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Pulmonary Support On Day 30 As A Predictor Of Morbidity And Mortality In Congenital Diaphragmatic Hernia

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Abstract

Purpose—Congenital diaphragmatic hernia (CDH) is associated with significant in-hospital mortality, morbidity and length-of-stay (LOS). We hypothesized that the degree of pulmonary support on hospital day-30 may predict in-hospital mortality, LOS, and discharge oxygen needs and could be useful for risk prediction and counseling.

Methods—862 patients in the CDH Study Group registry with a LOS ≥ 30 days were analyzed (2007–2010). Pulmonary support was defined as (1) room-air (n=320) (2) noninvasive supplementation (n=244) (3) mechanical ventilation (n=279) and (4) extracorporeal membrane oxygenation (ECMO, n=19). Cox Proportional hazards and logistic regression models were used to determine the case-mix adjusted association of oxygen requirements on day-30 with mortality and oxygen requirements at discharge.

Results—On multivariate analysis, use of ventilator (HR 5.1, $p=.003$) or ECMO (HR 19.6, $p<.001$) were significant predictors of in-patient mortality. Need for non-invasive supplementation or ventilator on day-30 was associated with a respective 22-fold ($p<.001$) and 43-fold ($p<.001$) increased odds of oxygen use at discharge compared to those on room-air.

Conclusions—Pulmonary support on Day-30 is a strong predictor of length of stay, oxygen requirements at discharge and in-patient mortality and may be used as a simple prognostic indicator for family counseling, discharge planning, and identification of high-risk infants.

Index Words

extracorporeal membrane oxygenation; mechanical ventilation; risk assessment; congenital anomaly

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Introduction

Congenital diaphragmatic hernia (CDH) is a severe birth defect associated with long hospital stays and significant short and long-term morbidity and mortality. Patients are frequently discharged on oxygen, requiring close long-term pulmonary and nutritional follow-up (1–3). The combination of long hospital stays, significant long-term morbidity and high risk of mortality can complicate both the counseling of patient families and planning for discharge home (4, 5). With considerable cross-institutional variation in treatment and outcomes in CDH (5, 6), there has been increasing interest in developing risk stratification systems to help identify “high-risk” patients across treatment centers (7–9); factors such as ventilation mode, use and length of ECMO, birth-weight, APGAR score, defect size, and the presence of cardiac anomalies have been shown to predict inpatient mortality (7–10). However previous prediction scores have often been complex and difficult to use in the clinical setting.

A previous analysis of the CDH study group registry (from 2001–2006) demonstrated that over 40 percent of CDH patients who required at least one-month of initial hospitalization also needed some form of supplemental oxygen at 30 days (11). The same study found that many known predictors of mortality could be used to predict the amount of pulmonary support required at this time point. However, there is also some evidence that the need for supplemental oxygen itself may be a significant independent predictor of future outcome: supplemental oxygen needs of CDH patients at hospital discharge have been shown to predict the severity of neurodevelopmental deficits over 1–2 years later (12).

The degree of pulmonary support, including whether a patient requires nasal cannula, ventilation, or ECMO, is routinely recorded for all patients in the international CDH Study Group at both 30 days and discharge. We hypothesized that 30-day requirements for pulmonary support, after adjustment for other known risk factors, could be a strong simple predictor of subsequent inhospital mortality, length of stay, and oxygen requirements at discharge; making this a useful tool both for family counseling and determining which patients may benefit from more intensive multidisciplinary follow-up due to a higher risk of long-term morbidity.

Methods

We performed a retrospective cohort study of all patients in the CDH Study Group registry who had a hospital length of stay (LOS) $\geq$ 30 days during 2007–2010. IRB Approval was obtained from Boston Children’s Hospital (IRB-P00002412). Thirty-three patients were missing 30-day pulmonary support status and therefore excluded. The primary outcome was mortality before hospital discharge. Secondary outcomes included need for a prolonged hospital stay (defined as a hospital stay longer than 60 days) and the need for oxygen supplementation at discharge for survivors of a long hospital stay. Pulmonary support status was subdivided into (1) room air or no supplemental oxygen requirement, (2) noninvasive oxygen requirement, including nasal cannula (NC) and continuous positive airway pressure (CPAP), (3) ventilator, including traditional mechanical ventilation or high frequency oscillatory ventilation (via either endotracheal tube or tracheostomy), and (4) extracorporeal

