

# Long term outcomes of early and late diagnosed congenital diaphragmatic hernia and pulmonary asymmetry

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## Abstract

**Aim:** It is to determine problems in long-term follow-up of patients operated in infancy and newborn period for congenital diaphragmatic hernia in our clinic before one year of age and to evaluate significance of perioperative findings on long-term results.

**Material and Methods:** Among patients, 16 patient above 8 years of age with outpatient control in the past year were investigated retrospectively. Patients were grouped regarding operation age as newborn and infancy period. Preoperative predictive data, early and late postoperative findings, diagnostic studies, disorders were evaluated.

**Results:** Male-to-female ratio was 3/1, right-to-left sided hernia was 1/15. Average age was 13.1(9-17). Average follow-up was 13years (8-17 years). Thirteen patients were diagnosed in newborn period, 3 in infancy. On follow-up, 85% of newborns and 33% of infants were found to have at least one disorder. Scoliosis presented in 6, asthma in 5, gastroesophageal reflux (GER) in 4, pectus excavatum in 4, undescended testis in 3, failure to thrive in 2 patients. All the musculoskeletal system deformities were diagnosed in only newborn period patients. Four cases (25%) were uneventful. Spirometry revealed obstructive dysfunction in 1, restrictive in 2 patients. CT showed increased aeration and pulmonary asymmetry.

**Conclusions:** Among evaluated patients, 75% showing disorders requiring treatment or observation indicates the need for follow-up until adolescence.

**Keywords:** Diaphragmatic Hernia; Long Term; Lung Volumetry; Pulmonary Asymmetry; Modified Ventilatory Index.

## INTRODUCTION

Congenital diaphragmatic hernia (CDH) is distinctive compared to other diaphragmatic disorders. Bilateral pulmonary hypoplasia and resultant pulmonary hypertension are main factors contributing to mortality and morbidity in CDH. With the improvement of neonatal intensive care conditions, accumulated experience in the treatment of pulmonary hypertension, new developments in ventilator technology and popularization of ECMO, mortality has reduced step by step. However, improved survival of patients and adverse effects of treatments gradually increased morbidity. Therefore, management of medical problems emerging in the long-term even after successful CDH surgery and require multidisciplinary approach.

In this study, we aimed to determine late term disorders in patients who were followed in our department after CDH operation, to compare features of patients who were

operated in neonatal and infantile periods in terms of morbidity factors, and to identify perioperative factors that predict long term morbidity. We also wanted to analyze the increased asymmetry at lung volumes obtained from the three-dimensional images in the cross-sectional imaging of the patients and its relationship with the clinical findings.

## MATERIAL and METHODS

We evaluated the hospital records of patients operated between 1990 and 2008. Patients younger than 8 years old were excluded in the study to increase the reliability of spirometry tests. Patients who were younger than 1 years and who attended follow-up visits after discharge were included in study.

Patients were grouped based on operation time: neonatal period vs infantile period. Then, patients who were operated in the neonatal period was subgrouped according to Modified Ventilatory Index (MVI= Peak inspiratory

**Received:** 17.11.2018 **Accepted:** 02.12.2018 **Available online:** 05.12.2018

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pressure \*partial pressure of carbon dioxide \*ventilation frequency /1000 ) values: High-risk group (>80) vs low-moderate risk group (<80).

Perioperative findings, predictive parameters and new problems that were diagnosed during follow-up retrieved from patient files. Diagnostic investigations performed during follow-up were reevaluated. All images of patients, who underwent computerized tomographic investigation, were recorded to Osirix Lite 8.0.2 (Pixmeo SARL, Switzerland) program in DICOM format. In axial plane, parenchymal regions (Broncho-vascular hilar structures were excluded) were defined as region of interest (ROI) by forming closed polygons with an 8mm interslice distance for each lung. Regions between marked sections were completed automatically, three dimensional (3-D) demonstrative images were formed and volumes (cm<sup>3</sup>) were calculated. These data were compared with themselves and spirometric measurements.

