



## Application of a postnatal prediction model of survival in CDH in the era of fetal therapy

K. Clohse<sup>a</sup>, M. Rayyan<sup>b</sup>, J. Deprest<sup>c,d</sup> , H. Decaluwe<sup>e</sup>, M. Gewillig<sup>f</sup> and A. Debeer<sup>b</sup>

<sup>a</sup>Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium; <sup>b</sup>Department of Neonatology, University Hospitals Leuven, Leuven, Belgium; <sup>c</sup>Academic Department of Development and Regeneration, Cluster Woman and Child, Biomedical Sciences, and Clinical Department of Obstetrics and Gynaecology, Maternal Fetal Medicine, University Hospitals Leuven, Leuven, Belgium; <sup>d</sup>Institute for Women's Health, University College London, London, United Kingdom; <sup>e</sup>Department of Thoracic Surgery, University Hospitals Leuven, Leuven, Belgium; <sup>f</sup>Department of Pediatric Cardiology, University Hospitals Leuven, Leuven, Belgium

### ABSTRACT

**Background:** The disease severity in patients with a congenital diaphragmatic hernia (CDH) is highly variable. To compare patient outcomes, set up clinical trials and come to severity-based treatment guidelines, a performant prediction tool early in neonatal life is needed.

**Objective:** The primary purpose of this study was to validate the CDH study group (SG) prediction model for survival in neonates with CDH, including patients who had fetal therapy. Secondary, we aimed to assess its predictive value for early morbidity.

**Methods:** This is a retrospective single-center study at the University Hospitals Leuven on all infants with a diagnosis of CDH live-born between April 2002 and December 2016. The prediction model of the CDHSG was applied to evaluate its performance in determining mortality risk. Besides, we examined its predictive value for early morbidity parameters, including duration of ventilation, respiratory support on day 30, time to full enteral feeding and length of hospital stay.

**Results:** The CDHSG prediction model predicted survival well, with an area under the curve of 0.796 (CI: 0.720–0.871). It had poor value in predicting infants who needed respiratory support on day 30 (area under the curve (AUC) 0.606; CI: 0.493–0.719), and correlated poorly with duration of ventilation, time to full enteral feeding and length of hospital stay.

**Conclusion:** The CDHSG prediction model was in our hands also a useful tool in predicting mortality in neonates with CDH in the fetal treatment era. Correlation with early morbidity was poor.

### RATIONALE

**Objectives:** (1) Validation of the CDHSG prediction model for survival in a cohort of neonates with CDH, in whom fetal endoscopic tracheal occlusion was applied according to the severity of lung hypoplasia. (2) Evaluation of performance of the model in the prediction of early morbidity.

**Main results:** (1) Confirmation of the predictive value of the model for survival in neonates with CDH in the era of fetal therapy. (2) No correlation of the model with early morbidity parameters.

### ARTICLE HISTORY

Received 13 June 2018  
Accepted 27 September 2018

### KEYWORDS

Congenital diaphragmatic hernia (CDH); morbidity; mortality; risk stratification

## Introduction

Congenital diaphragmatic hernia (CDH) is a challenging congenital anomaly for fetal medicine specialists, neonatologists and pediatric surgeons. It occurs in one out of 2000–5000 live born, isolated or in association with structural anomalies and/or genetic problems [1]. Mortality is about 20–35% and is mainly determined by the presence of associated anomalies, the degree of lung hypoplasia and the occurrence of pulmonary hypertension [2].

Over the past years, efforts were made to standardize postnatal management of infants with CDH and in Europe, a consensus protocol was established [3,4]. It includes lung protective ventilation with permissive hypercapnia, pulmonary vasodilator therapy and delayed surgical treatment. However, adoption of these treatments was not preceded by well designed multicenter clinical trials, and there is a lack of standardized treatment guidelines based on markers of disease severity [5].

