Survival Predictors In Congenital Diaphragmatic Hernia: Multivariate Analysis Of a 10-Year Experience

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The purpose of this study was to establish a method by which independent predictors of survival could be determined and used to select CDH patients who may benefit from rescue therapy. Data from our 10-year, single institutional experience of 62 infants with CDH were analyzed. Fifteen preoperative and seven intraoperative variables were analyzed. Stepwise logistic regression analysis yielded a prediction equation with four independent, statistically significant ($P<0.05$) predictors of survival: lower VI, higher BW, higher 5-minute APGAR, and lower $PaCO_2$. Using a survival probability of <20%, this equation yielded a sensitivity of 94% and specificity of 82% in selecting those patients with CDH who failed conventional management. We conclude that the preoperative values for VI, BW, 5-minute APGAR, and $PaCO_2$ of neonates with CDH in our institution can be used to select those patients with predicted high mortality who may benefit from salvage therapy. [Journal of Turgut Özal Medical Center 1997;4(2):225-229]

***Key Words**: Hernia, diaphragmatic, congenital, outcome, newborn, pediatrics*

Konjenital diafragma hernisinde yaşam prediktörleri : 10 yıllık deneyimin multivariate analizi

Bu çalışmanın amacı KDH'li hastalarda kurtarma tedavisine almak için hangi bağımsız yaşam prediktörlerinin olduğunun ve kullanılabileceğinin tespiti için bir metod geliştirmekti. Merkezimizin 10 yıllık bir süredeki 62 hastasının verileri analiz edildi. 15 preoperatif ve 7 intraoperatif değişken incelendi. Stepwise lojistik regresyon analizi dört adet bağımsız, istatistiksel olarak anlamlı ($P<0.05$) yaşam prediktörü olduğu sonucunu verdi: düşük VI, yüksek DA, yüksek 5 dakika APGAR sonucu ve düşük $PaCO_2$. Yaşam probabilitesi %20'den küçük kriterini kullanarak yapılan değerlendirme konvansiyel tedaviden fayda görmeyecek KDH'li vakaların değerlendirilmesinde %94 sensitivite ve %82 spesifite sonucunu verdi. Sonuç olarak VI in preoperatif değeri, DA, 5 dakika APGAR, ve $PaCO_2$ kurtarma tedavisinden fayda görebilecek, *yüksek mortalite öngörülen yenidoğanların seçiminde kullanılabilir düşüncesindeyiz. [Turgut Özal Tıp Merkezi Dergisi 1997;4(2):225-229]*

***Anahtar Kelimeler**: Konjenital, diafragmatik, herni, yenidoğan, pediatri*

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Congenital diaphragmatic hernia (CDH) is a medically complex anomaly affecting 1 in 4000 live births (1). Mortality due to associated pulmonary hypoplasia and persistent pulmonary hypertension remains high, approximately 60 to 65% for in-center births and 35 to 50% for referrals who survive transport (2). Currently, a variety of conventional management strategies are employed in an attempt to improve outcome for neonates with CDH. For example, there are differences in surgical approach (immediate v. delayed repair) (3-7), ventilator management (high frequency jet v. high frequency oscillatory v. intermittent mandatory ventilation) (8-9), and use of tube thoracostomies (10). As these management strategies differ widely among medical centers, it is paramount that each center develop its own criteria to predict survival (11). These criteria may then be used to assist in counseling parents of affected infants and selecting patients who may benefit from newer salvage therapies, such as preoperative extracorporeal membrane oxygenation (ECMO) (12) or nitric oxide (13).

The primary aim of this study was to devise a predictive model of survival for infants with CDH at our institution. Multivariate analysis of our 10-year, single institutional experience was performed. This method overcomes the limitations of univariate statistical analysis in distinguishing between markers of outcome and true independent prognostic indicators. The study was purposely limited to a single institution in order to minimize differences in neonatal management and operative strategy. The survival predictors were derived as factors of an exponential equation which could be used prospectively to estimate the probability of survival for individual neonates with CDH.

MATERIALS AND METHODS

Study Subjects:

The medical records of 62 neonates with CDH treated from January 1983 to October 1992 by Baylor College of Medicine staff neonatologists and pediatric surgeons were reviewed. During this period at our medical center, the aim of ventilatory management was to maintain a respiratory alkalosis ($pH > 7.5$, $PaCO_2 < 40$) using paralysis, sedation, and intermittent mandatory ventilation with the shortest possible inspiratory times (typically 0.2 seconds). Supplementary intravenous sodium bicarbonate was used to maintain alkalemia at the discretion of the staff neonatologist. None of the patients received high frequency jet ventilation, high frequency oscillatory ventilation, nor ECMO since these modalities were not available at our center during the study period.

