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The congenital diaphragmatic hernia composite prognostic index correlates with survival in left-sided congenital diaphragmatic hernia

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Abstract

Purpose—We developed the congenital diaphragmatic hernia congenital prognostic index (CDH-CPI) to incorporate all known prognostic variables into a single composite index to improve prognostic accuracy. The purpose of this study is to examine the ability of the CDH-CPI to predict survival in patients with left-sided congenital diaphragmatic hernia and to determine if the index has a stronger correlation with survival than each of the individual components.

Methods—A retrospective review of patients with left-sided congenital diaphragmatic hernia between 2004 and 2010 was conducted. Ten prenatal parameters of the CDH-CPI were collected, total score was tabulated, and patients stratified according to total score and survival.

Results—Sixty-four patients with a prenatal diagnosis of left-sided congenital diaphragmatic hernia were identified. Patients with a CDH-CPI score of 8 or higher had a significantly higher survival than patients with a CDH-CPI score of lower than 8. The CDH-CPI has the strongest correlation with survival compared with the individual parameters measured. The CDH-CPI correlates with extracorporeal membrane oxygenation use, and 75% of patients with a score of 5 or lower were placed on extracorporeal membrane oxygenation.

Conclusions—The CDH-CPI accurately stratifies survival in left-sided congenital diaphragmatic hernia. The amalgamation of 10 prenatal parameters of the CDH-CPI may be a better prenatal predictor than any single prognostic variable currently used.

Keywords

Congenital diaphragmatic hernia; Survival; Prognosis; CDH-CPI

Congenital diaphragmatic hernias (CDHs) remain among the most challenging congenital anomalies to manage despite advances in critical care, extracorporeal membrane oxygenation (ECMO) support, antipulmonary hypertensive therapies, and prenatal tracheal balloon occlusion. Although several prenatal prognostic factors have been reported such as lung-to-head ratio (LHR) [1,2] observed to expected LHR [3], percentage predicted lung volumes (PPLVs) [4], liver position [5], total lung volume (TLV) [6], and modified McGoon Index [7], no single prognostic variable adequately encompasses the broad range of severity and associated anomalies which may influence the prognosis.

The compelling rationale for an accurate prognostic stratification of CDH severity includes appropriate counseling of parents and likely outcomes. This will help define needs before delivery that may determine the site of delivery, indicate the need for alternative delivery options such as EXIT-to-ECMO, cesarean delivery with ECMO-standby, or in the most severe cases, consideration of fetal tracheal occlusion or comfort care only. Accurate risk stratification can also inform resuscitative efforts postnatally including initiation of more aggressive antipulmonary hypertensive management, or establishing a lower threshold to initiate ECMO support.

Many prenatal prognostic indicators such as LHR, PPLV, TLV, modified McGoon Index, and liver position have each been individually used to predict survival and need for ECMO support [4,7–11]. A composite of prognostic indicators, however, has never been reported despite that these prognostic indicators measure different aspects of CDH. Lung-to-head ratio, TLV, and PPLV measure lung volume; the modified McGoon Index measures pulmonary arteries; the lack of liver herniation or presence of a sac is indicator of less visceral herniation. In addition, the impact of associated anomalies such as karyotype abnormalities, congenital heart defects, and presence of chest masses such as congenital pulmonary airway malformations and bronchopulmonary sequestrations are not factored into individual prognostic variables.

To that end, we developed the CDH-Congenital Prognostic Index (CPI) to incorporate all known prognostic variables into a single composite index to improve prognostic accuracy. The purposes of this study are to examine in patients with left-sided CDH the ability of the CDH-CPI to accurately predict survival and the need for ECMO and to determine if the CDH-CPI has a stronger correlation with survival than the individual component parameters.