Statistical analyses were performed with SPSS 15.0 for Windows. Descriptive statistics included "n" and percentage for categorical variables and mean and standard deviation for continuous variables. Due to parametric test conditions were not satisfied, Mann-Whitney U test was used additionally to compare two independent groups for continuous variables. Fisher exact test was performed to compare percentages in two independent groups. If conditions were not satisfied, Monte Carlo simulation was used. Statistical significance was defined as p<0,05.

## RESULTS

Among 84 newborn patients, who were treated in our clinic between 1990 and 2008, 44 patients died in the intensive care unit. Forty patients (48%) survived. Sixteen patients who attended follow-up visits after discharge were included in the study. The mean age of patients included in the study was 13.1 years (9-17 years). There were 12 male and 4 female patients. Male/female ratio was 3/1. One patient had right CDH and the others had left CDH (right/left 1/15).

Thirteen patients were diagnosed during the neonatal period, while three patients were diagnosed in infancy. Two patients had prenatal diagnosis. In 11 of 13 patients (including those with prenatal diagnosis), the symptoms emerged in the postnatal 1st hour. Two patients were diagnosed incidentally in infantile period. The other patient was presented with tension gastrothorax.

Seven patients (43%) had associated anomaly. The most common associated anomaly was malrotation (n:5). Cardiovascular system anomaly was detected in two patients. Other congenital anomalies included renal hypoplasia, incomplete duplex system, undescended testis, and Chiari malformation. None of the patients had vertebra or extremity anomaly at the time of diagnosis. Although associated anomalies were more frequent in patients operated during the neonatal period, this difference was not statistically significant.

Mean MVI value was 49.1 (20-106) in neonatal patients receiving preoperative mechanical ventilation support. Two patients had an MVI over 80 and these patients were evaluated in the high-risk group. MVI was below 40 in 6 of remaining 7 patients. Patients who didn't require preoperative mechanical ventilation and patients with an MVI<80 constituted the low-moderate risk group.

The duration between birth and operation in patients operated in the neonatal period were 65 hours (23-144 hours). Neither ECMO nor NO used in patients. Primary repair with laparotomy was performed in all patients. A transdiaphragmatic drain was placed through a laparotomy incision. Hernia sac was present in 6 patients. Stomach was herniated in 11 of 15 patients with left CDH. Stomach and left lobe of liver were herniated in 4 patients.

The average time to extubation was 6.9 days (2-24 days) in 10 patients who were operated in the neonatal period and remained on the mechanical ventilator after the operation. The average hospitalization time after surgery was 20 days (5-77 days). The average hospitalization time in neonatal high-risk group was 53 days. Similarly, the average length of hospitalization in patients who had gastroesophageal reflux (GER) after surgery was 39 days, which was higher than average.

### Late Morbidity after Discharge

Thirty-seven pathological diagnosis, which requires long-term follow-up and treatment, were detected in 12 patients (75%). Eleven of these patients were operated during the neonatal period. The most common long-term diseases were scoliosis (n:6), asthma (n:5), GER (n:4), and pectus excavatum (n:4).

Diseases that require long-term follow up were detected in 85% of patients operated in neonatal period and 33% of patients operated in infantile period. The difference wasn't statistically significant (Table 1).

**Table 1. Long term disorders for each group and statistical significance**

Long term disorders	Newborn group N:13 (%)	Infancy group N:3 (%)	P
(+)	11 (84.6)	1 (33.3)	0.136
(-)	2 (15.4)	2 (66.7)	-

Stomach or liver herniation and presence of hernia sac didn't predict long-term problems.

The cardiac problem was detected in 2 patients in preoperative period and these patients were followed postoperatively. One of these patients underwent surgery with sternotomy (13%).

Gastrointestinal system related long-term pathology was detected in 8 patients. The most common pathology was GER and stomach was herniated into thorax in all patients (25%). Two patients had cholelithiasis. Midgut volvulus occurred in a patient, which was not corrected in neonatal period, after seven years from repair, and Ladd procedure was employed. Intestinal obstructions were emerged on three patients due to adhesions.

