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Early Clinical Outcomes of Congenital Diaphragmatic Hernia and Prognosis: A Retrospective Multicenter Study

Konjenital Diyafram Hernisinde Erken Klinik Sonuçlar ve Prognoz: Retrospektif Çok Merkezli Bir Çalışma

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Abstract

Objective: Investigation of possible prognostic factors affecting survival in the congenital diaphragmatic hernia.

Method: We included all congenital diaphragmatic hernia-diagnosed patients treated in neonatal intensive care units of two centers between 2016 and 2020. We recorded antenatal and birth histories, anthropometric measurements, and clinical features of the hernia. We assessed visceral herniation to the hemithorax, pneumothorax, severely decreased fetal lung volume (<15%), the need for emergency intervention due to pneumothorax in the operating/delivery room, and pulmonary hypertension effects on the survival status. We recorded the data retrospectively.

Results: We enrolled 31 patients in the study. The clinical conditions associated with high mortality were pulmonary hypertension (p=0.006), pneumothorax (p=0.009), severely decreased fetal lung volume (<15%) (p<0.001), hepatic (p=0.024) and gastric (p=0.029) herniations to the thorax. In a binomial regression model, PTX and hypoplastic lung were the most significant confounders (R^2_{McF}: 0.858, p<0.001). 19.4% of patients needed emergency intervention in the operating/delivery room. There was no statistically significant difference between deceased and alive patients in terms of postnatal day of surgery.

Conclusion: Operation time did not statistically affect mortality. Pneumothorax, severely decreased fetal lung volume, hepatic herniation, gastric herniation, and pulmonary hypertension statistically declined survival. PTX and hypoplastic lung were the most significant confounders.

Keywords: Congenital diaphragmatic hernia, pneumothorax, pulmonary hypertension

Öz

Amaç: Konjenital diyafram hernisinde sağkalımı etkileyen olası prognostik faktörlerin belirlenmesidir.

Yöntem: İki yenidoğan yoğun bakım ünitesinde 2016-2020 yılları arasında tedavi edilen tüm konjenital diyafram hernisi tanılı hastalar retrospektif olarak çalışmaya dahil edildi. Antenatal ve doğum öyküleri, antropometrik ölçümler, fıtığın klinik özellikleri, hemitoraksa visseral herniasyon, çok düşük fetal akciğer volümü (<%15) ve ameliyat/doğum odasında pnömotoraks nedeniyle acil müdahale ihtiyacı, pnömotoraks ve pulmoner hipertansiyon gelişimi durumu ve bunların sağkalım durumu üzerindeki etkileri kaydedildi.

Bulgular: Çalışmaya 31 hasta alındı. Pulmoner hipertansiyon (p=0,006), pnömotoraks (p=0,009), çok düşük fetal akciğer volümü (p<0,001), hemitoraksa karaciğer (p=0,024) ve mide (p=0,029) herniasyonunun mortaliteyi istatistiksel olarak artırdığı saptandı. Binomial regresyon modelinde, PTX ve hipoplastik akciğer en önemli karıştırıcı faktörlerdi (R^2_{McF}: 0;858, p<0,001). Hastaların %19,4'ünde ameliyathanede/doğum odasında acil müdahale ihtiyacı oldu. Ölen ve yaşayan hastalar arasında postnatal ameliyat olduğu gün açısından istatistiksel olarak anlamlı bir fark saptanmadı.

Sonuç: Postnatal ameliyat günü mortaliteyi etkilemedi. Pnömotoraks, çok düşük fetal akciğer volümü, pulmoner hipertansiyon, hemitoraksa mide ve karaciğer herniasyonunun sağkalımı azalttığı görüldü. PTX ve hipoplastik akciğer en önemli karıştırıcı faktörlerdi.

