brindle, and WHSRpf tools for early postnatal prediction of survival in infants with CDH. We also found the PF-PCO$_2$ tool to be most predictive of survival without ECMO, but not death despite ECMO. In our patient population, a score >−60 had an 84% PPV and 100% NPV to predict survival and a score >+80 had a 90% PPV and 89% NPV to predict survival without ECMO.

The CDHSG-PS and Brindle scores predicted survival the poorest in our patient population, with an AUC of 0.77 and 0.74, respectively. Javid et al. [17] showed that survival rates for infants with CDH in the Canadian Neonatal Network were better than that predicted by the CDHSG-PS tool. Similar results were obtained by Downard et al. [18] in an analysis of their CDH population, where actual versus predicted survival was 93% versus 68%, respectively. In contrast, Skarsgard et al. [12] and Baird et al. [19] found the CDHSG-PS tool predicted mortality well in their databases of infants with CDH from multiple centers in Canada. Gentili et al. [13] also found this model to be effective at predicting mortality (AUC 0.84) in their local population of infants with CDH. Furthermore, the CDHSG-PS model significantly predicted survival in a local population of CDH infants who underwent ECMO [10]. Regarding the Brindle tool, the tool stratified infants into low, inter-mediate, and high risk for mortality categories with an AUC

of 0.81 in the derivation model, but only 0.77 in the validation model [11]. Finally, Akinkuotu et al. [2] found the Brindle score to independently predict mortality at 6 months, but not risk for ECMO.

In our infants with CDH, the WHSRpf tool predicted survival second best, with an AUC of 0.80. Authors applying this tool to their local populations have shown good prediction of survival or mortality, with Shultz et al. [8] showing an AUC of 0.87 in their local derivation model and Gentili et al. [13] an AUC of 0.84. However, the predictive ability declined when applied to larger databases [8, 17]. In a CDH-ECMO population, Hoffman et al. [20] found the WHSRpf tool predicted survival in CDH infants who underwent ECMO with an AUC of 0.71.

It is unclear why the CDHSG-PS and Brindle tools had lower predictive scores for survival, survival without ECMO, and death despite ECMO in our population. One reason could be that the authors of these tools did not exclude infants with other major cardiac or chromosomal anomalies, both of which would increase the risk of mortality via the Brindle score. As infants with other major anomalies may frequently not be offered (or parents may decline) surgical intervention or ECMO, we excluded this group of patients to isolate the effect of the diaphragmatic hernia on mortality. Additionally, we excluded infants born at a gestational age of less than 34$^{0/7}$ weeks or birth weight less than 1800 g, as ECMO is not typically offered to these patients [21, 22] and low birth weight and prematurity increase mortality [11, 22, 23]. Including these infants

would likely reduce the predictive ability of the PF-PCO$_2$ equation, as factors other than pulmonary function could play a role in an infants' death. Finally, we excluded infants diagnosed after 24 h of life, because these infants typically have a mild defect and favorable prognosis [3]. Among the 19 infants we excluded due to diagnosis after 24 h, survival without ECMO was 100%. Thus, for this group of CDH infants, a tool predicting survival seems unnecessary. As

expected, the WHSRpf score had good predictive ability, with an AUC of 0.80 for survival. The PF-PCO$_2$ score likely performed better due to the inclusion of the PF ratio, rather than PaO$_2$ alone, thereby providing a better measure of oxygenation [14, 15]. An advantage of the PF-PCO$_2$ score is the ease with which it can be calculated at the bedside, in contrast to the CDHSG-PS and Brindle tools, which are algorithm based.

Our findings suggest that incorporating a better measure of oxygenation and ventilation allows the PF-PCO$_2$ tool to predict survival and survival without ECMO in infants ≥34 weeks gestation with isolated CDH. The severity of pulmonary hypoplasia determines outcome in these patients, including need for ECMO and mortality [2, 7–10]. Infants with CDH have decreased numbers of alveoli and accompanying vessels compared to normal term infants, although the total ratio is normal [24]. Furthermore, there is a greater percentage of peripheral arteries that are abnormally muscularized or hypertrophied [24], also contributing to pulmonary hypertension. When correlating postmortem findings with blood gas values, Germain et al. [25] found that the severity of pulmonary hypoplasia correlated with the level of hypoxemia in CDH infants. Finally, other investigators have shown that blood gas values predict survival in infants with CDH, including PaCO$_2$ [26] and the highest FiO$_2$ [9] and PaO$_2$ [27, 28]. Regarding ECMO risk, Kays et al. [29] showed that PaCO$_2$ and PaO$_2$ at 1 h of life correlated with an increased risk for ECMO in their group of infants with severe CDH, while Hoffman et al. [30] found that PaCO$_2$ independently predicted survival in CDH infants placed on ECMO. However, PaO$_2$ itself is not the best measure of oxygenation in a patient. Of the various measures of oxygenation or hypoxemia [14, 15], the PF ratio is easy to calculate and has been shown to be significantly different between survivors and non-survivors of CDH [13].

