Original Article

Pulmonary outcomes of congenital diaphragmatic hernia patients based on defect size (CDH Study Group Stage)

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Background: Congenital diaphragmatic hernia (CDH) is associated with significant pulmonary morbidity. Previous investigation has shown that postnatal inpatient morbidity is linked to diaphragmatic defect size. The objective of this study was to evaluate long-term pulmonary outcomes by CDH study group defect size.

Methods: A retrospective analysis was conducted for CDH patients (n=133) managed in a neonatal intensive care unit (NICU) at a single children's hospital within an adult hospital system and subsequently followed up at a comprehensive multidisciplinary CDH clinic (n=102) from January 2012 to April 2022. CDH patients were stratified according to Congenital Diaphragmatic Hernia Study Group (CDHSG) Stage, and then categorized as low-risk (LR), defect size A and B, or high-risk (HR), defect size C and D. Inpatient data, including the presence of pulmonary hypertension, extracorporeal life support (ECLS) utilization, and mechanical ventilation days, were collected. Post-discharge data including the prevalence of asthma, pulmonary hypertension, emergency department visits, the total number of hospitalizations, and average rehospitalization days were collected. Frequentist analysis was used.

Results: The outcomes for 133 NICU patients were analyzed (HR: n=54, LR: n=79). During NICU stay, the prevalence of pulmonary hypertension [HR: 16/54 (30%) *vs.* LR: 9/79 (12%), P=0.009], ECLS utilization [HR: 19/54 (35%) *vs.* LR: 4/79 (5%), P<0.001], and the average number of mechanical ventilation days [HR: 17 days (IQR: 12–27) *vs.* LR: 5 days (IQR: 2–9), P<0.001] were significantly higher in the HR CDH group. Post NICU discharge, the prevalence of asthma [HR: 20/54 (37%), *vs.* LR: 17/79 (22%), P=0.050)] and the total days of rehospitalization [HR: 9 (IQR: 2–27) *vs.* LR: 4 (IQR: 1–8), P=0.035] were significantly higher in HR group. Of the patients seen in the comprehensive multidisciplinary CDH clinic, obstructive lung disease measured by impulse oscillometry was increased in the HR CDH population compared to the reference group [median R5Hz was 12.95 kPa/(L/s) in CDH *vs.* 9.8 kPa/(L/s) (P=0.010)].

Conclusions: HR CDHSG Stage is associated with worse inpatient and long-term pulmonary outcomes.

Keywords: Congenital diaphragmatic hernia (CDH); Congenital Diaphragmatic Hernia Study Group Staging; pulmonary outcomes; asthma; impulse oscillometry

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Introduction

Congenital diaphragmatic hernia (CDH) affects 1 in 2,000–3,000 newborns annually (1). CDH is a cascade of events beginning with an early embryologic insult involving a diaphragmatic defect allowing subsequent migration of abdominal organs into the thoracic cavity. This dual hit, including fundamental pulmonary vasculopathy, alongside mechanical compression of the lungs, results in pulmonary hypoplasia and abnormal pulmonary vascular growth, with ensuing cardiopulmonary sequelae (2,3). Survivorship has steadily increased, largely a consequence of advances in pre and postnatal medical care, including delayed surgical repair, refinements in extracorporeal life support (ECLS) (4), and progression toward standardized treatment protocols (5-10). Despite treatment advances, it is well-recognized that almost all CDH patients have some degree of pulmonary compromise and suffer from disease-specific long-term morbidity (11-13).

About 30–50% of CDH survivors subsequently experience long-term pulmonary complications as a result of overarching pulmonary hypoplasia, including pulmonary hypertension, chronic lung disease, exacerbated susceptibility to respiratory tract infections, ventilator-associated lung injury, and ventilatory impairments, with an increased rate of readmissions post neonatal intensive care unit (NICU) discharge (14).

Highlight box

Key findings

- Large CDH defects (CDHSG C and D defects) are associated with worse long-term pulmonary outcomes.
- Impulse oscillometry can be useful tool for early detection of airway disease in CDH patients.

What is known and what is new?

- Previous studies have shown that postnatal morbidity is linked to diaphragmatic defect size.
- However, this study improves understanding of the substantial burden of pulmonary morbidity which persists following NICU discharge and introduces the value of impulse oscillometry in CDH patients.

What is the implication, and what should change now?