Anahtar kelimeler: Konjenital diyafram hernisi, pnömotoraks, pulmoner hipertansiyon

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Introduction

Congenital diaphragmatic hernia is a structural birth anomaly due to defective closure of the pleuroperitoneal folds between 4-10 weeks after fertilization, which causes severe neonatal morbidity and mortality (1), with a rate of 2.5 in ten thousand live births (2). It is left-sided in 80-85% of cases, right-sided in 10-15%, and rarely bilateral (1). Clinicians can detect this deformity by ultrasonography imaging in the antenatal period (3).

The etiology has not yet been fully clarified but is thought to be multifactorial (4). While it occurs as an isolated defect in 50-70% of the patients, 30-50% of cases have gene defects or substantial anomalies in cardiovascular (ventricular septal defect, atrial septal defect, tetralogy of Fallot), central nervous (neural tube defects, hydrocephalus), and musculoskeletal systems (polydactyly, syndactyly, small extremities) (4).

Since herniation occurs during a critical period of lung development, the lungs affect more prominent in the clinical manifestation of congenital diaphragmatic hernia (5); therefore, fetal lung volume is one of the most important survival factors (3). High mortality rates occur if the total lung capacity of the fetus is 25% of normal or less. The prognosis deteriorates if there is a liver herniation association, and patients may develop chronic lung disease (3). Lung compression may cause pulmonary hypoplasia by affecting pulmonary arterial and bronchial development. Decreased arterial branching causes muscular hyperplasia of the pulmonary arterial tree, resulting in pulmonary hypertension (5).

Despite advances in antenatal diagnosis and treatment of congenital diaphragmatic hernia, this birth anomaly challenges pediatricians, neonatologists, and pediatric surgeons. The mortality rate is 30% in centers that can perform extracorporeal membrane oxygenation (ECMO); however, most patients die due to pulmonary hypertension and its complications (6).

This study aimed to present the prognosis and accompanying clinical outcomes of patients with a congenital diaphragmatic hernia in two tertiary neonatal intensive care units.

Material and Methods

We included all patients diagnosed with a congenital diaphragmatic hernia and treated in the neonatal intensive care units of Marmara University and Güngören Hospital between 2016 and 2020, retrospectively. We recorded whether there was a pregnancy-termination recommendation in the prenatal follow-ups of the mothers, birth history, anthropometric measurements (height, weight, head circumference), hemithorax of the diaphragmatic hernia (right/left), liver/stomach/spleen herniation into the hemithorax, lung hypoplasia (in antenatal period) and the need for emergency intervention due to pneumothorax in the operating/delivery room, the development of pneumothorax and pulmonary hypertension in neonatal intensive care unit (NICU) and the survival status. This study aimed to present the prognosis and accompanying clinical outcomes of patients with congenital diaphragmatic hernia.

The ethical committee approval was obtained from Marmara University Ethical Committee (file number: 09.2022.24).

Statistical Analysis

Descriptive data were given as mean ± standard deviation and median (interquartile range) following the distribution pattern. Student's t-test, Welch's t-test, and Mann-Whitney U test were used according to distribution and variance types to compare two groups with continuous variables. The chi-square and Fisher's Exact tests were used to compare groups with categorical variables. In addition, we used a binomial regression test to detect possible confounding factors. The Jamovi 2.3.18 statistical package program was used for statistical calculations. $p<0.05$ was considered of statistical significance.

Results

A total of 31 patients (58.1% male) were eligible for the study. Median birth weight, length, and head circumference of the total patients were 38 (35.7-39.6) weeks, 3020 (2500-3240) grams, and 35 (33.5-36) centimeters, and mean birth length was 49.3±4.45. 83.9% (n=26) patients were born via cesarean section and 16.1% (n=5) with spontaneous vaginal delivery.

