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Risk factors and outcomes for congenital diaphragmatic hernia in neonatal intensive care unit patients

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ABSTRACT

Objectives. Congenital diaphragmatic hernia (CDH) is one of the most common and serious congenital disorders seen in the neonatal intensive care unit (NICU) and it is associated with a high mortality. In order to determine the risk factors and outcomes of CDH, we summarized data from a 10 year period.

Methods. A retrospective study was conducted on 38 CDH patients. Clinical characteristics and risk factors were compared and non-conditional logistic regression analysis was performed to determine independent predictors for mortality.

Results. Thirty patients, from a total of 38, underwent surgery for CDH. The total survival rate in patients with CDH was 63.2% (24/38) and the overall operative mortality was 20.0% (6/30). There was a significant difference between CDH patients who survived (n=24) and those who died (n=14) in the age on admission, 5-minute Apgar score, onset of respiratory distress, cardiac malformations and presence of persistent pulmonary hypertension of newborn (PPHN). Using logistic regression analysis, the following factors independently predicted mortality: the age on admission (OR: 8.15, 95%CI: 1.43 to 46.41) and cardiac malformations (OR: 18.54, 95%CI: 1.32 to 259.62). Moreover, when we compared CDH patients who survived after surgery (n=24) with those who died (n=6), there was a significant difference in the admission age, 1-minute Apgar score, presence of PPHN, lung hypoplasia, time of stabilization prior to surgery, and highest oxygenation index after surgery.

Conclusions. Mortality was very high in CDH patients and was associated with care procedures. Risk factors for mortality in neonatal CDH were the age on admission and associated malformations.

Key words: congenital diaphragmatic hernia, risk factor, neonatal intensive care unit

Introduction

Congenital diaphragmatic hernia (CDH) is one of the most challenging and perplexing malformations, associated with a high mortality (36% based on the CDH registry). (1) As one of the most common and serious congenital disorders in the neonatal intensive care unit (NICU), CDH has been the focus of research programs from dozens of investigative teams internationally. The estimated incidence of CDH was 1 per 2,000-5,000 live births and affects approximately 1,100 infants annually in the USA, (2) CDH occurs in between 1 in 2,500 to 1 in 4,000 live births. (3,4) Many initial clinical characteristics associated with poor outcome in infants with CDH have been identified as risk factors and they include birth weight, (1) the size of the diaphragmatic defect, (5,6) a low 5-minute Apgar score, (1,7,8) prematurity, (7) an air leak (7) and the presence of other structural defects or chromosomal abnormalities. (9) Moreover, in cases of isolated CDH, pulmonary hypoplasia and associated persistent pulmonary hypertension of newborn (PPHN) are the main causes of death. (10)

The key to successful postnatal management of CDH is the use of mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) to manage the pulmonary alveolar hypoplasia and the PPHN. Current management strategies consist of preoperative stabilization and delayed repair. (11)

However, ECMO facilities are not available in most Asian countries. Various other treatment strategies were developed by different centers to improve outcome. Many centers are now using high frequency oscillatory ventilation (HFOV) as an alternative to conventional ventilation because this will reduce the amount of ventilator induced lung injury. HFOV and inhaled nitric oxide (iNO) were first made available at our center in the late 1990s, but we found the overall mortality for neonates with CDH still high, and thus we conducted this retrospective study to determine the risk factors and outcomes of CDH and to identify the independent predictors for mortality in our NICU.