1. Methods

1.1. Patient data

A retrospective review of medical records for all patients with left-sided CDH evaluated prenatally at the Fetal Care Center (FCC) of Cincinnati and treated postnatally at Cincinnati Children's Hospital Medical Center between 2004 and 2010 was conducted. This study was approved by the institutional review board (IRB no. 2008-0894). Patients generally had 2 visits to the FCC with imaging performed at both visits. A fetal magnetic resonance imaging (MRI), ultrasound, and echocardiogram are performed at the early visit, and only fetal MRI and ultrasound are repeated at the second prenatal visit. The first visit occurred before 31 weeks of gestational age, and the second visit occurred after 31 weeks of gestational age. Ten prenatal parameters of the CDH-CPI were collected from both visits if available: (1)

karyotype, using amniocentesis; (2) presence of syndromes through the prenatal genetic counseling; (3) congenital heart disease (CHD) using fetal echocardiography; (4) left ventricle-to-right ventricle (LV/RV) disproportion using fetal echocardiography; (5) modified McGoon Index measured using MRI at the later visit; (6) presence of a sac using MRI; (7) liver position as determined using ultrasound or MRI; (8) LHR, using ultrasound; (9) PPLV using MRI; and (10) TLV using MRI.

1.2. Assessing the congenital diaphragmatic hernia congenital prognostic index score

The CDH-CPI is composed of information from four groups: genetic, cardiac, hernia, and lung representing 10 different prenatal prognostic parameters. Each parameter of the CDH-CPI was scored as either +1 or 0. In the genetics group of the scoring system, a normal karyotype scored +1 and an abnormal karyotype scored 0. Patients without any syndromic features scored +1, and any patients with syndromic characteristics such as Beckwith-Wiedeman scored 0.

In the cardiac group of the CDH-CPI, patients without any CHD scored +1 and patients with minor or easily correctable congenital heart lesions such as atrial septal defect, ventricular septal defect, and coarctation scored 0. On the basis of clinical experience, patients with significant CHD such as double outlet right ventricle received a score of -1 for the CHD parameter. Normal LV/RV ratio scored +1, and any LV/RV disproportion scored 0. The modified McGoon index measured via MRI at the later visit was also scored if available. A McGoon Index lower than 1.2 scored 0, and a McGoon Index greater than 1.2 scored +1 [7].

In the hernia group of the index, the presence of a sac visualized via imaging scored +1, whereas lack of mention of a sac scored 0. Liver position was also noted on both early and late visits via MRI and ultrasound when available. Intraab-dominal liver position scored +1, and any liver noted to be in the chest scored 0. Findings on the later gestational age evaluation took precedence over earlier studies; for example, two patients were noted to have normal liver position on early imaging but on imaging later in gestation, the liver was noted to be in the chest and was therefore scored as 0.

The lung group of the CDH-CPI consists of LHR measured via ultrasound early in gestation (the only gestational age for which its prognostic value has been validated [1,2]), and TLV and PPLV were measured late in gestation using MRI. We have previously shown later gestational age values to be more accurate for both of these measurements [12]. An LHR greater than 1.0 scored +1, whereas an LHR lower than 1.0 scored 0. A TLV greater than 18 mL scored +1, whereas a TLV less than 18 mL scored 0. Similarly, PPLVs greater than 15% scored +1, and those less than 15% scored 0. Early gestation measurements were used for TLV and PPLV if late gestation measurements were not available.

A total score was tabulated, and patients were stratified according to total score and 60-day survival. Patients with missing data automatically received 1 point per parameter except for the parameter *presence of hernia sac*. These patients were assumed to not have a sac and received a score of 0 in this parameter. Study exclusions include lethal anomalies/syndromes such as Fryn's syndrome and hypo-plastic left heart and patients not treated postnatally at Cincinnati Children's Hospital Medical Center.

1.3. Statistical analysis

Only patients who had follow-up and postnatal treatment at our institution were included in this study. When available, the 10 parameters of the CDH-CPI were used for statistical analysis. Fisher's Exact test and Student's *t*-test were used to compare composite scores and survival and nonsurvival. Results are summarized as mean $\pm$ standard error of mean for

continuous data and as percentages for categorical variables. The correlation between 60-day survival and the CDH-CPI score and the individual predictor variables was assessed by Pearson and Spearman rank correlation coefficients. To further define the ability of the CDH-CPI to predict survival, logistic regression and decision trees using classification and regression trees (CART) analysis as implemented in R packages was used [13]. Each variable in the CDH-CPI was weighted equally in the tabulation of the final composite score based on clinical experience. However, significant CHD was given a score of -1 because these patients are known to have poor outcomes [14]. Generalization and consistency of decision trees were estimated using multiple (100) runs of 10-fold cross-validation by using rpart function in R with explicit separation of training and control sets.