The diaphragmatic defect was on the left in 74.2% (n=26) and on the right side in 25.8% (n=5) patients. There was no statistically significant difference in terms of gender (p=0.16, chi-square test), birth weight (p=0.993, Mann-Whitney U test), birth length (p=0.395, Welch's t-test), birth week (p=0.445, Mann-Whitney U test), defect side (p=0.165, chi-square test) and delivery type (p=0.686) between groups who survived and deceased. Ultrasonographic imaging detected liver herniation to the thorax in 38.7%

(n=12) patients, which significantly increased (p=0.024, chi-square test) mortality [mortality rate of 91.7% (n=11) versus 52.6% (n=10) in the liver herniation and non-liver herniation groups, respectively]. There was no statistically significant difference in mortality in spleen herniation (p=0.69, chi-square test). Ultrasonographic imaging detected gastric herniation in 48.4% (n=15) patients, which significantly increased (p=0.029, chi-square test) mortality (mortality rate of 86.7% (n=13) versus 50% (n=8) in gastric herniation and non-gastric herniation groups, respectively).

Clinicians needed emergent tube thoracostomy intervention in 19.4% of the patients (n=6) due to pneumothorax in the first minutes of life in the delivery or operating room. There was no statistically significant difference in survival (p=0.634, Fisher's Exact test) between these patients and those who did not need intervention (mortality rate of 23.8% and 10% for the deceased and survived group, respectively).

During the treatment of the patients, 58.1% (n=18) developed a pneumothorax [48.4% (n=15) on the left side, 58.1% (n=18) on the right side, and 38.7% (n=12) bilateral]. Pneumothorax statistically affected (p=0.006, Fisher's Exact test) mortality (mortality rate of 88.9% (n=16) versus 38.5% (n=5) in pneumothorax and non-pneumothorax groups, respectively).

A total of 87.1% (n=27) patients developed pulmonary hypertension, which significantly increased (p=0.007, Fisher's Exact test) mortality [mortality rate of 77.8% (n=213) versus 0% in pulmonary hypertension and non-pulmonary hypertension groups, respectively].

A total of 45.2% (n=14) of the patients needed more than 30 mm H_2O mean airway pressure in "high frequency ossilation mode" to maintain >85% oxygen saturation while allowing permissive hypercapnia (partial pressure of carbon dioxide 45-65 mmHg with an arterial pH of >7.25). All these patients had below 15% of fetal lung volume. Severely decreased fetal lung volume statistically affected (p<0.001, Fisher's Exact test) mortality [mortality rate of 100% (n=14) and 41.2% (n=7) in severely decreased fetal lung volume and non-severely decreased fetal lung volume, respectively].

In a binomial regression model where collinearity assumption was met, we included PHT, PTX, hypoplastic lung, and liver and stomach herniations as they reached statistical significance and resulted in that PTX (odds ratio: 12.8) and hypoplastic lung (odds ratio: 40) were the most significant confounders in survival (R^2_{McF}: 0.858, X^2: 33.4, p<0.001) (Table 1).

The follow-up gynecologists had recommended pregnancy termination in 45.2% (n=14) of the patients due to associated anomalies incompatible with life; however, the families stated that they had refused medical abortion. None of these patients could survive until the operation as they died within two days. Seventeen patients were born with defects that might be compatible with life, and 58.8% (n=10) of them survived. The anthropometric measurements and gender of the patients with survival status comparison are in Table 2.

Table 1. Likelihood ratio tests of the binomial logistic regression model

Confounder	X^2	p-value
PHT	0	1
PTX	6.65	0.01
Hypoplastic lung	9.44	0.002
Hepatic herniation into hemithorax	2.09	0.148
Gastric herniation into hemithorax	2.09	0.148

PHT: Pulmonary hypertension, PTX: Pneumothorax

Table 2. Anthropometric measurements and gender of the operated patients comparing survival status

	Exitus (n=7)	Survived (n=10)	p-value
Birth week (weeks)	38.8±2.28	38.2±1.94	0.588*
Birth weight (gram)	3100±530	2940±290	0.449*
Birth length (cm)	49.6±4.5	48.5±2.0	0.57**
Head circumference (cm)	34.9±2.0	34.5±1.1	0.634*
Gender	85.7% (n=6) male 14.3% (n=1) female	40% (n=4) male 60% (n=6) female	0.134***

Data presented as mean+/-standard deviation and % (n), *Student's t-test, **Welch's t-test, ***Fisher's Exact test

Pneumothorax history significantly decreased survival in postoperative patients (p<0.05). The clinical problems encountered by the operated patients are shown in Table 3.