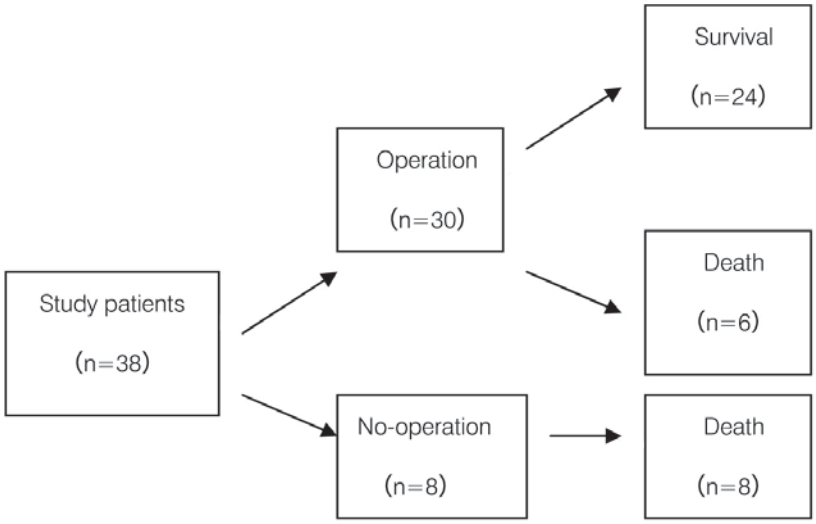
However, the relative rarity and clinical variability of CDH makes it difficult to conduct well-designed clinical studies at a single institution and to establish the most suitable treatment. The epidemiology and outcomes of CDH are well described in developed countries, (2-4) but few data exist for developing countries, particularly with respect to risk factors and outcomes such as morbidity, mortality, and hospital length of stay. Recently, Ruano R et al. (9) described the perinatal results of CDH among neonates in Brazil and Rohana J et al. (8) reported that low Apgar scores and high oxygenation index (OI) were associated with poor outcome in infants with CDH. However, there are limited data with respect to the risk factors and outcomes specific to CDH from China.

We summarized data from the last 10 years and included cases with CDH referred to a tertiary institute, to determine: 1. the survival rate of CDH, 2. the early outcomes of CDH after surgery, and 3. risk factors for mortality due to CDH. This is the first risk factor study on CDH in the NICU from a developing country, namely China.

Patients and methods

This study was conducted at the NICU of the Children's Hospital, Zhejiang University School of Medicine. This hospital is a tertiary referral center with neonatal surgery services. The medical records of 38 CDH patients, admitted to the NICU between 1 January 1999 and 31 December 2008, were reviewed retrospectively. The study population was divided into two clinical groups: survivor group and non-survivor group. A flow diagram showing the course and outcome of all CDH patients enrolled in this study is presented in figure1. The institutional research ethics committee approved this study.

Figure 1. Flow diagram showing the courses and outcomes of the 38 patients with congenital diaphragmatic hernia (CDH) enrolled in this study.



Data on patient demographics, underlying disease, procedures, and medications were collected for analysis. CDH mortality was studied using multiple regression analysis of relevant factors: gestational age (GA), birth weight, the age at admission, sex, Apgar score, onset of respiratory distress, cardiac malformations, side of diaphragmatic hernia (left or right), air leak, presence of PPHN, preoperative respiratory management (conventional mechanical ventilation, CMV or HFOV), lung hypoplasia, the size of the diaphragmatic defect, the time of stabilization prior to surgery, profiles of postoperative respiratory care (highest oxygenation index, duration of mechanical ventilation) and closed thoracic drainage.

The onset of respiratory distress was defined as the time of respiratory distress starting after delivery. Cardiac malformations were diagnosed by echocardiography. PPHN was defined as a preductal or postductal saturation difference greater than 10% and confirmed by echocardiography. The size of the diaphragmatic defect was determined by the surgeon at the time of repair. Stabilization was defined by the following criteria: (a) normal hemodynamic variables (mean blood pressure >40 mm Hg); (b) disappearance of the preductal or postductal saturation difference and signs of PPH on echocardiography without iNO; (c) a switch to CMV well tolerated with moderate values of peak inspiratory pressure (15-20 cmH2O) and adequate oxygenation achieved with $FiO2 \leqslant 0.4$. OI was calculated with the following formula: $(MAP \times FiO2 \times 100)$/ postductal PaO2, where MAP was the mean airway pressure (in cmH2O), FiO2 was the fractional inspired oxygen, and PaO2 was the partial pressure of oxygen in arterial blood (in mmHg). Duration of mechanical ventilation was defined as the days of ventilation after surgery.

The odds ratio (OR) associated with a given factor was an estimate of the risk for mortality of CDH when the factor was present relative to that when the factor

Table1. Comparison of CDH patients: survivors vs. non-survivors.