Surgical correction was performed after a period of preoperative stabilization in an attempt to optimize arterial blood gases. The indication for use of a prosthetic diaphragmatic patch was a large diaphragmatic defect which could not be repaired primarily, as determined by the operating surgeon.

Study Variables:

Fifteen preoperative and 7 intraoperative variables were selected for analysis. The preoperative variables included: gestational age (GA), birth weight (BW), 5-minute APGAR, age at operation, side of defect, $PaCO_2$, PaO_2, pH, oxygenation index (OI) (14), ventilation index (VI) (15), Bohn's criteria (16), presence of a preoperative pneumothorax, antenatal diagnosis, inborn v. outborn status, and gender (Tables 1 and 2). Arterial blood gas data used in this study were postductal and obtained immediately prior to surgery. Bohn's criteria were plotted in 49 neonates for whom the data were complete. The intraoperative variables included: operating room (OR) v. neonatal intensive care unit (NICU) location, use of a tube thoracostomy, placement of diaphragmatic prosthetic patch, presence of a hernia sac, presence of an intrathoracic stomach, laparotomy v. thoracotomy incision type, and ability to close the abdorninal fascia (Table 3). Survival was defined as survival to hospital discharge. The data were complete for all variables in 35 neonates. Continuous variables were expressed as the mean +/- standard deviation (SD).

Data Analysis:

Univariate analysis was performed using Minitab® software (release 8, PC version, State College, PA) on a microcomputer. Multivariate, stepwise logistic regression analysis was performed using the BMDP biomedical statistical package on a DEC-VAX 8810 mainframe computer. From the multivariate analysis. independent predictors among the study variables were identified and used to generate an exponential equation for predicting survival. Results were considered significant if *P* was less than 0.05.

RESULTS

Sixty-two neonates with CDH were studied. Descriptive data are included in Tables 1 - 3.

Overall survival was 66% and did not change significantly over the 10-year period. Univariate analysis demonstrated the statistically significant variables associated with outcome to be: 5-minute APGAR, Bohn's criteria, the location of surgery (OR v. NlCU), the presence of a hernia sac, preoperative presence of a pneumothorax (7), placement of a prosthetic diaphragmatic patch, and the ability to close the abdominal fascia. Multivariate analysis revealed the only independent, statistically significant predictors of survival to be: lower VI, higher BW, higher 5-minute APGAR, and lower $PaCO_2$. An exponential prognostic exuation was derived:

probability of survival = $[1 + e^x]^{-1}$

where, x= 4.9 - 0.68(APGAR) - 0.0032(BW) + 0.0063(VI) + 0.063($PaCO_2$)

with a range from 0 (lowest survival) to 1 (highest survival)

When the predicted survival was set at the current standard of less than 20% (2), this prognostic equation yielded a sensitivity of 94% and a a specificity of 82% in identifying those neonates who expired after failing conventional management.

Table 1. Continuous preoperative variables among 62 neonates with CDH

	Mean+/- SD	Range
Gestational age (wk)	38.7 +/- 2.3	29-42
Birthweight (gm)	3050+/-671	1280-4710
5 minute APGAR	6.1+/-2.2	2-9
PaO_2 (torr)	90+/-79	11-365
$PaCO_2$ (torr)	47+/-20	18-90
pH	7.32+/-0.16	6.70-7.59
Ventilation index	804+/-447	228-2520
Oxygenation index	31.4+/- 54.9	1.29- 326.3
Age at operation (h)	56.1+/-155.3	1-720

Table 2. Dichotomous preoperative variables among 62 neonates with CDH

	No. of Patients	%
Gender		
• Males	34	55
• Females	28	45
Side of defect		
• Left	48	77
• Right	14	23
Bohn's criteria		
• A	20	41
• B	17	35
• C	9	18
• D	3	6
Antenatal diagnosis	12	19
Presence of pneumothorax	11	18
Site of birth		
• inborn	26	43
• outborn	34	57

Note. A, B, C, D = Bohn's quadrants (16) , A: $PaCO_2 > 40$, VI < 1000; B: $PaCO_2 < 40$, VI < 1000; C: $PaCO_2 > 40$, VI > 1000 (predicted 0% survival); D: $PaCO_2 < 40$, VI > 1000.