Therefore, a generally applicable risk assessment tool is needed. It allows targeting clinical trials to high-risk populations, thereby maximizing the likelihood that a true benefit will be detected and minimizing the unnecessary exposure of low-risk patients to experimental therapies [6]. It makes a comparison of outcomes in and between centers possible, and helps in counseling the family of an affected infant.

Different pre- and postnatal prediction models based on image findings and clinical parameters were constructed for that purpose:

Prenatally, fetal medicine specialists make an estimate of the survival chances based on the presence of chromosomal abnormalities, preferentially assessed by array comparative genomic hybridization (array CGH), the presence of associated congenital anomalies, the position of the liver and the size of the fetal lungs as a proxy for the degree of pulmonary hypoplasia, as assessed by ultrasound and/or magnetic resonance imaging (MRI) [7–9].

The most widely used measure of fetal lung size is the observed over expected lung-to-head ratio (O/E LHR). It consists in measuring the area occupied by the lung contralateral to the lesion at the four-chamber view, dividing it by the head circumference, and expressed as a percentage to the normal value in a fetus of the same gestational age (GA) [10,11].

On MRI, the total fetal lung volume (TFLV) is measured using consecutive two-dimensional sections. Again, the effect of GA is offset by expressing the measured volume as a percentage of what volume is expected in a normal fetus of similar body volume (observed/expected volume ratio) [8].

Collection and analysis of multi-institutional postnatal data on CDH started in 1995 with the foundation of the Congenital Diaphragmatic Hernia Study Group (CDHSG). Participating centers over 10 different countries prospectively record demographic, treatment-related and outcome data on all live-born infants with CDH until hospital discharge or death.

In 2001, the CDHSG developed a postnatal prediction model to predict mortality based on Apgar score at 5 minutes of life and birth weight [12]. Later on, the Canadian Neonatal Network used the SNAP-II score, calculated from six empirically weighed physiologic measurements, in combination with GA [13]. The Wilford Hall/Santa Rosa clinical prediction formula was generated from arterial blood gas values obtained during the initial 24 hours of life [1]. Other authors evaluated the Modified Mcgoon Index (MGI) and Pulmonary Artery Index (PAI), calculated from

echocardiographic measurements, as surrogates for the development of the pulmonary circulation [14,15].

Many of these models have been developed in small populations, are of limited generalizability or lack proper validation [14,15]. Some are difficult to apply, others have only moderate predictive performance [12,16].

In 2014, the CDHSG published a new clinical prediction model that was created and validated on randomly selected subgroups within the CDHSG registry from January 2007 to October 2011. Mortality is predicted based on birth weight, 5-minute Apgar score, the presence of severe pulmonary hypertension, and the finding of a cardiac or chromosomal anomaly. It was made easily applicable by modifying all predictors into binary variables [6].

The first aim of our study was to apply the latter clinical prediction model in patients treated at our center, which adheres to the European standardized neonatal management model and where a significant number of patients eligible for fetal therapy are assessed, hence some of them eventually being treated *in utero*. Given the medium and long-term morbidity of CDH, we also aimed to examine whether the score is predictive for early neonatal morbidity.

## Materials and methods

### Patient population

All CDH patients admitted to the Neonatal Intensive Care Unit (NICU) of the University Hospitals Leuven between April 2002 and December 2016 were included.

### Data collection

Prenatal data were collected from maternal records and included prenatal age at diagnosis (weeks), side of the defect and position of the liver, array CGH result (normal or not), use of fetal endoscopic tracheal occlusion (FETO) and GA at birth.

Neonatal data included birth weight, Apgar scores, and presence of associated congenital anomalies. All infants had a cardiac ultrasound within 24 hours after birth to assess structural defects and to diagnose pulmonary hypertension.

The primary outcome parameter was early mortality, defined as death before discharge from the NICU. Secondary outcome parameters indicating neonatal morbidity were the duration of ventilation, need of respiratory support on day 30, time to full enteral feeding and length of NICU stay.

### Definitions used

Prenatally, the defect is characterized by its side (left-sided, right-sided or bilateral) and the position of the liver, categorized as either partly intra-thoracic (“up”) or confined to the abdomen (“down”), based on ultrasound assessment.

