Population-Based Validation of a Clinical Prediction Model for Congenital Diaphragmatic Hernias

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Objective To examine the external validity of a well-known congenital diaphragmatic hernia (CDH) clinical prediction model using a population-based cohort.

Study design Newborns with CDH born in California between 2007 and 2012 were extracted from the Vital Statistics and Patient Discharge Data Linked Files. The total CDH risk score was calculated according to the Congenital Diaphragmatic Hernia Study Group (CDHSG) model using 5 independent predictors: birth weight, 5-minute Apgar, pulmonary hypertension, major cardiac defects, and chromosomal anomalies. CDHSG model performance on our cohort was validated for discrimination and calibration.

Results A total of 705 newborns with CDH were extracted from 3 213 822 live births. Newborns with CDH were delivered in 150 different hospitals, whereas only 28 hospitals performed CDH repairs (1-85 repairs per hospital). The observed mortality for low-, intermediate-, and high-risk groups were 7.7%, 34.3%, and 54.7%, and predicted mortality for these groups were 4.0%, 23.2%, and 58.5%. The CDHSG model performed well within our cohort with a c-statistic of 0.741 and good calibration.

Conclusions We successfully validated the CDHSG prediction model using an external population-based cohort of newborns with CDH in California. This cohort may be used to investigate hospital volume-outcome relationships and guide policy development. *(J Pediatr 2018;■■:■■-■■).*

Congenital diaphragmatic hernia (CDH) has a reported incidence of 1.76-2.3 per 10 000 live-births.[1-3] Despite the low incidence, the projected burden of patients with CDH may exceed $250 million annually in the US, especially if patients require aggressive treatment such as extracorporeal membrane oxygenation.[4] Along with these high costs, there is a large burden of mortality that has only decreased from approximately 34% to 29% in the last 2 decades.[5]

There have been a number of clinical prediction models attempting to risk stratify infants with CDH based on their presentation.[6-10] Institutions and hospital networks have used these models to demonstrate systematic improvement in the outcomes of CDH.[11-14] A standardized risk adjustment tool could better compare therapeutic strategies and outcomes by stratifying patients across institutions and hospital systems.

In 2014, Brindle et al and the Congenital Diaphragmatic Hernia Study Group (CDHSG) published an updated, simplified clinical prediction rule to stratify infants with CDH based on disease severity. This prediction model used the CDHSG registry to develop a total CDH risk score from clinical indicators at birth based on birth weight, 5-minute Apgar score, severe pulmonary hypertension, and the presence of major cardiac or congenital anomalies. The model can be easily applied within the first few hours of life to accurately stratify CDH newborns into low-, intermediate-, and high-risk of mortality groups,[15] and has been shown to have good discrimination between the risk groups in a single institution's cohort.[16] However, the CDHSG model has not been externally validated at the population level. External validation of clinical prediction models uses novel participant level data to examine whether the model's predictions are reliable in individuals for clinical use.[17] The aim of our study was to externally examine the validity of the CDHSG clinical prediction model on a nonvoluntary, statewide cohort of newborns with CDH.

Methods

We used the Vital Statistics and Patient Discharge Data (VS-PDD) Linked Files from the California Office of Statewide Health Planning and Development (OSHPD) for our data. This dataset links the Vital Statistic birth records to maternal and infant hospital inpatient discharges from all nonfederal hospitals in the State of

CDH	Congenital diaphragmatic hernia
CDHSG	Congenital Diaphragmatic Hernia Study Group
ICD-9	*International Statistical Classification of Disease, Ninth Revision*
OSHPD	Office of Statewide Health Planning and Development
VS-PDD	Vital Statistics and Patient Discharge Data

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California. Each record captures a single hospital encounter and includes birth vital statistics, patient demographics, facility identification, dates of services, and codes for diagnoses and procedures during that encounter. All diagnosis and procedural codes are categorized according to the *International Statistical Classification of Disease, Ninth Revision* (ICD-9). Neonatal and maternal information from the VS-PDD are linked through a probabilistic matching algorithm internal to the OSHPD and produces a unique birth identification number that allows us to identify all hospital encounters for a particular infant in the state of California before 1 year of age. This database has been used previously to examine health outcomes in neonates.[18,19]