A total of 54.8% (n=17) of all patients could be stabilized for the operation. There was no statistically significant difference between the deceased and survived groups (3.4+/-1.4 versus 4.5+/-3, respectively p=0.34, Welch's t-test). In the operated cases, the survival rate was 58.8% (n=10).

Discussion

Congenital diaphragmatic hernia is more common in boys than girls, and the male gender is a defined risk factor (7). There was a male predominance at a 58.1% rate in our study. However, there was no statistically significant difference between the sexes in terms of mortality.

In the literature, it is reported that herniation is in the left hemithorax in most patients (80-85%) (1,4,8). We observed left hemithorax diaphragmatic hernia at a rate of 74.2% of our patients. The right hemithorax diaphragmatic hernia rate is between 10 and 15% in the literature (1,4,8). Thus, this rate was 25.8% in our study.

In infants with a congenital diaphragmatic hernia, visceral organs (including the stomach, liver, and spleen) may enter the thoracic cavity and displace the heart contralaterally, resulting in compression, growth restriction, and dysfunction of both lungs (1). As a result, intrapleural herniation causes pulmonary hypoplasia (3). A study reported that herniation of the stomach and liver results in a poor prognosis in antenatal ultrasonographic imaging, but liver herniation affects more to the severity of clinical outcome (1). Hepatic herniation to the hemithorax results in a very severe clinical course; even 80% of the patients with liver herniation need ECMO (4). Therefore, the position of the liver is used to predict prognosis in the antenatal period and indicates a poor prognosis (4,9). Hepatic herniation to hemithorax was statistically significantly associated with mortality (p=0.024) in our patient group. Spleen herniation did not statistically affect mortality (p=0.69). But gastric herniation statistically increased mortality (p=0.029).

Pneumothorax is one of the factors affecting mortality. The pneumothorax rate is 14% (10) and 10.5% (11) in studies. However, the patients had isolated congenital diaphragmatic hernias. Another study reported that all babies who developed pneumothorax died (12). The pneumothorax rate was 52.9% in our study group and also statistically increased mortality in our study (p=0.009).

In patients diagnosed with a congenital diaphragmatic hernia, urgent intervention may be required in the delivery/operating room in the first minutes of life due to pneumothorax. The intervention needs for pneumothorax in the delivery/operating room was 19.4% in our patient series. This ratio shows the necessity of preparation for tube thoracostomy in the delivery/operating room, and a portable X-ray device should be ready for imaging.

Decreased pulmonary vascularization, increased pulmonary artery pressure, and pulmonary vascular tonus leads to pulmonary hypertension in congenital diaphragmatic hernia-diagnosed patients. Pulmonary hypertension is one of the leading causes of mortality (1), though ECMO therapy increases the chance of survival (13). A study reported that pulmonary hypertension occurs in 30% to 50% of patients diagnosed with a congenital

Table 3. Clinical problems in operated patients and comparison of survival status