membrane oxygenation (ECMO). The presence and type of pulmonary support was recorded at day 30 and on the day of discharge by each treating institution. Variables compared between groups included gender, birth-weight (kilograms), estimated gestational age at birth (EGA, weeks), 1-minute and 5-minute APGAR, the presence of major cardiac abnormalities (defined as any cardiac defect more severe than an isolated atrial or ventricular septal defect), the presence of a chromosomal abnormality, size of defect, type of repair (primary versus patch), and use of extracorporeal membrane oxygenation (Short ECMO Length was defined as 25th percentile or 7 days and extended ECMO length was considered > 7 days). One-minute APGAR was used in multivariate analysis as it was presumed more independent of center-specific treatment differences than 5-minute APGAR. Defects are graded size A to D, with A representing a small defect often amenable to primary repair and D representing agenesis of the diaphragm.(13) Center level data included center case volume (high volume was defined as 30 cases during the study period). All patients with LOS 30 days were included in analysis of in-patient mortality. To determine if the level of pulmonary support at 30 days could predict an outcome > 1 month in the future, only patients with a prolonged hospital stay (LOS 60) days were included in the assessment of discharge oxygen requirements.

First, unadjusted analyses were used to assess the characteristics associated with 30-day oxygenation status. All categorical analyses were performed using the Fisher's exact test. Normally distributed data were compared with non-paired t-test and ANOVA, and non-parametric data were compared with the Wilcoxon rank sum test. A Cox Proportional Hazards model was used to examine the adjusted association of 30 day pulmonary support with survival. Only significant (p .05, Table 2) predictors of mortality in unadjusted analyses were included in the multivariate models. As there were fewer size A and B defects, these were combined. Logistic regression was used to examine the independent association of 30 day pulmonary support with supplemental oxygenation requirements at discharge in survivors of prolonged hospitalization. Area under the receiver operating curve analysis was used to determine the degree of model fit. A p-value 0.05 was considered significant. All analyses were performed using JMP Pro 64-bit 9.0.2 (SAS Institute Inc. Cary, NC).

Results

Unadjusted Analysis

862 CDH patients in the CDH study group registry had a LOS 30 days and had information regarding their need for pulmonary support. There were 320 patients on room air on hospital day 30 and 542 (62.9%) required some form of pulmonary support. Of those who required oxygen, 244 (45.0%) required only nasal cannula or CPAP, 279 (51.5%) needed some form of mechanical ventilation, and 19 (3.5%) were on ECMO support (Figure 1). 30-day pulmonary support was associated with significant differences among known predictors of disease severity (Table 1). Need for invasive pulmonary support on day 30 (mechanical ventilation or ECMO) was associated with a significantly greater proportion of diaphragmatic agenesis and defects requiring patch repairs. Invasive oxygenation requirements were also associated with lower birth-weight, lower APGAR scores, and a

greater proportion of cardiac anomalies than those on room air or only requiring noninvasive supplemental oxygen. Patients requiring a greater degree of pulmonary support at 30 days were also significantly more likely to have required ECMO previously in their hospital course than those with lower oxygen requirements. Additionally, those with invasive oxygen needs at 30 days were more likely to have required a longer duration of ECMO compared to those with lesser degrees of pulmonary support.

The use of noninvasive supplementation or room air at 30 days was associated with lower oxygen requirements at discharge and lower mortality compared to the use of invasive pulmonary support at the same time point. The proportion of patients on oxygen at discharge was 0.6% in those on room air, 43.2% among those requiring noninvasive supplementation, and 63.3% among those requiring mechanical ventilation at 30-days ($p<.001$). The majority of patients who required ECMO at 30 days did not survive to discharge, however of the 5 survivors, 2 (40%) required oxygen at discharge. Furthermore, the relative level of pulmonary support at 30-days foreshadowed the relative level of pulmonary support required at discharge; While only 2.6% patients who were on noninvasive supplementation on day 30 required mechanical ventilation at discharge, 16.8% of patients using mechanical ventilation on day 30 continued to require mechanical ventilation by discharge ($p<.001$).

Patients on room air on day 30 and those only requiring noninvasive oxygen had rates of survival to discharge of 99.7 and 98 percent respectively, compared to 75 and 26 percent in ventilated and ECMO patients respectively ($p<.001$). Kaplan Meier survival analysis of patients with a LOS over 30 days confirmed these findings, showing that the level of pulmonary support at 30 days was strongly associated with mortality before discharge. While there was no difference in survival between those on room air at 30 days and those requiring noninvasive oxygen ($p=.31$), patients requiring invasive pulmonary support, such as a ventilator or ECMO, had significantly greater subsequent inpatient mortality than those on room air or noninvasive supplementation ($p<.001$, Figure 2).