2. Results

2.1. Study population

Of a total of 73 cases of CDH evaluated prenatally at the FCC, we identified 64 patients with a prenatal diagnosis of left-sided CDH and postnatal treatment at our institution. The average gestational age of patients seen during the first visit is 24 5/6 weeks (range, 19 1/7–30 2/7 weeks), and the average gestational age of patients seen at the second visit is 34 1/7 weeks (range, 31–37 5/7 weeks). The overall survival of this population is 65.6% (42/64). Table 1 contains the data of the 10 individual prenatal prognostic variables for this study population.

2.2. Congenital diaphragmatic hernia congenital prognostic index correlation with improved survival

The CDH-CPI score of 8 or higher (based on the average CDH-CPI mean score of survivors) has a significantly higher percent survival than patients with a CDH-CPI score of lower than 8 (89% vs 38%) (Fig. 1A). The CDH-CPI scores of survivors and nonsurvivors were found to be significantly different between the two groups (7.97 ± 0.20 vs 6.27 ± 0.31) (Fig. 1B).

2.3. Congenital diaphragmatic hernia congenital prognostic index correlation with survival and extracorporeal membrane oxygenation use

Congenital diaphragmatic hernia CPI has a stronger positive degree of correlation with survival ($r = 0.539$, $P = .00000093$). Liver position, TLV, and LHR had weaker but still statistically significant positive correlation with survival in patients with isolated left CDH ($r = 0.37$, $P = .0032$; $r = 0.45$, $P = .00027$; and $r = 0.40$, $P = .0014$, respectively). There was no significant correlation between survival and CHD, LV/RV disproportion, presence of a hernia sac, karyotype, syndromes, modified McGoon index, and PPLV. To ensure that there was a positive correlation between the CDH-CPI and the 4 most commonly used prenatal predictors correlation coefficients were obtained: LHR ($r = 0.611$, $P = .000000027$); PPLV ($r = 0.589$, $P = .000000088$ and TLV ($r = 0.589$, $P = .00000094$); and liver position ($r = 0.627$, $P = .00000011$).

Regression analysis showed a significant relationship between survival and CDH-CPI. Goodness of fit measured by area under a receiver operating characteristic curve had a value of 0.8019 ($P = .0003$). Recursive partitioning with CART decision tree was used to determine the optimal CDH-CPI score that independently predicts survival. Consistent with the survival data observed in univariate analysis, a CDH-CPI of 7.5 or higher independently predicts survival.

Congenital diaphragmatic hernia CPI has a negative correlation with the use of ECMO ($r = -0.384$, $P = .002$). The mean CDH-CPI score of those patients who had ECMO use $6.36 \pm$

1.539 vs those patients with nonuse of ECMO 7.7 ± 1.39 . Of those patients with a CDH-CPI score of 6 or lower, 63% used ECMO, and of those with a CDH-CPI score of 5 or lower, 75% used ECMO.

3. Discussion

The results of this single institution retrospective study suggest that the CDH-CPI may provide useful information for the counseling of parents with a fetus that has been diagnosed with an isolated left-sided CDH. There is a positive correlation between CDH-CPI score and survival. Patients with a score of 8 or higher have excellent outcomes with survival approaching 90%, whereas patients with scores lower than 8 had significantly decreased survival. A primary end point of this study was to determine if the CDH-CPI has a stronger correlation with survival than each of the individual component parameters. Our data suggest that of the 10 individual parameters, only TLV, LHR, and liver position significantly correlated with survival. In comparison, the CDH-CPI had a stronger degree of correlation than each of these individual parameters. This is probably because of the all-encompassing nature of this scoring index, which allows for more comprehensive prenatal counseling. It must be mentioned that it is counterintuitive that some other parameters did not significantly correlate with survival such as karyotype abnormality or CHD. This is probably because of the small number of patients who we had in each of these groups therefore no statistical significance. We additionally used logistic regression analysis to analyze the validity of our index to predict outcome in our data set. The CDH-CPI was able to accurately predict both survival and ECMO use.