Neonates with CDH in California born between January 1, 2007 and December 31, 2012 were extracted from the VS-PDD Linked Files. The criteria for inclusion was a newborn with a birth record containing an ICD-9 diagnosis code "congenital anomalies of diaphragm" (756.6).[20] Only newborns with a deidentified birth identification code were included, and these infants were tracked until in-hospital death or discharge from the acute care setting. CDH surgical repair was identified using ICD-9 procedure codes 53.70-53.84, and excluded "plication of the diaphragm" (53.81) and "repair of parasternal hernia" (53.82). CDH was considered lethal if not repaired; therefore, newborns with ICD-9 code of 756.6 and discharged alive without surgical repair were considered to have diaphragmatic eventration and were excluded. A similar method has previously been used to identify infants with CDH based on ICD-9 codes.[21] Infants with incomplete birth information necessary for the CDHSG prediction model were also excluded.

CDH newborn encounters were reviewed for clinical data including gestational age, birth weight, and 5-minute Apgar score. Severe pulmonary hypertension was identified at the birth hospital encounter and defined by the ICD-9 code for "persistent pulmonary hypertension" (747.83). Major cardiac anomalies were identified by ICD-9 code diagnoses and defined as all anomalies excluding patent atrial septal defects or patent ductus arteriosus.[15,22] Chromosomal anomalies were defined as any ICD-9 diagnostic code 758.0-758.9. Binary independent predictors were created, as defined in the CDHSG model, for low birth weight (<1500 g), low 5-minute Apgar score (<7), missing 5-minute Apgar score, and the presence of pulmonary hypertension at birth, major cardiac defects, and chromosomal anomalies.

The CDHSG clinical prediction model was applied to the binary independent predictors to calculate a total CDH risk score (**Table I**). The total CDH risk scores (range 0-8) were used to stratify newborns into 3 risk groups: low-risk (0), intermediate-risk (1-2), and high-risk (3-8).[15]

Table I. Values for each of the independent predictors to calculate the total CDH risk score according to the 2014 CDH Study Group Clinical Prediction Model

Model variables	Value
Low birth weight	1
Low 5-min Apgar	1
Missing 5-min Apgar	2
Pulmonary hypertension at birth	2
Major cardiac anomaly	2
Chromosomal anomaly	1
Total CDH risk score	0-8

Statistical Analyses

Newborn characteristics at baseline are described using medians and IQRs for continuous variables and percentages for categorical variables. Bivariate comparisons between baseline characteristics and death before discharge were made using the Fisher exact test for categorical variables and nonparametric Wilcox rank-sum test for continuous variables. The CDHSG model was used to calculate individual predicted outcome probabilities. The predicted outcome was then compared with the observed outcome in the study cohort. The model performance was assessed for discrimination using the c-statistic.[23] The c-statistic ranges between 0.5 (poor discrimination) to 1.0 (perfect discrimination) and represents the probability that among a randomly selected pair of observations with different outcomes, predicted outcome risk is higher in the case with the outcomes of interest.[24] The predicted and observed outcomes were also assessed for calibration by plotting a calibration curve, by performing the Hosmer-Lemeshow test, and deriving Harrell E-Statistic. Harrell E-statistic, the mean absolute difference between predicted and smoothed observed values, estimates the degree of variability in the estimation between the observed and predicted values based on a fitted logistic regression.[25] All statistical tests were 2-tailed, and a P value of <.05 was considered statistically significant. Data analysis was performed using R (R Core Team, Vienna, Austria) and STATA/MP 12.1 (StataCorp LP, College Station, Texas).

This retrospective population-based cohort study was performed after obtaining institution review board approval from both Tufts Medical Center (Boston, Massachusetts) (#11349) and the Committee for Protection of Human Subjects in the State of California (14-09-1714).

Results

There were 3 213 822 live-births in California between January 1, 2007 and December 31, 2012. A total of 753 newborns had an ICD-9 diagnosis of 756.6. Forty-eight infants were excluded due to incomplete birth information or incomplete hospital discharge records leaving a total of 705 newborns with CDH in our study cohort (**Figure 1**; available at www.jpeds.com). The average incidence of CDH was 2.2 per 10 000 live-births or 1 in 4430 live-births. The overall survival rate was 68.7%.

The majority of newborns in our cohort were male (58.6%). The median gestational age was 38.7 weeks, and median birth weight was 3000 g. The neonates had a median 5-minute Apgar score of 8. Pulmonary hypertension or major cardiac anomalies were present in 212 (30.1%) and 130 (18.4%) infants, respectively. Overall, 56 (7.9%) infants had a chromosomal anomaly. The most common major congenital cardiac defects

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