- These observations could be an essential component to identify at risk CDH groups who might benefit from a nuanced and comprehensive pulmonary management approach, by developing screening tools, protocolized management, and guidance for families regarding CDH-related long-term morbidities in accordance with defect size.

Given the heterogenous clinical challenges, pulmonary function testing is the central component of disease characterization and management. Pulmonary function abnormalities are reported in 28–52% of patients, with obstructive ventilatory impairment being the predominant finding (15,16). Early diagnosis of pulmonary function abnormalities is instrumental to prevent long-term remodeling of the airways and improve prognosis. Impulse oscillometry (IOS), is a type of forced oscillation technique delivering a spectrum of frequencies on the airway during tidal breathing to determine lung function, and compared with spirometry, this test does not require the patient's special cooperation, is effort independent, simple, noninvasive, repeatable, and provides comprehensive respiratory physiological parameters. IOS measurements can be used to identify and monitor the disease progression of asthma in at-risk younger patients (mainly over 3 years) (17).

Multiple studies have sought indicators and tools that can assist healthcare providers to predict post-discharge morbidity for CDH survivors (14). Several patient characteristics including prenatal diagnosis and major cardiac or chromosomal anomalies predict the types and frequency of morbidity that affect these infants in the postnatal inpatient setting (18-20); however, the staging system developed by the Congenital Diaphragmatic Hernia Study Group (CDHSG) based on diaphragmatic defect size is the strongest predictor of many outcomes, including morbidity at discharge (13).

In this study, defect size A and B are categorized as low-risk (LR) and defect size C and D as high-risk (HR) to compare pulmonary outcomes (*Figure 1*). We hypothesized that HR CDH survivors (C/D), as opposed to LR (A/B), experience more significant adverse pulmonary morbidities after discharge. Given the variable severity that characterizes this disease, these observations could be essential to identifying groups who might benefit from a comprehensive pulmonary management approach. In addition, the introduction of IOS testing to clinical practice could contribute to a better understanding of postnatal lung growth and the prevention of chronic lung morbidity. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-14/rc).

Methods

Study subjects

Patients with Bochdalek CDH (n=133) were seen between

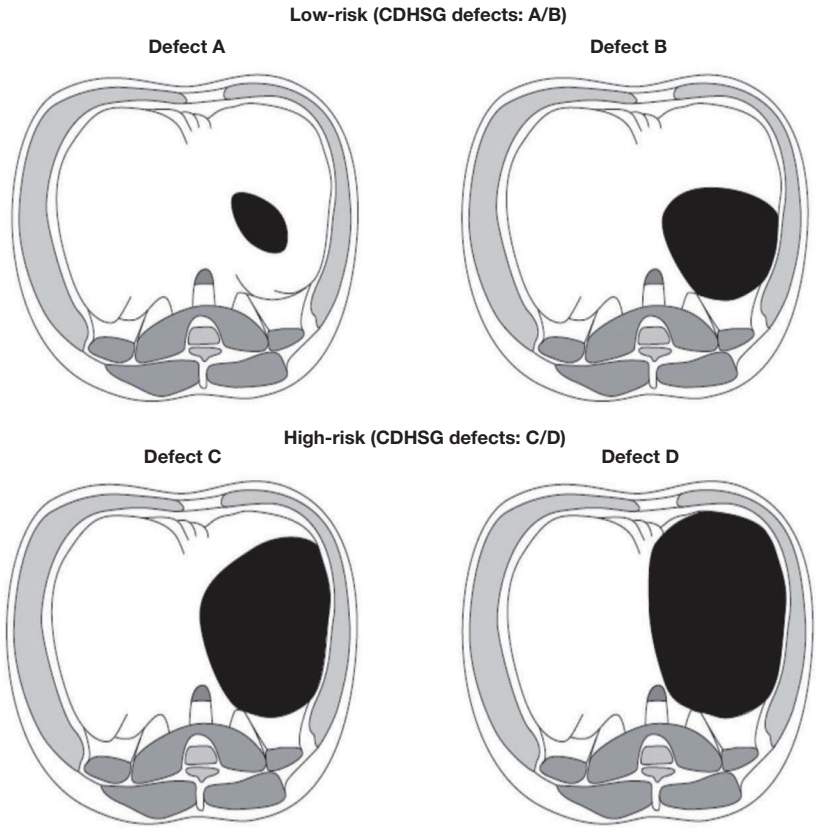

Figure 1 CDH defect size categorization into low- and high-risk CDH. Low-risk defects are CDHSG defects (A) and (B). High-risk defects are CDHSG defects (C) and (D). Defects are shown as a left CDH would be viewed from the peritoneal cavity. CDH, congenital diaphragmatic hernia; CDHSG, Congenital Diaphragmatic Hernia Study Group.