	Survivors (n=24)	Non-survivors (n=14)	*P*
Gestation weeks	39.6±1.21	39.9±2.23	0.527
Birth weight g	3272.9±291.91	3276.4±430.22	0.976
Age on admission hr	44.5(2 to 625)	12.5(2 to 336)	0.005
Sex			
Male	17	10	1.000
Female	7	4	
1-min Apgar score	8.4±1.50	7.2±2.52	0.072
5-min Apgar score	8.7±1.08	7.1±2.54	0.043
Onset of respiratory distress hr	5.5(0.5 to 300)	0.75(0.25 to 336)	0.043
Cardiac malformations			
No	23	10	0.052
Yes	1	4	
Side of diaphragmatic hernia			
Left	21	11	0.650
Right	3	3	
Air leak			
No	16	11	0.488
Yes	8	3	
PPHN			
No	24	10	0.014
Yes	0	4	
Preoperative ventilation			
No	18	6	0.081
Yes	6	8	
HFOV			
No	23	10	0.052
Yes	1	4	
Hospital length of stay d	16.5(9 to 25)	1.5(1 to 11)	<0.001

CDH, Congenital diaphragmatic hernia; d, days; HFOV, high frequency oscillatory ventilation; PPHN, persistent pulmonary hypertension of newborn.

was absent; 95% confidence intervals (95% CI) were used as a measure of the statistical precision of each odds ratio. Adjustment for other confounding variables was also made by multiple forward stepwise logistic regression analysis. Comparisons of data were made by $\chi 2$ test, Fisher exact test or Student's t test when appropriate. The Mann-Whitney U test was used for non-normally distributed variables. A p-value of 0.05 or less was considered statistically significant.

Table 2. Multinomial logistic regression analysis of risk factors for mortality in neonatal CDH.

Factors	β-coefficient	OR	95%CI	P
Age at admission	2.098	8.15	1.43 to 46.41	0.018
Cardiac malformations	2.920	18.54	1.32 to 259.62	0.030

Results

A total of 38 patients were enrolled in the study. The total survival rate of CDH was 63.2% (48/76). Eight (21.1%) of the patients did not undergo surgery, and all died. The overall operative mortality was 20.0% (6/30).

The mean hours of life that patients were admitted were 88.4 ± 157.55 hr (median age: 26.5 hr; range: 2 to 625 hr). Prenatal diagnosis was made in 10 (26.3%) patients: 9 (90.0%) of 10 infants were diagnosed before the 28th week of gestation. Mean gestational age at birth of the whole series was 39.7 ± 1.59 w (median age: 40 w; range: 34 to 43 w) and mean birth weight was 3274.2 ± 343.52g (median weight: 3300 g; range: 2200 to 3970 g). 30 patients underwent diaphragmatic repair at a mean age of 136.6 ± 166.45 hr (median age: 81 hr; range: 3 to 625 hr).

When comparison was made among survivors (n = 24) and non-survivors (n = 14), hospital length of stay was significantly longer for survivors with CDH (median day: 16.5 d; range: 9 to 25 d vs 1.5 d; 1 to 11 d; $P<0.001$). However, the side of the diaphragmatic hernia did not affect survival. (21/24, 87.5% and 11/14, 78.6%; $P=0.650$).

Univariate analysis comparing survivors and non-survivors is summarized in table 1. Comparison between survivors with CDH and non-survivors demonstrated that there was no association with gestational age, birth weight, sex, and side of the diaphragmatic hernia. Death due to CDH was associated with the following factors: the age on admission, 5-minute Apgar score, onset of respiratory distress, cardiac malformations and presence of PPHN. Following multivariate analysis, only the age on admission and cardiac malformations remained significant in the forward stepwise logistic regression model (table 2).

Because eight CDH patients did not undergo surgery and consequently died, we compared clinical characteristics of CDH patients who survived after surgery (n=24) and those who died post-operatively (n=6). There was significant difference in the admission age, 1-minute Apgar score, presence of PPHN, lung hypoplasia, time of stabilization prior to surgery, and highest OI after operation (table 3).