Table 3. Intraoperative variables among 62 neonates with CDH

	No. of Patients	%
Thoracostomy tube	38	62
Prosthetic diaphragmatic patch	15	24
Hernia sac	11	19
Intrathoracic stomach	23	45
Able to close abdominal fascia	56	92
Surgery location		
• OR	46	74
• NICU	16	26
Incision type		
• LAP	59	97
• THOR	2	3

Abbreviations: OR, operating room; NICU, neonatal intensive care unit; LAP, laparotomy; THOR, thoracotomy.

DISCUSSION

These results suggest that lower VI, higher BW, higher 5-minute APGAR, and lower $PaCO_2$ are independent predictors of outcome in neonates with CDH at our institution. Further, multivariate analysis yielded a highly sensitive and specific predictive equation to select those patients with low predicted survival (<20%). Thus, by performing multivariate analysis on data from our 10-year experience, we have developed a clinically useful method to predict survival in neonates with CDH at our institution.

The inherent strength of multivariate analysis is two-fold. First, it defines those variables which are independently associated with outcome. There are many markers of poor outcome but relatively few independent predictors of survival. For example, when comparing the survival in the 62 neonates with CDH using univariate analysis, the patients in whom it was necessary to place a diaphragmatic patch for hernia closure had a statistically significant lower survival rate than those treated without a patch (40% versus 70%, $P < 0.05$ by chi-square analysis). This may lead one to believe that a patch should not be placed because it is associated with significantly decreased survival. However, this is so merely because the more severely ill infants received the patch. This is confirmed by multivariate analysis, whereby the placement of the patch was not of any additional prognostic value. Hence, patch placement was only a marker for decreased survival rather than an independent predictor of survival.

Another example is that of Bohn's criteria. Like that of the diaphragmatic patch, Bohn's criteria were found to be statistically significant by univariate analysis with relation to outcome, but they were excluded as independent predictors of survival by multivariate analysis. The weakness of univariate analysis is that it presumes an equal and linear relationship between VI and $PaCO_2$, the two variables of Bohn's criteria. Instead, it is possible that VI and $PaCO_2$ are not linearly related and/or have different relative strengths of prediction. This explanation was substantiated by multivariate analysis. Both VI and $PaCO_2$ were found to be significant independent predictors of survivaI, but VI was a stronger predictor than $PaCO_2$ by an order of magnitude. Thus, predictors of survival selected from univariate analysis can be misleading, and multivariate analysis is a more powerful analytic tool in detecting true independent predictors of outcome.

Second, multivariate analysis provides an exponential equation for predicting outcome based upon each variable's relative predictive strength. A possible disadvantage of multivariate analysis is that it may yield an equation which is too complex or impractical for use in a clinical setting. To overcome this complexity, we have designed and implemented a simple bedside computer program formulated with our probability equation using readily available spreadsheet software. All that is needed at the bedside is to enter values for BW, 5-minute APGAR, $PaCO_2$, ventilatory rate, inspiratory time, peak inspiratory pressure (PIP), and positive end-expiratory pressure (PEEP). From these data, the VI is calculated automatically using a standard equation for mean airway pressure (MAP)(17), and it is incorporated into the probability equation along with the three other independent variables. The end result of the equation is a number from O to 1 indicating an increasing probability of survival.

We conclude that lower VI, higher BW, higher 5-minute APGAR, and lower $PaCO_2$ independently predict survival of infants with CDH at our institution. Using multivariate analysis, a reliable predictive equation has been formulated which is highly sensitive and specific. This is the first known report using multivariate analysis to generate an accurate and clinically useful predictive equation. Moreover, the methodology can be used by other institutions to determine their own prognostic equations for CDH. The prompt and accurate identification of those infants with CDH likely to fail conventional management may facilitate parental counseling and may permit earlier institution of newer salvage therapies in an attempt to improve the outcome in this highly lethal condition.

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ABBREVIATIONS

BW: Birthweight
CDH: Congenital diaphragmatic hernia
ECMO: Extracorporeal membrane oxygenation
Et: Expiratory time
FiO_2: Fraction of inspired oxygen
GA: Gestational age
It: Inspiratory time
MAP: Mean airway pressure = [(It/TRC)PIP + (Et/TRC)PEEP]
NICU: Neonatal intensive care unit
OI: Oxygenation index = (FiO_2 x MAP x 100 / PaO_2)
OR: Operating room
$PaCO_2$: Partial pressure of carbon dioxide, arterial
PaO_2: Partial pressure of oxygen, arterial
PEEP: Positive end-expiratory pressure
PIP: Peak inspiratory pressure
RR: Respiratory / ventilatory rate
SD: Standard deviation
TRC: Total time of respiratory cycle
VI; Ventilation index = (MAP x RR)

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