Table 2. Prognostic Features and Long Term Disorders

PERIODS	PATIENTS AND PROGNOSTIC FEATURES										LONG TERM DISORDERS						
	RISK GROUPS CASES	Del. time (week)	Birth weight (gram)	Onset time of symp.	Postop mec. vent. (hour)	MVI	Hernia sac	Sto. up	Liv. up	Postop disch. time (day)	FTT	CVS	GIS	RS	GUS	CNS	MSS
HIGH	17, M, LCDH	38	3510	10 min	192	92	-	+	+	77	-	-	GER, Hernia rec. Cholelithiasis	-	Und. testis	Chiari, Epilepsy, MMR	Scoliosis (65°), Extremity cont.
RISK	12, M, LCDH	40	3410	1 ho	312	106	-	+	-	30	+	-	-	-	-	-	Scoliosis (25°), Pectus exc. (28mm), Extremity contr.
	17, M, LCDH	40	3200	1 ho	48	54	-	-	-	9	-	-	Reactive airway disease	-	-	-	Pectus exc. (12mm)
N	17, F, LCDH	40	3400	1 ho	-	-	-	+	-	9	-	-	-	-	-	-	-
E	14, M, LCDH	36	3190	Asymp.	-	-	+	+	-	8	-	-	Cholelithiasis	-	-	-	Scoliosis (12°)
W	13, F, RCDH	33	1860	10 min	576	28	-	-	+	48	-	-	Hernia rec.	-	-	-	Scoliosis (13°)
B	13, M, LCDH	40	3950	1 ho	-	-	-	-	-	11	-	-	-	Und. testis	-	-	-
O																	
R																	
LOW	13, M, LCDH	40	3100	1 ho	96	37	+	+	-	25	-	-	GER	Reactive airway disease	-	-	Pectus exc. (13mm)
AND																	
MODERATE	13, M, LCDH	40	3250	1 ho	48	36	-	+	-	25	-	-	GER, Intestinal obstruction	Reactive airway disease	Renal calcula	-	Pectus exc. (15mm)
RISK	13, M, LCDH	40	3900	1 ho	96	39	+	+	+	9	-	-	MVP; PHT	Reactive airway disease	-	-	Scoliosis (12°)
	12, M, LCDH	40	3190	1 ho	48	-	-	-	-	14	-	-	Wandering spleen	-	Renal calcula	-	-
	12, M, LCDH	40	3350	24 ho	120	20	-	+	-	14	-	-	-	Reactive airway disease	-	-	Scoliosis (12°)
	9, M, LCDH	38	3750	10 min	120	30	+	+	+	12	-	-	Midgut volvulus	Reactive airway disease	-	-	-
	17, F, LCDH	40	2700	11 mo	-	-	+	-	-	5	-	-	-	-	-	-	-
INFANCY	19, M, LCDH	40	2950	11 mo	-	-	+	+	-	29	-	-	GER, Intestinal obstruction	-	Und. testis	-	-
	9, F, LCDH	40	4500	4 mo	-	-	-	+	-	5	-	-	PDA, ASD, PHT	-	-	-	-

(Del: Delivery, Symp-Symptom, Mec:Mecanical, Vent:Ventilation, MVI:Modified ventilatory index, Sto:Stomach, Liv:Liver, Postop:Postoperative, Disch: Discharge, FTT: Failure to thrive, CVS: Cardiovascular system, GIS:Gastrointestinal system, RS: Respiratuar system, GUS: Genitourinary system, CNS: Central nervous system, MSS: Musculoskeletal system, LCDH: Left CDH, RCDH: Right CDH, MMR:Motor and mental retardation, Cont:Contracture, Exc:Excavatum, Asymp: Asymptomatic, Rec:Recurrence, Und:Undescended, MVP:Mitral valve prolapse, PHT:Pulmonary hypertension, PDA: Patent ductus arteriosus, ASD: Atrial septal defect)

The most common musculoskeletal problems were scoliosis (n:6) and pectus excavatum (n:4). Half of all the patients had problems related to musculoskeletal system. Cobb angle was 65 degrees and 25 degrees in two patients in high-risk neonatal group. However, lower extremity contractures related to muscle and tendon strain was observed only in these patients. Both chest deformities and scoliosis were milder in other patients compared to these 2 patients (Table 2). In addition, another remarkable point was that musculoskeletal problems were observed only in patients operated in neonatal period and none of the patients operated in infantile period had these problems. This difference was not statistically significant (Table 3).