Of all of the prenatal prognostic studies, LHR is the only validated prenatal predictor of CDH outcome [1,2] but focuses purely on the lung hypoplasia component of the CDH with no significance given to the pulmonary hypertension, presence of genetic syndromes or the attributes of the hernia. Total lung volume [12] and PPLV [4] have shown promise in predicting survival but have only been examined in small case series and suffer from the same limitation as LHR of assessing only the lung hypoplasia component. The limitation of these measurements (LHR, TLV, PPLV) of lung hypoplasia is evident in the example of a fetus who may have a favorable LHR, but in light of a significant genetic syndrome or a significant cardiac defect, survival can potentially be greatly diminished. We have previously reported that significant heart defects can result in a 3-fold increase in mortality in patients with CDH [14]. Liver herniation has also shown to be useful as it not only addresses the attributes of the hernia but also is a surrogate marker for lung hypoplasia. The main advantage of the CDH-CPI is that it takes into account several aspects of the fetus' overall state of health and severity of the CDH, from the genetic and cardiac perspective and further includes both assessment of the pulmonary hypoplasia and the significant pulmonary hypertension that can be associated with CDHs. This may account for the stronger correlation with survival of the CDH-CPI as compared with the other individual parameters. We use this prognostic index in each of our prenatal CDH consults seen at the FCC of Cincinnati to counsel patients and provide expectant mothers on the likelihood of survival at our institution.

The CDH-CPI also positively correlated with ECMO use. Seventy-five percent of patients with a score of 5 or lower were placed on ECMO. This prenatal information is helpful in identifying high-risk fetuses who should be delivered at an institution offering advanced supportive measures such as ECMO. Furthermore, we use the lower CDH-CPI scores to identify high-risk babies who may be offered an alternative delivery strategy, such as EXIT to ECMO or have their cesarean delivery performed at the Children's Hospital with the ECMO circuit primed and available in the same operative theater. This strategy in theory minimizes the potential risks to the baby during transport.

The limitations of this study include its retrospective nature allowing for possible observational bias. In addition, the data presented in this study are institutional specific, as postnatal CDH management is not standardized among major children's institutions. Furthermore, albeit 64 patients included in the study is a clinically significant sample size, it is statistically small. This is especially true of the subset of patients who required ECMO use (19 patients), but our data would suggest that a CDH-CPI score of 5 or lower increased the likelihood for the need for ECMO (Fig. 1D). These limitations can only be overcome by a much larger prospective study of the CDH-CPI in a multicenter collaboration.

In conclusion, the results of this study demonstrate that patients with a left-sided CDH and a CDH-CPI score of 8 or higher have a significantly higher rate of survival than patients with a CDH-CPI score lower than 8. These results may allow the surgeon to prenatally predict potential outcomes and appropriately counsel expectant mothers on severity and likely outcomes associated with CDH while potentially predicting the need for ECMO support. Such a tool may enable pediatric surgeons to objectively stratify patients and alter their delivery and postnatal management strategy.

