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ORIGINAL ARTICLE

Congenital Diaphragmatic Hernia – Analysis of Possible Prognostic Factors Predicting the Outcome

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Summary
Introduction. Congenital diaphragmatic hernia (CDH) - a relatively rare developmental defect due to a failure of pleuroperitoneal canal closure. The size of the defect between abdominal and thoracic cavities may be variable and it may have a significant impact on the clinical manifestation and prognosis. In this study we set out additional factors to determine if they affect the outcome of the newborns with CDH.
Aim of the Study. To investigate and analyze the influence of selected postnatal prognostic factors for predicting the outcome. The primary outcome measure was survival.
Material and methods. The present study is retrospective including the data collection and analysis of medical documentation of patients born with CDH and treated in the Children's Clinical University hospital between 2012 and 2017. The selected prognostic factors included antenatal diagnostics, Apgar score at 1' and 5', need for an early intubation (≤ 3 h after birth), initial blood gases in first 24 h of life, time interval between delivery and surgical therapy, the stomach and liver presence in the thorax, additional congenital abnormalities, a type and duration of invasive ventilatory support. Outcome parameters were compared between survivors (S) and non-survivors (NS).
Results. 19 patients (pts) were identified - 14 S and 5 NS. Total mortality rate - 26%. 17/19 had left-sided, 2/19 – right-sided CDH. 17/19 pregnancies were monitored, prenatal diagnosis was made in 8 pts – 3 of them NS. The mean Apgar score at 1' in S group was 5,5, NS - 5,0. At 5' - 6,7 and 5,6. Need for an early intubation was 64% for S, 100% - NS. Initial blood gases in S (n=11) and NS (n=5) showed the mean pH value of 7,18 and 7,02. Mean PaCO2 - 62,92 and 77,42 mm Hg. 16/19 underwent the operation. 2 pts died before and 3 after surgical therapy. The average time interval between delivery and surgical therapy in S group was 31,6 hours, NS - 73,7 h. The intrathoracic liver was observed in 3 pts, 2 of them died, the intrathoracic stomach – 2, none of them died. 14/16 pts had a primary surgical repair (PR), 2/16 - Silo closure before total repair. 6 pts had additional congenital defects - 2/14 S and 4/5 NS. 5 out of all 6 had cardiac anomalies. The average required conventional ventilation time in S (n=9) was 175,9 h, NS (n=3) - 25,7 h. High-frequency oscillatory ventilation for S (n=6) was applied for 255 h, NS (n=5) 157,3 h.
The results showed statistically significant relationship between the outcome and additional abnormalities ($r(17)=.623$, $p=0.017$) and time interval between delivery and surgical therapy ($r(11)=.768$, $p=.014$).
Conclusions. The possible predictors of outcome were additional abnormalities and time interval between delivery and surgical therapy.
Key words: congenital diaphragmatic hernia, prognostic factors, outcome

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is relatively rare and severe developmental defect due to a failure of pleuroperitoneal canal closure, causing abnormal lung development and function (1, 12). The size of the defect between the abdominal and thoracic cavities and degree of pulmonary hypoplasia may be variable and it may have a significant impact on clinical manifestation and prognosis (12, 16).
The incidence of CDH varies between 1 in 2500 – 5000 live births, but it is believed to be higher due to accompanying lethal anomalies (11, 14, 16). Despite improved antenatal imaging, the sensitivity of prenatal ultrasound screening for CDH reaches 50 - 85% (7, 8, 10, 13).
Antenatal diagnostics has an advantage of possibility of planning childbirth at hospital with an appropriate intensive care and surgical treatment of the defect (12, 14). Despite advances in perinatal and neonatal intensive care, the mortality remains high (13). Death is mainly due to associated congenital abnormalities, pulmonary hypoplasia and subsequent persistent pulmonary hypertension as serious consequences of CDH (1, 13, 14).
Many prenatal factors have been proposed to explain the prognosis of the high mortality of CDH. In this study we set out additional postnatal factors to determine if and how they affect the outcome in neonates with congenital diaphragmatic hernia.

AIM OF THE STUDY

The aim of the study was to investigate and analyze the influence of selected postnatal prognostic factors for predicting the outcome. The primary outcome measure was survival.