The CDHSG score is calculated as follows: 1 (low birth weight) + 1 (low Apgar) + 2 (missing Apgar) + 2 (severe pulmonary hypertension) + 2 (major cardiac anomaly) + 1 (chromosomal anomaly) = total CDH score.

Based on this score, patients can be stratified into three mortality-risk groups: a score of 0 is predicting a low risk (<10%), a score of 1–2 – an intermediate risk (25%) and a score of  $\geq 3$  a high risk of death (50%).

Low birth weight is defined as a weight <1500 g and low Apgar score as a score <7 at 5 minutes of life. Severe pulmonary hypertension is defined as the right to left shunting through a patent ductus arteriosus or pulmonary pressures estimated as higher than systemic pressure. Major cardiac anomalies are classified as all anomalies other than patent foramen ovale or patent ductus arteriosus.

### Statistical analysis

Statistical analyses were conducted using the IBM SPSS package version 24 (New York). As most of the data, with the exception of birth weight, were not normally distributed, we used nonparametric statistics for all analyses. Medians and interquartile ranges were used to describe continuous variables. Frequencies and percentages were used to describe categorical data.

Comparisons were performed by the chi-square test for independence (with Yates’ continuity correction for 2 by 2 tables) for categorical variables and by the Mann–Whitney *U*-test for continuous variables. When the lowest expected frequency in 1 cell of the 2 by 2 table was less than 5, the Fisher’s exact probability Test was used instead of the chi-square test for independence (indicated by \*).

To determine the strength of the relationship between the prediction model and the outcome parameters, Spearman Rank Order correlation ( $\rho$ ) was used. A *p* value of <.05 was considered statistically significant. A  $\rho$ -value of 0,10–0,29 indicates small, a value of 0,30–0,49 medium and a value of 0,50–1,0 large correlation.

Receiver-operating characteristic curves (ROC-curves) were constructed to determine the accuracy of the CDHSG score in predicting survival and the need for respiratory support on day 30 (C statistic). An area

under the curve (AUC) of 0,5 is completely random whereas an AUC of 1,0 indicates perfect discrimination.

## Results

### Demographics and patient outcomes

Patient characteristics are summarized in Table 1.

Most mothers were referred prenatally for structural assessment, risk stratification and in selected cases fetal intervention.

Eleven (6.9%) infants had a chromosomal anomaly or were clinically diagnosed with a syndrome; one (0.6%) had a familial, non-syndromal form of a diaphragmatic hernia.

A major cardiac defect was diagnosed in 7 patients (4.4%): two had a tetralogy of Fallot, two a critical coarctation of the aorta, two a hypoplastic left heart, and one an atrioventricular septal defect (AVSD).

Twenty-nine (18.1%) presented with other associated congenital anomalies, affecting the ocular (coloboma, cataract), upper and lower respiratory (cleft palate, congenital cystic adenomatoid malformation), gastrointestinal (oesophageal atresia, intestinal atresia), urogenital (posterior urethral valves, hypospadias, cryptorchidism) and skeletal (vertebral and limb anomalies) system.

The survival rate was 101/162 (62.3%). For isolated CDH, this was 95/138 (68.8%). The majority of deaths occurred in the early neonatal period: 34/61 (55.7%) within 48 hours after birth, and 50/61 (82.0%) before surgical repair was performed, which was median on day 3 of life (IQR day 2–5). In 86 (76,8%), the size of the defect was too large for primary closure and a prosthetic patch was used.

In survivors, the median duration of ventilation was 11.5 days (IQR 6–22 days). On day 30, 39 patients (39.8%) still had some form of respiratory support: seven (17.9%) received low-flow oxygen, 11 (28.2%) were on high-flow oxygen, 9 (23.1%) were on nasal CPAP, and 12 (30.8%) were still mechanically ventilated.