Musculoskeletal deformity	Newborn group N:13 (%)	Infancy group N:3 (%)	p
(+)	8 (61.5)	0 (-)	0.200
(-)	5 (38.5)	3 (100)	-

Seven patients developed reactive airway disease requiring medical treatment and pneumonia attacks in postoperative period. Two patients had GER and underwent fundoplication. Except for these patients, whose symptoms reduced after operation, reactive airway problem requiring treatment continued in five patients (31%). Symptoms relieved after 2 years of age in one patient and in adolescence in 4 patients and routine medical treatment was stopped.

#### Respiratory System: Long Term Consequences of CDH

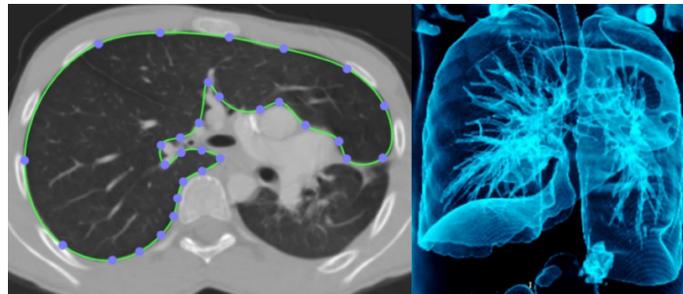
Fourteen patients underwent spirometry during follow-up visits. Two patients had restrictive and 1 patient had mild obstructive functional disorders. One of the patients with restrictive disorder had thorax deformity and scoliosis; the other patient had a history of sternotomy. Patient with obstructive pattern had reactive airway disease. On the other hand, spirometry tests were normal of 6 patients who had asthma or pectus excavatum or scoliosis.

Nine patients underwent CT examination due to long-term problems (Reactive airway disease, scoliosis, chest deformity). None of the images showed pulmonary vascular anomaly. Agenesis, obstruction or branching anomaly was not detected in bronchial structures including segmental levels. Five patients with reactive airway disease had lobar or totally increased aeration pattern.

The volumes of both lungs were calculated by forming 3D volumetric images of each lung (Figure 1). Mean age of the patients in this group was 13.2 (9-17 years) and all of the 9 patients were male with left CDH. Average right lung volume was 1.67 Lt (985-3178 ml) and average left lung volume was 1.26 Lt (507-2636 ml). Increased asymmetry between the lungs remained in adolescence period. This asymmetry was more pronounced in two patients.

Two patients had renal calculi (13%), three boys had

undescended testis (25%) and one patient had a wandering spleen.



**Figure 1.** Determination of cross-sectional pulmonary area in axial plane with "Region of Interest (ROI)" (Patient-9: 13 year old male, left CDH. Right upper lobe was crossed through to mediastinum and grew up to left hemithorax. Right lung volume:2288ml, left lung volume:754ml)

Weight and length percentiles of two patients were less than 3rd percentile in their respective age group. Body mass indexes of these patients were less than 5th percentile. These patients who were followed for growth retardation since infantile period were those in high-risk group in the neonatal period.

Hernia recurrence was observed in two patients were operated in neonatal period.

## DISCUSSION

Reduced mortality and increasing long-term problems have made the postoperative follow-up of CDH patients even more important in recent years. Accordingly, follow-up protocols for these patients have been established in recent years and it has been stated that these patients should be followed up to adolescence (1,2). The approach of our clinic is to follow-up the patients with CDH until early adulthood. It is thought that investigating the long-term follow-up of treatment-requiring diseases in CDH patients will help us to determine modifiable problems in this patient group.

The frequency of associated anomalies varies between 10-50%. Malrotation was the most common anomaly in our patients. In our study, it was found that associated anomalies were more common in the patients diagnosed in neonatal period, but no statistically significant relation was found.