MATERIAL AND METHODS

The present study is retrospective with the data

collection and analysis of medical documentation of patients born with congenital diaphragmatic hernia and treated in the Children's Clinical University hospital between January, 2012 and December, 2017.
The selected prognostic factors included antenatal diagnostics, additional congenital abnormalities, Apgar score at the 1st and 5th minute, need for an early intubation (≤ 3 h after birth), initial blood gases in the first 24 h of life, time interval between delivery and surgical therapy, the stomach and liver presence in the thorax, a type and duration of invasive ventilatory support. The outcome parameters were compared between survivors and non-survivors.
The data were summarized and analyzed with MS Excel and IBM SPSS Statistics 22. The relationship between the outcome and potential prognostic factors was investigated by using Chi-squared test and Fisher's exact test for categorical variables and by using T-test for continuous variables. P value of .05 or less was considered to indicate statistical significance.
The study was approved by the Ethics Committees of the Children's Clinical University Hospital and Riga Stradins University.

RESULTS

During the study period, 19 live-born patients (pts) with congenital diaphragmatic hernia were identified. The data were grouped and analyzed according to survivors (S) and non-survivors (NS). The total amount of S was 14, NS - 5. The age distribution of these patients is shown in Figure 1. The total mortality rate was 26%.
17/19 pregnancies were monitored and prenatal diagnosis was made in 8 pts – 5 of which were survivors and 3 – non-survivors. 17/19 patients had the isolated left-sided CDH and 2/19 – the isolated right-sided CDH. Both the right–sided CDH's were diagnosed antenatally, 1 survived and the other one did not. All prenatally diagnosed cases were made between 26 - 36 weeks of gestational age. The prematurity rate was 2/19 and both of them died.
Table 1 shows the results of selected prognostic factors.
The mean Apgar score at 1st minute in S group was 5,5 (range: 3 - 8), in NS group - 5,0 (r.: 2 - 6). At the 5th minute - 6,7 (r.: 5 - 9) and 5,6 (r.: 3 - 7). Need for an early intubation up to 3 hours after birth was in 64% of cases in S group, 100% for NS. Initial blood gases in the first 24 h of life in S (n=11) and NS (n=5) showed the mean pH value of 7,18 (r.: 6,90 - 7,37) and 7,02 (r.: 6,73 - 7,28). Mean $PaCO_2$ - 62,92 mm Hg (r.: 41 - 102) and 77,42 mm Hg (r.: 45 - 111,6).
16/19 patients underwent the operation(s), 14/16 pts had a primary surgical repair (PR), 2/16 - Silo closure before the total repair. 3 pts died after the surgical therapy – 2/3 after PR and 1/3 after Silo without getting a total closure. 3/19 patients did not get any surgical therapy - 2 neonates died before it and 1 patient presented beyond the neonatal period did not get a surgery in the period of the study.
The average time interval between delivery and surgical therapy in S (excluding 2 cases presented beyond the neonatal period) was 31,6 hours (r.: 11,1 – 59,3), NS – 73,7 h (r.: 46,6 – 100,9). The intrathoracic liver was observed in 3 neonates and 2 of them died, the intrathoracic stomach was in 2 cases, none of them died. 6 pts had additional congenital defects - 2/14 S and 4/5 NS. 5 of them had cardiac anomalies. The most common postoperative complications were pneumothorax (n=5), chylothorax (n=4), sepsis (n=3), hydrothorax (n=2), pneumonia (n=2) and there was a case of ileus and intestinal malrotation. 10/19 CDH's had developed a pulmonary hypoplasia, information was not available for 4 pts.
4/5 non-survivors had a pulmonary hypoplasia.
The average required conventional mechanical ventilation time in S (n=9) was 175,9 h (r.: 51,9 – 287,3), in NS (n=3) 25,7 h (r.: 2,5 – 39,8). High - frequency oscillatory ventilation for S (n=6) was applied for 255 h (r.: 90 – 455,5), NS (n=5) - 157,3 h (r.: 3,28 – 492,5). Children's Clinical University hospital does not have an extracorporeal membrane oxygenation (ECMO), also nitric oxide (NO) treatment was not used to stabilize patients before or after surgical therapy in any of cases.
The results showed statistically significant relationship between the outcome and additional abnormalities ($r(17)=.623$, $p=.017$) and time interval between delivery and surgical therapy ($r(11)=.768$, $p=.014$).