	Operated patients (n=17)	Exitus (n=7)	Survived (n=10)	p-value
Hemithorax % (n)	Left 82.4% (n=14)	35.7% (n=5)	64.3% (n=9)	0.537
	Right 17.6% (n=3)	66.7% (n=2)	33.3% (n=1)	
Splenic herniation % (n)	35.2% (n=6)	33.3% (n=2)	66.7% (n=4)	1
Gastric herniation % (n)	29.4% (n=5)	60% (n=3)	40% (n=2)	0.593
Hepatic herniation % (n)	23.5% (n=4)	75% (n=3)	25% (n=1)	0.25
PTX % (n)	52.9% (n=9)	77.8% (n=7)	22.2% (n=2)	0.002
Left PTX % (n)	35.2% (n=6)	83.3% (n=5)	16.7% (n=1)	0.035
Right PTX % (n)	52.9% (n=9)	77.8% (n=7)	22.2% (n=2)	0.002
Bilateral PTX % (n)	29.4% (n=5)	83.3% (n=5)	16.7% (n=1)	0.035
PTX in the operating/delivery room % (n)	17.6% (n=3)	66.7 (n=2)	33.3 (n=1)	0.537
PHT % (n)	76.5% (n=13)	53.8% (n=7)	46.2% (n=6)	0.103

Fisher's Exact test. PHT: Pulmonary hypertension, PTX: Pneumothorax

diaphragmatic hernia (14). The pulmonary hypertension rate was 87.1% in our study was as statistically significantly affected by mortality (p=0.007) in parallel with the literature.

Pulmonary hypoplasia is also one of the crucial factors affecting mortality (1). Determination of fetal lung volume in prenatal ultrasonographic imaging is critical in predicting prognosis in the antenatal period (9). In our study, all patients with severely decreased fetal lung volume (<15%) died. These patients had not undergone in-utero intervention and had been recommended termination in the antenatal period. Fetal lung volume lower than 15% increases mortality by 88% (3,4,9). For these reasons, interventions that increase the lung capacity in the antenatal period, such as fetal tracheal occlusion, are beneficial (15). In our study, mortality was statistically significantly higher in patients with lower than <15% fetal lung volume (p<0.001), and none of the patients had undergone fetal intervention.

The surgical procedure is one of the essential and indispensable treatment steps. Although there is no published randomized controlled trial, it is crucial to stabilize the patient (16) and particularly wait for the resolution of pulmonary hypertension before surgery (17). Our patients had undergone an operation after stabilization and resolution of pulmonary hypertension. There was no statistically significant difference between the deceased and surviving patients in terms of operation day.

A study in Turkey reported an overall survival rate of 32.5% and 61% in operated newborns (18). Another study reported 50% overall survival rate (19), where the survival rate in our study was 32.3% in all patients and 58.8% in the operated newborns. Prenatal interventions are crucial for increasing successful surgery (18).

Study Limitations

The sample size was small. ECMO was not obtainable during the study dates. We could not reach intra-operational details.

Conclusion

Pregnancy termination-indicated cases affected mortality rates in this case series. Hepatic and gastric herniation to the hemithorax, pulmonary hypertension, pneumothorax, and antenatal severely decreased fetal lung volume (<15%) affected survival. Operation time did not statistically affect mortality.

As patients tend to develop a pneumothorax, clinicians should anticipate an emergency intervention with tube thoracoscopy in the delivery/operating room, where a portable X-ray device is underhand.

Ethics

Ethics Committee Approval: The ethical committee approval was obtained from Marmara University Ethical Committee (file number: 09.2022.24).

Informed Consent: Since the study was retrospective and was written with a file scan, patient consent information was not sent.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: İ.K., A.Y., Z.A.Ü., S.G.K., M.T.K., Design: İ.K., A.Y., Z.A.Ü., S.G.K., M.T.K., Data Collection or Processing: İ.K., A.Y., S.G.K., Analysis or Interpretation: İ.K., A.Y., M.T.K., Drafting Manuscript: İ.K., A.Y., Z.A.Ü., S.G.K., M.T.K., Critical Revisation of Manuscript: İ.K., A.Y., Z.A.Ü., Final Approval and Accountability: İ.K., A.Y., Z.A.Ü., S.G.K., M.T.K., Technical or Material Support: İ.K., A.Y., Z.A.Ü., S.G.K., M.T.K., Supervision: A.Y., Z.A.Ü., Writing: İ.K., A.Y., Z.A.Ü., S.G.K., M.T.K.

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