The level of pulmonary support at 30 days was also strongly associated with the need for a longer hospital stay ($p<.001$). When examining all survivors (Table 2), we found that increased need for pulmonary support at 30 days also predicted the type of pulmonary support used at discharge; patients requiring a ventilator at 30 days were more likely to require a ventilator at discharge compared to those on noninvasive oxygen, and those on nasal cannula at 30 days were more likely to require oxygen at discharge compared to patients on room air at 30 days (both $p<.001$).

Adjusted Analysis

Mechanical ventilation and ECMO at 30-days were found to be the only significant independent predictors of mortality when adjusting for other known risk factors in a cox proportional hazards model (Table 2, Column 1). Patients who required only nasal cannula or CPAP at 30-days did not have a significantly higher adjusted risk of mortality compared to those on room air (Hazard Ratio 0.91, CI .2–4.5). However patients with a ventilator requirement at 30-days had a 5.1 fold (CI 1.7–22.3) increased adjusted risk of mortality compared with those on room air, and ECMO requirements at 30 days increased the adjusted risk of mortality by a factor of 19.6 (CI 5.1–97.7). The degree of pulmonary support at 30

days alone predicts the vast majority of in-patient mortality. When this single variable is placed in a logistic model of mortality it generates an area under the receiver operating curve (AUC of ROC) of 85.6%; demonstrating that this risk factor alone correctly classifies 85.6% of subsequent in-patient deaths.

The use of pulmonary support at 30 days was noted to be the greatest independent risk factor for discharge oxygen requirements in survivors of long hospital stays (Table 2, Column 2). The use of nasal cannula or CPAP at 30 days was associated with a 22 fold increased odds of being discharged on oxygen ($p<.001$) compared to patients who did not require pulmonary support at 30 days. Furthermore, ventilator use at 30 days was associated with a 43 fold increased odds of supplemental oxygen use at discharge compared to those who were on room air at 30 days ($p<.001$). One-minute APGAR ($p=.04$), birthweight ($p=.003$), major cardiac abnormalities (.004), ECMO (“short” $p.01$, “extended” $p=.04$) were also independently associated with discharge oxygen needs, however to a lesser degree than our primary predictor.

Discussion

We hypothesized that the degree of pulmonary support at 30 days could be used as a simple prognostic indicator for both late mortality and pulmonary morbidity in high-risk patients. We found that pulmonary support status at 30 days is the strongest independent predictor of both late mortality and pulmonary morbidity in survivors at discharge. This single factor can correctly predict over 85 percent of all subsequent inpatient deaths, and is a stronger independent predictor of mortality and discharge oxygen requirements than previously noted risk factors such as low APGAR score, low Birth-weight, large defect size, major cardiac disease, low case volume, and even greater length of ECMO.

While CDH results from a diaphragmatic defect, it is the severity of the resulting pulmonary disease that best foretells outcome. Many recent predictive indices have used proxy measures in an attempt to assess the severity of pulmonary disease in CDH (11). APGAR score and birth-weight were two of the earliest factors to be associated with outcome (9). These ubiquitous measures are obtained early on in the course of disease and can therefore be used in stratifying the severity of disease across institutions prior to stabilization or operative treatment. More recently, graded defect size has been shown to be one of the strongest predictors of mortality and morbidity (8). Major congenital heart defects have also been shown to be associated with outcome (14), but they are only observed in a minority of patients. Prenatal MRI has been used to measure the total lung volume, and is highly correlated with both defect size and mortality. However none of these risk factors allow us to directly measure the most important component of CDH severity: the degree of *functional* pulmonary insufficiency. One attempt to use a measurement of lung function to predict outcome was the Wilford Hall-Santa Rosa (WHSR) formula. Calculated from arterial blood gas measurements in the first 24 hours of life, this formula has been correlated with mortality (15). However more recently there has been disagreement about its ability to predict later outcomes (16, 17).

We determined that patients who were on room air at 30 days had an overwhelmingly positive prognosis. Over 99% of these patients survived, over 85% were discharged home before 60 days on room air, and of those who required a longer stay almost 98% were discharged without oxygen requirements (Figure 1). While patients on noninvasive oxygen supplementation at 30 days (nasal cannula/CPAP) had no increased adjusted risk of inpatient mortality, they did have a significantly increased risk of supplemental oxygen use at discharge. Patients who required greater levels of pulmonary support, such as those on a ventilator or ECMO at 30 days, had survival rates of only 74.9% and 26.3% respectively. The majority of these patients then required a hospital stay over 60 days, and between 40 and 62% of patients required oxygen at discharge, many in the form of ventilators. While we noted that patients who had low 1 minute APGAR (<4), low birthweight (<2.8), a large lesion or previous ECMO requirements also had an increased risk of being discharged on supplemental oxygen, none of these factors appeared to be as strong of a predictor as the degree of pulmonary support at 30 days.