January 2012 and April 2022 at a single children's hospital within an adult hospital system, with a subset seen at the comprehensive multidisciplinary CDH clinic (n=102), were enrolled. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of The University of Texas Health Science Center at Houston of Institutional Review Board approval (No. HCS-MS-18-1036) and individual consent for this retrospective analysis was waived. CDH survivors with other primary chronic pulmonary conditions, such as cystic fibrosis, primary ciliary dyskinesia, and immunodeficiency disorders with pulmonary manifestations were excluded.

Study participants were categorized based on hernia defect size as established by the CDHSG (21). Defects are categorized on an increasing gradient scale with "A" defects being the smallest, and "D" defects being the largest. "A" defect is the smallest, usually confined "intramuscular," with >90% of the hemidiaphragm present; this defect involves <10% of the circumference of the chest wall. "B" defect is 50–75% of the hemidiaphragm present; this defect involves <50% of the chest wall. "C" defect is <50% of the hemidiaphragm present; this defect involves >50% of the chest wall. "D" defect is the largest (previously known as "agenesis") with the complete or near complete absence of the diaphragm and <10% hemidiaphragm present; this defect involves >90% of the chest wall. Surgically, it is an absent posterior rim beyond the spine, an absent posterior-lateral rim, and an anterior/anterior-medial rim which is minuscule.

The categorization into LR (A/B) and HR (C/D) is appropriate based on the alignment of outcomes among these groups in previous publications (13,21). Pulmonary outcomes included: the prevalence of asthma, pulmonary hypertension, the need for ECLS, the number of days of mechanical ventilation during the NICU stay, oxygen

at discharge, spirometry, IOS, and perfusion scans to determine compromise on the ipsilateral side.

NICU course and follow-up

The retrospective analysis included patients treated at a single children's hospital within an adult hospital system NICU (n=133) and patients who were followed in our comprehensive multidisciplinary CDH clinic (n=102/133). Data on demographics, birth weight, gestational age, prenatal diagnosis, intrathoracic liver, observed/expected lung head circumference ratio (o/e LHR), type of repair, pulmonary hypertension at the time of discharge, the need for ECLS, need for oxygen at discharge, and a number of mechanical ventilation days were recorded. Pulmonary hypertension was based on echocardiogram findings of indirect signs of pulmonary hypertension such as increased tricuspid jet, elevated right ventricular systolic pressure, and/or interventricular septal flattening. In addition, for the purpose of this study, patients with evidence of pulmonary hypertension on echocardiogram and warranting treatment for pulmonary hypertension such as O_2, sildenafil, and/or bosentan were included. CDH patients surviving NICU discharge were followed longitudinally to determine prospective events of asthma prevalence, all-cause rehospitalization (counting each rehospitalization as one event), emergency room visits (ER) (counting each visit as one event), and the total number of days of rehospitalizations. In addition, spirometry and IOS were performed on some of the patients followed at our comprehensive multidisciplinary CDH clinic.

Comprehensive multidisciplinary CDH clinic

A subset of 102 patients (77%) surviving hospital discharge whose families decided to continue care at the dedicated comprehensive multidisciplinary CDH clinic was followed longitudinally. All CDH patients have the opportunity for follow-up in the clinic, though patients managed prior to the establishment of the clinic did not have access. The comprehensive multidisciplinary CDH clinic was established in 2016 and central components include pediatricians, pediatric surgeons, pediatric pulmonologists, a dietician, a social worker, and a pediatric neuropsychologist. Comprehensive pulmonary management was delivered through the enhanced medical home with open access to manage acute respiratory conditions to the clinic, Monday through Friday. There is 24/7 direct access via phone to primary care physicians, who can schedule same/next day visits or call ER as needed on nights and weekends. In addition, this medical home has a low patient-provider ratio (≤1:100) and has weekly meetings to discuss all ER visits, hospital, and intensive care unit admissions. The follow-up visits are scheduled based on the CDH subtype (LR: A/B *vs.* HR: C/D). LR CDH patients were seen 2–4 weeks post-discharge, then every 3 months until 12 months of age, and annually thereafter. In contrast, HR CDH patients were followed more closely as follows: 2–4 weeks post-discharge, monthly visits until 3 months of age, every 3 months until 2 years of age, every 6 months until 4 years of age, and then annually. Patients were assessed for risk of pulmonary complications at each visit.