DISCUSSION

Congenital diaphragmatic hernia is a rare developmental defect, which can and should be detected antenatally and corrected after birth. Herniation of visceral organs during fetal development complicates and impairs lung development leading to a pulmonary hypoplasia and persistent pulmonary hypertension (1, 10, 12). Abnormal lung development is a primary cause of neonatal morbidity and mortality (1, 7), and it increases mortality rates up to 30-50% (16, 17). In our study 10 patients out of 19 had developed a pulmonary hypoplasia and 4 of these cases (21%) were lethal. The total mortality rate has been reported between 20 – 60 % in worldwide (8). In our six year study it was 26%.
Prenatal diagnosis of congenital diaphragmatic hernia can improve the outcome by planning delivery at a high-volume tertiary perinatal centre or close to the pediatric surgical unit (13). The survival among those infants with an effective management has improved over the years (1, 8, 12, 13), in isolated CDH up to 85% (1). In our study antenatal diagnosis was made only in 8 cases (42%) without any data about prenatal prognostic factors. This may be explained by the subjective interpretation of fetal sonography. Diagnosis was more frequent among survivors compared to the non-survivors and that could be explained by an accurate and mobile afterbirth management.
Up to 80 - 85% of CDH cases are isolated left – sided Bochdalek hernias (1, 12), - 17/19 cases (89%) as in our study. It could be related to earlier closure of the right pleuroperitoneal canal. Larger defects are more often recognized at birth because of difficulty to establish breathing (8, 12). Smaller defects become apparent

during the first day of life as air swallowing increases the volume of displaced organs in the thorax and produces respiratory distress (1, 12).

There was no statistically significant relationship between the outcome and need for an early intubation and initial blood gases in survivor and non-survivor groups. However, the intubation was used in all the non-survivor cases. Infants and children may not present with less-severe CDH for months, even for years (8, 10, 14). When they become symptomatic, presentation may include respiratory infection or gastrointestinal symptoms (10, 14). Also in our study 2 patients presented with symptoms of an acute viral illness after the neonatal period.

Herniation of the left lobe of the liver into the thorax suggests a large structural defect and more impact on the organs in the chest cavity, resulting in worse pulmonary hypoplasia and hypertension. It is a poor prognostic factor, herniation of the liver increases mortality up to 65% (7). During the study period, the intrathoracic liver was observed in 3 neonates, 2 of them died.

CDH has been observed with associated congenital malformations in up to 40 % cases (6, 10, 16), sometimes as a component of syndromes, also in about 10% cases with some chromosomal anomalies (8, 12). Malformations predominantly involve the cardiovascular, genitourinary and central nervous systems (12). In the six year period of our study, 6 patients did have additional congenital abnormalities, 5 of them were single or multiple cardiac anomalies – the atrial septal defect, ventricular septal defect, mitral atresia, mitral insufficiency, aortic atresia, coarctation of the aorta, hypoplastic left heart syndrome, patent ductus arteriosus. The results showed statistically significant relationship between the outcome and additional malformations – 4 out of 6 patients were non-survivors. Respectively, CDH, together with any other congenital abnormality, worsened the outcome of these patients, which also coincides with the results of other studies (8, 16).

In this study, 84% of the patients were treated surgically, 68% of them survived, a primary closure was performed in 14 out of 16 patients. In other studies, a primary closure was performed in 60 – 70 % of cases (14). The analysis of results showed a statistically significant relationship between the outcome and the average time interval between delivery and surgical therapy – in the non-survivor group it was more than twice longer than in the survivor one – 73,7 hours and that can be explained by their haemodynamic instability. The optimal timing for the repair of CDH is at 24 – 36 – 48 hours after birth. There is no need for urgent surgical operation of the defect (7, 14). It should be done after stabilizing the cardiorespiratory functions in the setting of a transitional circulation (7). If delay till the operation becomes longer than optimal timing, we can predict a worse outcome for the patient.