Discussion

We performed a retrospective cohort study of CDH in NICU patients, controlling for underlying illness to measure risk factors for mortality and outcomes of CDH. To the best of our knowledge, few previous studies of this size, describing risk factors and outcomes of CDH in NICU patients, have been published in China

According to various recent studies, the overall survive rate of CDH among patients in NICU ranges between 21% and 83%. (12-14) The apparently wide variation in mortality rates among different series was explained by "hidden mortality", because of failure to include those who remained highly unstable and died before transfer for surgery. In our study, we found a total survive rate of CDH in newborns to be 63.2% and the overall operative mortality was 20.0%. The survive rate of CDH in NICU appears, therefore, to be similar in comparison to recent studies in high-risk CDH patients, (6,13) but to be lower in comparison to some other studies in isolated CDH patients. (14,15) In our study, we compared CDH patients who survived with non-survivors, and found that survivors were associated with an excess NICU length of stay. This result suggests that CDH patients have a high mortality rate in early life. This may reflect the fact that survivors had less severe pulmonary hypoplasia and absence of lethal associated anomalies and that the combined degree of pulmonary hypoplasia and pulmonary hypertension determine the survival rate. (16,17)

Risk factors for CDH offer prognostic information about the probability of poor outcomes in CDH patients as well as help us to understand some of the mechanisms that may predispose to CDH. This may lead to development of effective prophylaxis and may allow risk stratification to target high risk patients for prevention strategies. There was significant difference in the age on admission, 5-minute Apgar score, onset of respiratory distress, cardiac malformations and presence of PPHN between CDH patients who survived and died. Using logistic regression analysis, only the age on admission and associated malformations was an independent risk factor for mortality.

The age on admission, onset of respiratory distress and presence of PPHN were high-risk factors related to the severity of clinical characteristics in CDH patients, however, only the age on admission remained significant in the forward stepwise logistic regression model and we found that the age on admission increases the risk of death in CDH 8.15 fold. The median age on admission was 44.5hr in the survivors and 12.5hr in the non-survivors. This result suggests the more severe the clinical characteristics such as respiratory distress and the earlier the onset, the higher the mortality. Cardiac malformations have been described by previous investigators as risk factors for poor

Table 3. Comparison of CDH patients with survivors and non-survivors after surgery.

	Survivors (n=24)	Non-survivors (n=6)	P
Gestation (W)	39.6±1.21	39.8±0.98	0.645
Birth weight (g)	3272.9±291.91	3436.7±340.39	0.244
Age at admission (hr)	44.5 (2 to 625)	4.5 (2 to 336)	0.031
Sex Male Female	 17 7	 4 2	1.000
1-min Apgar scores	8.4±1.50	5.3±2.58	0.001
5-min Apgar scores	8.7±1.08	6.7±2.81	0.136
Onset of respiratory distress (hr)	5.5 (0.5 to 300)	0.5 (0.25 to 336)	0.060
Cardiac malformations No Yes	 23 1	 5 1	0.366
Side of diaphragmatic hernia Left Right	 21 3	 5 1	1.000
Air leak No Yes	 16 8	 3 3	0.641
PPHN No Yes	 24 0	 3 3	0.005
Preoperative ventilation No Yes	 18 6	 2 4	0.141
HFOV No Yes	 23 1	 3 3	0.018
Lung hypoplasia No Yes	 14 10	 0 6	0.019
Size of the diaphragmatic defect (cm)	4.1±1.65	5.0±1.10	0.196
Time of stabilization prior to surgery (hr)	31.0 (2 to 116)	3.5 (1 to 65)	0.040
Duration of mechanical ventilation (hr)	46.0 (5 to 214)	37.5 (20 to 192)	0.756
Postoperative highest (OI)	2.95 (1.3 to 17.7)	30.9 (4.8 to 57)	0.001
Postoperative closed thoracic drainage Yes No	 20 4	 6 0	0.557
Hospital length of stay (d)	16.5 (9 to 25)	2 (1 to 11)	<0.001

CDH, Congenital diaphragmatic hernia; d, days; HFOV, high frequency oscillatory ventilation; PPHN, persistent pulmonary hypertension of newborn; w, weeks.

outcomes in CDH patients. (18,19) We also found an association between cardiac malformations and the risk of death which was increased 18.54 fold. Cardiac malformations are the most common anomalies associated with CDH but their etiology is still unclear. Most of the CDH-associated cardiac malformations contribute to the worsening of hemodynamic status, which is already severely compromised in patients with CDH. Furthermore, the associated cardiac malformations in CDH patients will increase the possibility that the parents may ask for surgery to be cancelled and in our study the cancellation rate was 60% (3/5).