In this analysis we were limited to adjusting for risk factors available in the CDH study group database. While most known risk factors of mortality in CDH are included, there may be unmeasured confounders. Additionally, supplemental oxygen use at 30 days and discharge may be confounded by treatment strategies. Some centers may use supplemental oxygen for indications other than treatment of pulmonary insufficiency, including the encouragement of growth. Controlling for nutritional information may be helpful in future validation of oxygenation supplementation as a prognostic indicator. As invasive oxygenation techniques such as mechanical ventilation or ECMO are unlikely to be used for non-pulmonary treatments, we feel confident that the association between 30-day pulmonary support and mortality is real. Even if centers differ slightly in their ventilator or ECMO strategy, we believe that the use of invasive pulmonary support is a true marker for higher risk disease. Finally, as previous analyses have demonstrated that the use of oxygen at discharge is correlated with more severe neurodevelopmental deficits over 1–2 years later, we believe that the use of oxygen at discharge, whether it is for pulmonary reasons or to help growth, is an important outcome variable with longer term significance (12). Previous analyses have suggested that certain types of ventilation, such as HFOV, can be risk factors for longer term pulmonary morbidity (11). In the present analysis we considered only whether or not the patient was on a mechanical ventilator at 30 days and did not examine the specific ventilator strategy. We believe that ongoing prospective analysis will be needed to both validate the results of this study and to determine if ventilator strategy may further stratify high-risk disease.

Congenital Diaphragmatic Hernia is associated with significant mortality and long-term morbidity (3, 18, 19). As the use of new technologies such as extracorporeal membrane oxygenation, high-frequency oscillatory ventilation, and nitric oxide have become more prevalent, a greater proportion of high-risk infants are now surviving (4, 20). In this way, the average severity of disease in survivors has increased significantly, resulting in a proportional increase in the total long-term disease burden (21). The need for invasive pulmonary support such as ECMO, has been associated with many late complications including diminished lung function and decreased exercise tolerance in the school ages (22), and increased long-term neurodevelopmental difficulties (23). Some studies have even

shown increased pulmonary disease as long as 10–20 years after birth, including increased requirements for inhaler medications in CDH survivors (24).

The use of invasive pulmonary support at 30 days is the strongest independent prognostic indicator of both mortality and pulmonary morbidity in patients requiring prolonged hospital stays. Even the use of noninvasive supplementation at 30 days is highly correlated with the use of supplemental oxygen at discharge, an outcome that is itself tied to greater longer-term disease morbidity (12). For all centers, regardless of their resources, the degree of pulmonary support at 30-days could be a useful and simple predictor of future outcome. Patients who do not require pulmonary support at 30-days appear to have an overwhelmingly positive outcome. While it has been shown that all CDH survivors benefit from life-long multidisciplinary follow up (3), these patients may be at lower risk of long-term complications, and may require less intensive or less frequent follow up visits. Conversely, patients who require invasive pulmonary support at 30 days, or even noninvasive pulmonary support, appear to have far worse outcomes in terms of both mortality and pulmonary morbidity. We may speculate that for this higher risk group, intensive long-term multidisciplinary follow-up, including surgical, pulmonary, nutritional and developmental specialists could be of even greater benefit. The ability to predict which patients are likely to require oxygen or ventilation support at discharge and which patients are at risk of a longer hospital stay could also be useful for both family counseling and multidisciplinary discharge planning. The degree of pulmonary support at 30 days is a simple and powerful predictor of morbidity and mortality in CDH patients and could be used as a powerful tool for the optimization of care.

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Figure 1.

Flow diagram representing all CDH patients in the CDH study group registry stratified by the degree of pulmonary support on day 30.

Figure 2. Survival analysis of congenital diaphragmatic hernia patients with LOS ≥ 30 days by type of pulmonary support used on hospital day 30 (censored at day 200).

Comparison of predictors and outcomes of CDH patients by pulmonary support on hospital day 30. CDH Study Group Registry, 2007–2010 (N = 862). All patients in this sample had a length of stay of at least 30 days.