MVI is a value obtained by combining blood gas parameters and ventilator parameters. MVI is associated with prognosis (3). Patients who were followed up with postductal blood gasses and patients with an MVI > 80 were found to have postoperative hospitalization 20 days longer than overall average. Except this, extremity contractures and severe growth retardation were seen only in these patients. In addition, scoliosis in these patients was more serious than other patients. All these findings are statistically insignificant.

Although some long-term problems in CDH resolve spontaneously over time or with medical treatment, some

of them are difficult to detect in younger ages and develop in older ages. GER, pulmonary hypertension, respiratory and neurological problems tend to decline with advancing age. On the other hand, musculoskeletal system problems such as chest deformities and scoliosis may be expected to develop or persist in older ages. At least one disease requiring surgery or medical treatment and follow-up was found in all patients except 2 patients who were operated during the neonatal period and 2 patients who were operated during the infantile period (75%). Although the diseases requiring long-term follow-up were seen more frequently in neonatal period patients than late diagnosed and operated patients, this was not statistically significant. The most common problem in CDH in relation to gastrointestinal tract was GER. Fundoplication was required for an average of 20% of these patients who mostly require medical treatment following early postoperative period (4). Most important risk factors are defect size and patch repair (4,5). In our study, GER was detected in 25% of patients. It was found that stomach was herniated in all of the patients with GER, but this was not statistically significant. However, when postoperative hospitalization time of these patients was evaluated, it was found that they were hospitalized longer (39 days) in accordance with literature. This was statistically significant.

The frequency of musculoskeletal system disorders increases with age. Although pathophysiology can't be clearly elucidated, some authors suggest tense diaphragm repair, some suggest intervening with thoracotomy, and others suggest small residual intrathoracic space secondary to pulmonary hypoplasia in affected site [6]. Their average frequency is 16-48% (6,7). Predictively; it has been reported that these deformities are associated with defect diameter, patch and muscle flap repair, symptom onset time, postoperative ventilation duration, and ECMO use (6). Scoliosis and/or pectus excavatum were detected in 50% of patients in our study. Scoliosis was detected in 6 patients (38%) and pectus excavatum in 4 patients (25%). All of these deformities were seen in patients who were operated in neonatal period. Considering the fact that pulmonary hypoplasia is also mild in late-onset patients, musculoskeletal deformities may be related to the degree of pulmonary hypoplasia and concomitant intrathoracic low volume rather than strain or diaphragm repair with a patch. Comparisons of perioperative findings in late-onset patients with neonatal period patients in a larger patient series may show preventable musculoskeletal problems.

Growth retardation is seen in 22-58% of patients during the early postoperative period and at discharge, but with a tendency to regress with advancing age (2,8). The underlying causes are thought to be increased catabolic stress, oral intake incompatibility, and increased energy expenditure due to GER and ongoing respiratory burden (7). Predictive factors were associated with defect size, birth weight and height, patch repair, long hospital stay, home oxygen therapy, longer ventilation support duration, ECMO and GER status in various publications (7,8). In our study, there was a sustained growth retardation in the

adolescence period in 2 patients in the high-risk group of neonatal period (13%). In accordance with the literature, the length of hospitalization in these patients was longer than average.

Respiratory system problems such as chronic lung diseases, bronchopulmonary dysplasia, reactive airway diseases, recurrent pneumonia attacks are seen in 22-54% of the patients in different age groups (2,9). Hypoplastic lungs and bronchial hyperreactivity, pulmonary hypertension, damage caused by mechanical ventilation, and accompanying GER play a role in etiology.