Predicting survival in patients born with CDH is a challenge. Finding accurate predictive factors would help with adequate counseling of parents (7, 16), expecting prenatal/postnatal events and the risk of possible outcome and long-term morbidities (13). In this study we have found two possible postnatal prognostic factors for predicting the outcome, but these findings are very limited because the study included only 19 patients for that period. This is too small number of patients for making definitive conclusions and there are no similar studies on postnatal factors to compare with. It is needed to continue this study in a prospective way.

CONCLUSIONS

The development of lungs remains as a critical aspect of having an influence on the prognosis of newborns with congenital diaphragmatic hernia. In this study the possible predictors of outcome were additional abnormalities and interval between delivery and surgical therapy. Despite progress in medicine, CDH patients still remain a serious therapeutic problem, and we suggest that an improvement in the prenatal diagnosis of these patients is needed.

Conflict of interest: None

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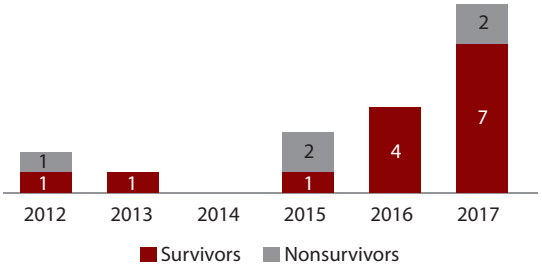

Fig. 1. Total number of survivors and non-survivors per year

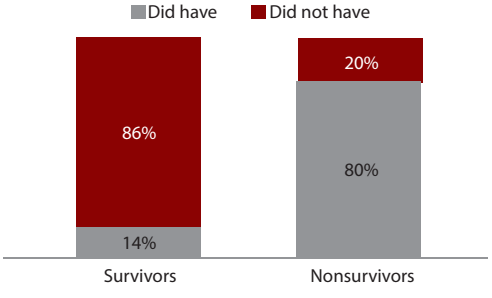

Fig. 2. Additional congenital abnormalities in survivor and non-survivor groups

Table 1. Results of selected prognostic factors, presented as the total patient count, as average numbers or percents

Selected prognostic factors	Survivors n=14	Non-survivors n=5
Antenatal diagnostics (n=8)	n=5	n=3
The average Apgar at 1'	5.5	5.0
The average Apgar at 5'	6.7	5.6
Need for an early intubation	64%	100%
Initial blood gases: Mean pH Mean $PaCO_2$	 7.18 62.92	 7.02 77.42
The average time interval between delivery and surgery	31,6 h (n=12)	73,7 h (n=3)
The stomach presence in the thorax	n=2	n=0
The liver presence in the thorax	n=1	n=2
Additional congenital abnormalities	n=2	n=4
Type of invasive ventilatory support: CMV HFOV	 n=9 n=6	 n=3 n=5
The average time of required invasive ventilatory support: CMV HFOV	 175,9 h 255 h	 25,7 h 157, 3 h

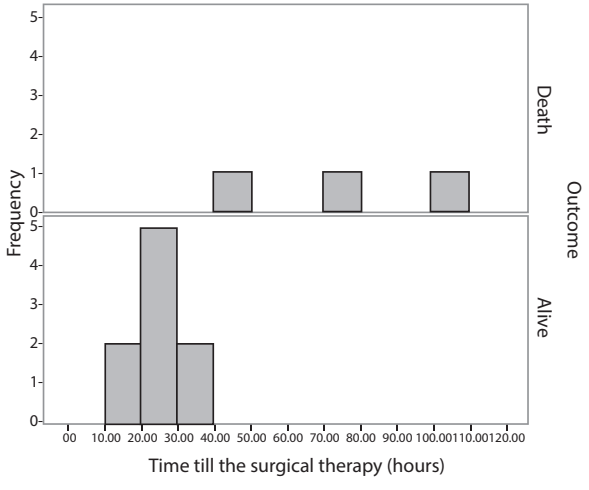

Fig. 3. Time interval between delivery and surgical therapy in survivor and non-survivor groups