Table 1

	Degree of Pulmonary Support on Day 30				
Risk Factors	Room Air (n = 320) N (%)	NC/CPAP (n=244) N (%)	Ventilated (n=279) N (%)	ECMO (n = 19) N (%)	p-value
Birth weight, kg, mean ± SD	3.1 ± 0.5	3.0 ± 0.6	2.8 ± 0.7	3.0 ± 0.4	<.001*
Gestational age, weeks, mean ± SD	38.0 ± 1.8	37.6 ± 2.2	37.1 ± 2.7	38 ± 1.7	<.001*
APGAR - 1 min, median (IQR)	6 (4 – 8)	5 (3 – 7)	4 (2 – 6)	5 (2.5–6.5)	<.001*
APGAR - 5 min, median (IQR)	8 (7 – 9)	7 (6 – 8)	7 (5 – 8)	5 (4 – 7.5)	<.001*
Major Cardiac abnormality	12 (3.8)	13 (5.3)	39 (14.0)	0 (0)	<.001*
Chromosomal abnormality	9 (2.8)	11 (4.5)	12 (4.3)	1 (5.3)	0.52
Size of Lesion (if repaired)					
A (Small)	32 (11.2)	14 (6.3)	7 (2.9)	0 (0)	<.001*
B (Medium)	151 (52.6)	74 (33.5)	38 (15.8)	1 (6.3)	
C (Large)	89 (31.0)	96 (43.4)	129 (53.5)	10 (62.5)	
D (Agenesis)	15 (5.2)	37 (16.7)	67 (27.8)	5 (31.3)	
Repaired with Patch	150 (47.0)	172 (70.5)	238 (86.6)	16 (94.1)	<.001*
High Volume Center (30 cases, 2007–2010)	221 (69.1)	192 (78.7)	220 (78.9)	16 (84.2)	<.001*
ECMO Length, days, median (IQR)	27 (8.4) 7.5 (5.0–10.3)	85 (34.8) 8 (6.0 – 11.0)	179 (64.2) 12 (8.0 – 17.0)	19 (100.0) 26 (18.0 – 33.0)	<.001* <.001*
Outcome					
Long-Stay (LOS 60 days)	42 (13.2)	113 (47.3)	178 (85.2)	5 (100.0)	<.001*
Survival	319 (99.7)	239 (98.0)	209 (74.9)	5 (26.3)	<.001*

Degree of Pulmonary Support on Day 30					
Risk Factors	Room Air N (n = 320) N (%)	NC/CPAP N (n=244) N (%)	Ventilated N (n=279) N (%)	ECMO N (n = 19) N (%)	p-value
Pulmonary Support at D/C					
<i>Room Air</i>	317 (99.4)	133 (56.8)	77 (37.0)	3 (60.0)	<.001*
<i>NC/CPAP</i>	2 (0.6)	95 (46.6)	96 (46.2)	1 (20.0)	
<i>Ventilator/Tracheostomy</i>	0 (0)	6 (2.6)	35 (16.8)	1 (20.0)	

IQR = interquartile range. All categorical data compared by exact test. Birth-weight compared by t-test, all other continuous variables compared by non-parametric rank sum test.

Table 2**Multivariate Analysis**

Cox proportional hazards analysis of predictors of mortality and nominal logistic multivariate model of predictors of oxygen status at discharge in long-stay survivors.

	Risk of Mortality		Odds of Supplemental Oxygen Use at Discharge	
Variable	Hazard Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
1-min APGAR (unit odds ratio)	0.93 (0.83–1.04)	.22	0.87 (0.77–0.99)	.04*
Birthweight (unit odds ratio)	0.98 (0.67–1.44)	.91	0.52 (0.33–0.81)	.003*
Major Cardiac Abnormality	1.18 (0.22–4.51)	.63	4.21 (1.52–13.46)	.004*
Defect Size				
<i>A/B-Reference</i>	1.0		1.0	
C	1.02 (0.55–2.00)	.95	1.35 (0.68–2.68)	.39
D	0.88 (0.43–1.84)	.72	2.22 (0.99–5.07)	.054
30-Day Oxygenation				
<i>Room Air-Reference</i>	1.0		1.0	
NC/CPAP	0.91 (0.21–4.51)	.90	21.94 (4.26–402.99)	<.001*
Ventilator	5.07 (1.65–22.30)	.003*	43.24 (8.51–790.81)	<.001*
ECMO	19.47 (5.07–97.72)	<.001*	6.32 (0.20–204.31)	.26
ECMO				
<i>None-Reference</i>	1.0		1.0	
Short (7 days)	0.98 (0.40–2.19)	.96	2.93 (1.24–7.15)	.01*
Extended (>7 days)	1.32 (0.64–3.19)	.39	2.08 (1.04–4.26)	.04*
High Volume Center	0.83 (0.51–1.41)	.49	1.74 (0.88–3.50)	.11