While most studies have looked at survival or mortality alone, we also determined the ability of the PF-PCO$_2$ equation to predict survival without ECMO and death despite ECMO. The equation performed well for predicting survival without ECMO, but not for death despite ECMO. These outcomes are clinically relevant, because infants with
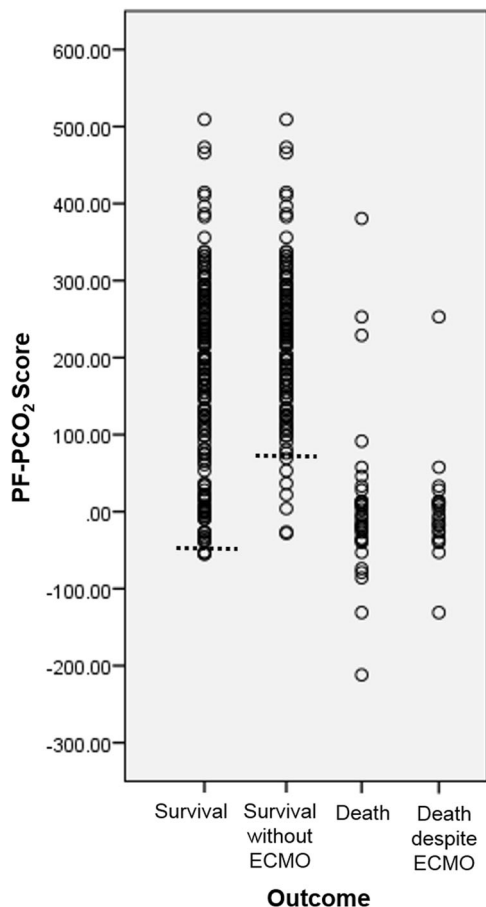

Fig. 3 Scatterplot of PF-PCO$_2$ values for outcomes of survival, survival without ECMO, death, and death despite ECMO. Dotted lines represent proposed optimal cutoff points of >−60 for survival and >+80 for survival without ECMO. *PF-PCO$_2$* (PaO$_2$/FiO$_2$)-PCO$_2$ equation, *ECMO* extracorporeal membrane oxygenation

Table 3 Positive and negative predictive values for the PF-PCO$_2$ tool at various cutoff points for outcomes of survival and survival without ECMO. Death despite ECMO is not shown due to poor predictive ability at all cut offs

Outcome		Cutoff								
		>−80	>−60	>−40	>−20	>0	>+20	>+40	>+60	>+80
Survival	PPV	83%	**84%**	84%	87%	90%	94%	95%	97%	97%
	NPV	100%	**100%**	64%	54%	50%	48%	45%	46%	43%
Survival without ECMO	PPV	61%	61%	63%	68%	74%	83%	87%	88%	*90%*
	NPV	100%	100%	100%	92%	95%	95%	93%	91%	*89%*

Bolded values indicate optimal predictive cutoff for each outcome

ECMO extracorporeal membrane oxygenation

CDH who require ECMO have a greater risk of mortality and long-term morbidity, including adverse neurodevelopmental outcomes and chronic lung disease [3, 31]. Thus, knowledge of an infants' risk for ECMO and death despite ECMO is important not only when considering the risks versus benefits of ECMO, but also when providing informed consent to families regarding this intervention. To date, no model has shown good predictive ability for the isolated outcome of death despite ECMO with CDH.

There are several limitations to this study. This study may have limited generalizability, given that it was a retrospective review conducted at a single center serving a predominantly Caucasian population. Differences in initial care may have contributed to patient outcome, as 42% and 34% of patients in the survived and died groups, respectively, were outborn. Sample size is also relatively small. Additionally, differences in ventilator management can affect $PaCO_2$, PaO_2, and FiO_2, which may produce different results in another center. Although our center has written guidelines directing the care of infants with CDH, including a gentle ventilation strategy with relative permissive hypercapnia and criteria for ECMO initiation, we do not have data on compliance with this protocol. We also did not assess whether including ventilator parameters, particularly mean airway pressure, would change the predictive ability of the $PF-PCO_2$ equation. Finally, we were unable to validate the $PF-PCO_2$ tool in another population, including the CDHSG registry, as it does not contain data on FiO_2. Thus, while we showed good predictive ability of this tool in our population, this may decline when applied to a different population. We plan to test this tool in a much larger independent data set.

This study's strengths include use of a prospectively maintained database with multiple data points, including physiologic measures of respiratory function as well as morbidity and mortality information. Additionally, data were available for all patients to calculate CDHSG-PS and Brindle scores and all but 7 patients to calculate WHSRpf and $PF-PCO_2$ scores. Furthermore, our exclusion criteria attempted to hone in on a subpopulation of CDH infants in whom a predictive tool would be clinically useful. Specifically, CDH infants, who are eligible for ECMO ($\geq 34^{0/7}$ weeks gestation and >1800 g), do not have a mild defect (diagnosed <24 h of life), and do not have other conditions that could influence their outcome. Although this study was limited to a single center, the University of Utah and Primary Children's Hospital NICU's are academic level III and IV units, respectively, and receive neonatal and maternal transfers from across Utah and neighboring states. Finally, despite this study covering a long time period, there were no differences in survival of or ECMO use in patients with CDH.

In summary, the $PF-PCO_2$ tool predicted survival better than the CDHSG-PS, Brindle, and WHSRpf tools in our local population of infants with CDH. This easy to use clinical tool may aid in postnatal therapeutic decisions and counselling of families of CDH infants. Further studies applying this tool to other populations are necessary to validate this equation. Additional studies should also consider analysis of the $PF-PCO_2$ tool at different time points within the first 24 h of life.

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