Spirometry, which is recommended clinically and used frequently, is not specific. But, abnormal spirometry is reported in 28-52% of patients without complaints (10,11). Patients have been shown to have obstructive, restrictive, or combined functional impairment, and it is believed that this phenomenon is also associated with airway disease and breast deformities secondary to CDH (9,10,11). When compared to the normal population; FEV1 is lower, FVC is lower, flow rates are slower than normal, and FEV1/FVC tend to be lower (7,11,12). These are the most commonly detected spirometry findings in CDH patients in agreement with reactive airway disease (9). Accompanying chest problems are significantly more common in patients with abnormal spirometry findings (9). In our study, reactive airway disease was detected in 5 patients (31%). It was seen that the complaints of one of these patients reduced after 2 years of age. Apart from this, 4 patients who received inhaled corticosteroids and bronchodilator treatments had their complaints alleviated with advancing age. In these patients, GER was not detected in any of the upper GIS passage graphs. On the spirometric examinations, pathological spirometry was observed in 3 patients (21%); restrictive findings in two patients and obstructive findings in one patient. The patient with the obstructive pattern was one of the 5 asthmatic patients in the study. One of the patients with spirometric findings compatible with restriction had pectus excavatum and scoliosis. In the other patient, although there were no chest deformity or scoliosis, there was a median sternotomy story due to the cardiac anomaly. In contrast to previous literature, spirometry was normal in most of the patients with either reactive airway disease or chest deformity or scoliosis (80%). This finding suggests that spirometry may not be indicative of underlying and comorbid diseases in patients without complaint.

In this study we used a simple and effective method for measuring the lung volumes. This method is popular in measuring liver volumetry in adults. However, this method can simply be adapted for measuring lung volumes in late childhood. In contrast to the literature, total lung volume in the volumetric measurements obtained on CT images of patients did not correlate with spirometric FVC measurements in our study (12). In a study published in 2011, Chen F et al. showed and formulated this correlation in non-CDH patients ( $FVC = 606.4 + 0.67 \times TLV$ ) (12). When the findings of asymmetry in the volumetric lung

measurements were taken into account, the average ratio of lung volumes in the nine male patients with left CDH was 1360/1015 (right/left). An autopsy study of patients who died in the neonatal period revealed that the mean volume of both lungs was below normal and the ipsilateral lung was smaller than the half of the contralateral lung (13). Autopsy studies on healthy adult populations show that the right lung is larger than the left lung in both genders (14). In studies conducted by Molina et al. in 2012 and 2015, the ratio of right to left lung masses was as 445/395 for men and 340/299 for women (14). This ratio, which can be calculated as approximately 1.12/1 in males in a normal population, was found to be 1.34/1 in CDH patients in our study. The ratio of right lung to left lung was higher than 1.2/1 in 6 of 9 patients (Figure 1). These findings indicate that ipsilateral severe hypoplasia in the neonatal period recovers at a great rate in the forthcoming period, but it may not completely improve.

### Limitations

Limitations of this study: the number of patients in the infantile group was insufficient for statistical comparison; MVI did not have high predictive value for long-term problems in high-risk patients; lack of patients with severe morbidity (such as O<sub>2</sub> therapy need, tracheostomy, ventilator use at home) in the study group since the number of high-risk patients was low at the time of study, although their frequency is currently getting higher.

### CONCLUSION

As a result, the detection of long-term acute and chronic diseases in 75% of the patients suggests that follow-up should continue until adolescence period and detailed investigations should be conducted. One statistically significant finding was seen that stomach was among the herniated organs in patients with GER; none of the cases without stomach herniation had any clinical or radiological finding suggesting GER; the length of hospitalization in patients with GER was longer than average.

In addition, there are some critical points that were remarkable but not statistically significant due to limitations: The incidence of congenital anomalies was higher in patients diagnosed in the neonatal period compared to those diagnosed in the infantile period. When we exclude congenital coexisting diseases in late onset or incidentally diagnosed patients, it has been found that long-term problems are less frequent; especially musculoskeletal system problems were only seen in patients operated in the neonatal period. Three-dimensional demographic images and lung volume measurements obtained from cross-sectional studies of patients showed that increased pulmonary asymmetry continues until adolescence. Spirometry test findings were normal in most patients.

The pulmonary asymmetry data, findings about skeletal deformities only seen in patients who were operated during the neonatal period, the test data to question the

necessity of spirometry in the follow-up of these patients are observations which deserve to be investigated in larger patient series and suggest that significant results can be obtained.

*Competing interests: The authors declare that they have no competing interest.*

*Financial Disclosure: There are no financial supports*

*Ethical approval: This study was approved by the Ethics Committee of the Istanbul University Cerrahpasa Medical Faculty (Date:07/15/2016 Number: 257231).*

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