Full enteral feeding (orally and/or by feeding tube) was achieved at a median time of 25 days (IQR 17–34 days). At discharge, 47 (46.5%) patients had full oral feeding, 43 (42.6%) were at least partially fed by a nasogastric and 11 (10.9%) by a gastrostomy feeding tube.

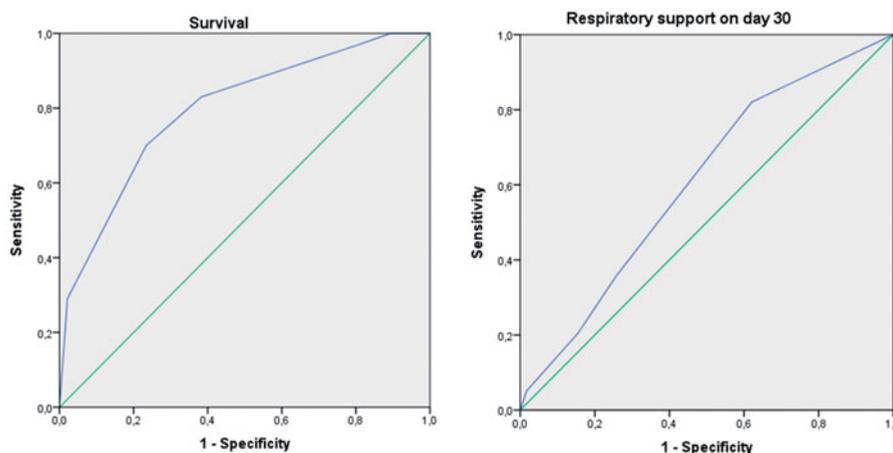
The median length of stay in the NICU was 37 days (IQR 23–64 days). Forty-eight patients (47.5%) could be discharged home, the other 53 (52.5%) were transferred to a lower-level care unit or another hospital.

**Table 1.** Descriptive statistics of all patients included ( $n = 162$ ) and categorized according to survival.

Variable	Patients included		Survivors		Nonsurvivors		<i>p</i> Value
			<i>n</i> (%)				
All patients	162	(100.0)	101	(62.3)	61	(37.7)	
Prenatal diagnosis	145/162	(89.5)	87/101	(86.1)	58/61	(95.1)	.125
Left-sided defect	130/162	(80.2)	90/101	(89.1)	40/61	(65.6)	.001
Liver up	115/159	(72.3)	59/100	(59.0)	56/59	(94.9)	<.001
FETO	77/162	(47.5)	36/101	(35.6)	41/61	(67.2)	<.001
Major cardiac anomaly	7/159	(4.4)	1/101	(1.0)	6/58	(10.3)	.010*
Other congenital anomaly	29/160	(18.1)	15/100	(15.0)	14/60	(23.3)	.266
Chromosomal anomaly	8/160	(5.0)	0/100	(0.0)	8/60	(13.3)	<.001*
			Median (range)				
Gestational age at birth, postmenstrual weeks	36.7	(27.5–41.0)	37.5	(27.5–40.2)	34.5	(28.3–41.0)	.001
Birth weight, g	2662	(930–4200)	2900	(1000–4200)	2380	(930–4025)	<.001
5-minute Apgar score	6	(1–10)	6	(1–10)	5	(1–9)	<.001
CDHSG score	1	(0–5)	1	(0–4)	3	(0–5)	<.001

Numbers do not always add up due to missing values.

\*Fisher's exact test.



**Figure 1.** ROC curves for prediction of survival (left) and need for respiratory support on day 30 (right) by the CDHSG score.

### Prediction of survival

Applying the CDHSG prediction model, the survival rate was 96.7% in the low risk, 76.1% in the intermediate risk and 37.0% in the high risk group ( $\rho = -0.474$ ,  $n = 147$ ,  $p < .001$ ). Figure 1 displays the accuracy in predicting survival by a ROC-curve. The AUC was 0.796 (CI: 0.720–0.871), indicating a good predictive value.