References

1. Lipshutz GS, Albanese CT, Feldstein VA, et al. Prospective analysis of lung-to-head ratio predicts survival for patients with prenatally diagnosed congenital diaphragmatic hernia. *J Pediatr Surg.* 1997; 32:1634–6. [PubMed: 9396544]
2. Metkus AP, Filly RA, Stringer MD, et al. Sonographic predictors of survival in fetal diaphragmatic hernia. *J Pediatr Surg.* 1996; 31:148–51. [PubMed: 8632269]
3. Jani J, Nicolaides KH, Keller RL, et al. Observed to expected lung area to head circumference ratio in the prediction of survival in fetuses with isolated diaphragmatic hernia. *Ultrasound Obstet Gynecol.* 2007; 30:67–71. [PubMed: 17587219]
4. Barnewolt CE, Kunisaki SM, Fauza DO, et al. Percent predicted lung volumes as measured on fetal magnetic resonance imaging: a useful biometric parameter for risk stratification in congenital diaphragmatic hernia. *J Pediatr Surg.* 2007; 42:193–7. [PubMed: 17208564]
5. Hedrick HL, Danzer E, Merchant A, et al. Liver position and lung-to-head ratio for prediction of extracorporeal membrane oxygenation and survival in isolated left congenital diaphragmatic hernia. *Am J Obstet Gynecol.* 2007; 197:422, e1–4. [PubMed: 17904987]
6. Lee TC, Lim FY, Keswani SG, et al. Late gestation fetal magnetic resonance imaging-derived total lung volume predicts postnatal survival and need for extracorporeal membrane oxygenation support in isolated congenital diaphragmatic hernia. *J Pediatr Surg.* 2011; 46:1165–71. [PubMed: 21683216]
7. Vuletin JF, Lim FY, Cnota J, et al. Prenatal pulmonary hypertension index: novel prenatal predictor of severe postnatal pulmonary artery hypertension in antenatally diagnosed congenital diaphragmatic hernia. *J Pediatr Surg.* 2010; 45:703–8. [PubMed: 20385274]
8. Balassy C, Kasprian G, Brugger PC, et al. Assessment of lung development in isolated congenital diaphragmatic hernia using signal intensity ratios on fetal MR imaging. *Eur Radil.* 2010; 20:829–37.
9. Kilian AK, Schaible T, Hofmann V, et al. Congenital diaphragmatic hernia: predictive value of MRI relative lung-to-head ratio compared with MRI fetal lung volume and sonographic lung-to-head ratio. *AJR Am J Roentgenol.* 2009; 192:153–8. [PubMed: 19098195]
10. Neff KW, Kilian AK, Schaible T, et al. Prediction of mortality and need for neonatal extracorporeal membrane oxygenation in fetuses with congenital diaphragmatic hernia: logistic regression analysis based on MRI fetal lung volume measurements. *AJR Am J Roentgenol.* 2007; 189:1307–11. [PubMed: 18029863]
11. Busing KA, Kilian AK, Schaible T, et al. MR lung volume in fetal congenital diaphragmatic hernia: logistic regression analysis—mortality and extracorporeal membrane oxygenation. *Radiology.* 2008; 248:233–9. [PubMed: 18566175]

12. Lee TC, Lim FY, Keswani SG, et al. Late Gestation Fetal MRI-Derived Total Lung Volume (TLV) Predicts Postnatal Survival and Need for ECMO Support in Isolated Congenital Diaphragmatic Hernia. *J Pediatr Surg.* 2011; 46:1165–71. [PubMed: 21683216]
13. Therneau, TM.; Tirkonda, P.; Taylor, C. Recursive partitioning. 2009. <http://CRAN.R-project.org/package=rpart>
14. Cohen MS, Rychik J, Bush DM, et al. Influence of congenital heart disease on survival in children with congenital diaphragmatic hernia. *J Pediatr.* 2002; 141:25–30. [PubMed: 12091847]

Fig. 1.

(A) There is a significant difference in survival between patients with CDH-CPI scores of 8 or higher compared with patients with score of lower than 8 ($P = .0001$). (B) There is a significant difference between survivors and nonsurvivors and their mean CDH-CPI score ($P = .000013$). (C) When patients are stratified according to their CDH-CPI score, there is increasing percentage survival. (D) There is a negative correlation between ECMO use and CDH-CPI score ($P = .002$). Patients with scores of 5 or lower had a 75% change of requiring ECMO.

Table 1**Scoring system**

		1	0	-1
Genetics	Karyotype	Normal (97%)	Mild (3%)	
	Syndrome	No (98%)	Yes (2%)	
Cardiac	Congenital heart disease	None (89%)	VSD/ASD/Coarctation (9%)	Double outlet heart disease (2%)
	LV/RV	No (97%)	Yes (3%)	
	McGoon	1.2 (33%)	<1.2 (67%)	
Hernia	Sac	Yes (5%)	No (95%)	
	Liver	Down (29%)	Up (71%)	
Lung	Lung-to-heart ratio	1 (66%)	<1 (34%)	
	PPLV	15% (77%)	<15% (23%)	
	Total lung volume	18 mL (73%)	<18 mL (27%)	

The congenital diaphragmatic hernia congenital prognostic index scoring system consists of 4 groups: genetics, cardiac, hernia, and lung with 10 parameters. Each parameter and characteristics for scoring are depicted. The study population defined for each variable is represented by a percentage of available data.

LV/RV indicates left ventricle-to-right ventricle disproportion; VSD, ventricular septal defect; ASD, atrial septal defect; PPLV, percentage predicted lung volume.