In our data, there were 8 non-survivors of CDH who did not undergo surgery, and thus we realized that it was necessary to analyze the clinical characteristics between the CDH patients who survived surgery and those who did not. We found that there was a significant difference in the admission age, 1-minute Apgar score, presence of PPHN, lung hypoplasia, time of stabilization prior to surgery, and highest OI after operation between the survivors and non-survivors post-operatively.

Low 1-minute and 5-minute Apgar scores have been said to be major independent predictors of total mortality rate. (7,18) Our results also suggest that the non-survivor group of CDH patients had lower Apgar scores compared to the survivors. Apgar scores are a strong early marker of lung function, cardiovascular adaptation, and response to resuscitation in infants with CDH. The lower the Apgar scores, the more severe the asphyxia, and thus early prenatal diagnosis and elective intubation following birth and resuscitation (avoiding barotraumas to the hypoplastic lung) should be led by a highly skilled neonatology team. Bag-mask ventilation is contraindicated as this increases gastric and intestinal distension worsening mediastinal shift and respiratory distress. (20)

The size of the diaphragmatic defect has been described by previous investigators to be a risk factor for poor outcome of CDH. (5,6) It has been shown to correlate well with mortality, as well as morbidity in liveborn infants with CDH. Defect size is likely to be a marker for the degree of pulmonary hypoplasia. Animal models suggest that a large defect is associated with much smaller lungs. It is possible to modify the degree of lung hypoplasia in the lamb model by the size of the defect created. (21) Our results did not confirm that defect size is an independent predictor for mortality, but we found that the degree of lung hypoplasia and PPHN correlated well with survival as well as morbidity. Lung hypoplasia is the major determinant of survival (22) and the degree of pulmonary hypoplasia may also correlate with the severity of pulmonary hypertension. Our data have also shown that the CDH patients who died in our study had a median highest OI of 30.9. A higher OI predicts a high mortality and has been widely used as criteria for ECMO. Moreover, the higher OI also reflects more severe PPHN in comparison to survivors.

The operation for CDH is no longer an emergency procedure. It is increasingly recognized that stabilization of labile physiology is paramount and delayed repair is now frequently employed in most pediatric surgical centers. (10,23) Preoperative stabilization aims to optimize respiratory function and allow full clinical and cardiac assessment. The median time of stabilization prior to surgery in survivors of CDH was 31 hr and longer than that for non-survivors (3.5hr). Our findings also showed that emergency surgery did not influence the outcome of CDH.

Furthermore, HFOV has been advocated as the ventilation modality of choice in the management of CDH and HFOV combined with use of inhaled nitric oxide to optimize ventilator strategies and control of pulmonary hypertension in infants with CDH. (24) However, in our study, we did not find any benefit of HFOV in CDH patients whether they underwent surgery or not. The reason for this finding was that we used HFOV as a rescue mode and these CDH patients were supported with HFOV when conventional ventilation was ineffective. Thus, when used as the initial mode of therapy, HFOV may be a more effective mode of ventilation support than conventional ventilation.

In summary, we performed a retrospective cohort study to determine survive rates, risk factors, and outcomes of CDH in a NICU. We found a relatively high mortality rate of CDH and identified independent predictors for mortality of CDH, including the age on admission and cardiac malformations. Studies of interventions to decrease the mortality of CDH are needed in NICU patients. However, the sample size and the small number of events per group, as well as retrospective study design, substantially limit our conclusions. In order to confirm these conclusions, a large and prospective randomized controlled trial is mandatory and studies of interventions such as pre- and postoperative respiratory management; rescue ventilator strategies and the effect of timing of surgery might be achievable.

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