### Prediction of early neonatal morbidity

Stratifying our population using the CDHSG prediction model, the need for respiratory support on day 30 among survivors was 24.9% in the low risk, 47.1% in the intermediate risk and 47.1% in the high-risk group ( $\rho = 0.187$ ,  $n = 97$ ,  $p = .066$ ). The AUC for predicting respiratory support on day 30 was 0.606 (CI: 0.493–0.719), indicating a poor predictive value (Figure 1).

Using Spearman rho, there was only a small correlation between the CDHSG score and duration of ventilation/hospitalization (Table 2). Correlation with time to full enteral feeding was not statistically significant.

### Discussion

The CDHSG prediction model was validated internally and externally in different populations [5,6]. It is easily applicable in a clinical setting, and it utilizes readily available data in the early neonatal course, allowing prediction of outcome early in the treatment path [17].

Herein, we evaluated the CDHSG prediction model on a single-center cohort, as part of its validation in the era of fetal treatment. We could confirm that the CDHSG model predicted neonatal survival well. The mortality risk was 4.5, 24.6 and 63.6% in the low, intermediate and high-risk groups respectively, which is

**Table 2.** Relationship of CDHSG risk score with secondary outcome measures.

	Low risk		Intermediate risk		High risk		rho	p-Value
				median (range)				
Duration of ventilation	7	(1–32)	14	(1–64)	18	(3–37)	0.284	0.005
Time to full enteral feeding	21.5	(8–61)	25	(14–69)	26	(14–97)	0.202	0.076
Length of hospital stay	28	(6–116)	38	(10–570)	43	(17–193)	0.219	0.029

completely in line with the predicted risk (<10, 25 and 50%).

The initial model was developed on a population of neonates that did not undergo intrauterine treatment. Application of the model on a mixed population of neonates, some undergoing fetal therapy and others being expectantly managed, seems not to affect its performance.

Two variables in the model are potentially influenced by fetal therapy, the birth weight and the degree of pulmonary hypertension. The mean birth weight in the group of patients undergoing fetal therapy is lower because of a higher rate of premature births in this group. Controversies exist on the effect of tracheal occlusion on the pulmonary circulation.

Despite not being designed to predict morbidity, one might speculate that patients at higher risk to die early in the course of the disease, may also be at higher risk for early morbidity. However, in the population of neonates that survived in the early neonatal period, the model was not able to predict the need for respiratory support at day 30, the time to full enteral feeding and the length of the NICU stay. As opposed to the CDHSG prediction model, the prenatally calculated O/E LHR provided a significant prediction of the duration of assisted ventilation, need for supplemental oxygen at 28 days, and incidence of feeding problems in a multicenter study by Jani et al. in which our center participated [11]. In the same way, Lee et al. showed a clear correlation between the MRI derived TFLV and the length of hospital stay [18]. Probably, these prenatal imaging predictors do better predict early morbidity as they quantify lung size and act as surrogate measures for pulmonary hypoplasia, the most important contributor to pulmonary morbidity.

One of the limitations of our study may be the time frame of 14 years where changes in postnatal management have occurred. For instance, postnatal management became officially standardized only at the end of the 2000s [3], and an update of this guideline was made based on the results of the VICI trial [19].

We need to clarify that the population treated prenatally is not representative of the entire group of

severely hypoplastic CDH-fetuses. Fetuses undergoing FETO who deliver more prematurely because of membrane rupture or preterm labor do stay for postnatal management at our center, whereas those who have an uneventful postoperative course and elective balloon removal are transferred to the referring units, and deliver there beyond 34 weeks [20]. The latter population is not represented in this cohort [21].

In conclusion, we confirmed the predictive value of the postnatal CDHSG prediction model for survival in a single-center population of CDH patients including patients undergoing fetal therapy for severe pulmonary hypoplasia. The model, however, did not predict short-term morbidity.

### Acknowledgements

We acknowledge Mr. Ben Van Calsteren for his support with the statistical analyses.

### Disclosure statement

No potential conflict of interest was reported by the authors.

### ORCID

J. Deprest  <http://orcid.org/0000-0002-4920-945X>

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