Asthma

Asthma diagnosis was determined post-NICU discharge based on the pulmonologist's clinical assessment, considering clinical history, physical examination findings, and pulmonary function tests (IOS and spirometry) for patients seen at the comprehensive multidisciplinary CDH clinic (22-26). Spirometry and IOS were performed to determine the prevalence of asthma in the subset of patients who were ≥3 years of age for IOS, and ≥5 years of age for spirometry and/or were able to perform the maneuvers. For patients not seen in our comprehensive multidisciplinary CDH clinic, diagnosis of asthma was based on the validated asthma screening questionnaire (22,23,26) consisting of seven questions in English or Spanish, administered by a pulmonologist via a phone interview after verbal consent. A positive score on the asthma screening questionnaire was based on a previously described complete algorithm termed Models A to G, involving various combinations of four or five question elements (22), and a three-question abbreviated algorithm (23) with a "yes" to question 1 (asthma) or positive responses to both questions 4 (exercise-related respiratory symptoms) and question 6 (daytime respiratory symptoms). A positive score on the abbreviated algorithm is particularly sensitive and specific in detecting subjects with the highest risk for persistent asthma, based on the National Institutes of Health Guidelines for the Evaluation and Treatment of asthma (27).

Impulse oscillometry

IOS is one type of forced oscillation technique that delivers a spectrum of frequencies in an impulse on the airway

during tidal breathing. This determines lung function by measuring the mechanical properties of the lung. The sound waves are transmitted along the bronchial tree by oscillating sound signals of various frequencies, typically 5 and 20 Hz. IOS provides a measure of the total airway resistance [resistance at 5 Hz (R5)], the proximal airway resistance [resistance at 20 Hz (R20)], and the peripheral airway resistance (R5-R20). Reactance at 5 Hz (X5) relates to the physical properties of the lung parenchyma and its ability to expand and facilitate alveolar filling. Frequency response (Fres) is the point at which reactance is zero (when forces of inertia and capacitance are equal). The reactance area is the sum of all the frequency values from X5 to the Fres frequency, that is, it quantifies the respiratory reactance between 5 Hz and Fres. Patients with asthma have increased R5Hz and Fres, while the X5Hz is more negative (28,29).

IOS system (Jaeger MasterSuite, CareFusion, Hoechberg, Germany) was calibrated as per the manufacturer's recommendations. Testing and analysis were performed in accordance with European respiratory society/American thoracic society guidelines using existing reference values (30,31). Testing was performed with the patient sitting and breathing at tidal volume, the head held in a neutral position, a nose clip in place, legs uncrossed, and the cheeks firmly supported by either the patient or another individual such as the examiner or caregiver.

IOS measurements were compared between all CDH patients (including HR and LR combined) and a CDH reference group. The measurements were also compared between the HR and LR patients, and their respective HR and LR reference group. The reference group consisted of predicted values of healthy children of the same age, height, race, and gender.

Spirometry

Spirometry (Jaeger Master Screen, CareFusion, Hoechberg, Germany) was performed in the clinic, following American Thoracic Society (ATS)/European Respiratory Society guidelines (32). ATS predicted normative values expressed as percent predicted were based on global lung initiative 2012 values (33). Traces not meeting quality and reproducibility criteria were excluded. Spirometry results including FEV1/FVC <80% of predicted fixed lower limit of normal (LLN), concave shape of the flow-volume loop, flow-time curve, and FEF 25–75% were interpreted based on established guidelines. The obstructive airway pattern was defined as FEV1< LLN with FEV1/FVC < LLN (34).

Lung perfusion scan (V/Q scan)

V/Q scans were done as part of our defect size-based protocol implemented in our comprehensive multidisciplinary CDH clinic. V/Q scan for LR (defect size A/B) patients was done at 12 months and 3 years of age. HR (defect size C/D) patients had V/Q scans at 12 months and 3–5 years of age, depending on findings and clinical presentation. V/Q scans were performed to determine the split perfusion ratio on the CDH-affected side as part of routine clinical care. Perfusion scintigraphy was accomplished by microembolization with radiolabeled particles. 99mTc albumin aggregated (Tc-MAA) was injected into a peripheral vein of CDH survivors aged 12 months and older by a pediatric radiologist. Tc-MAA was injected slowly during 3–5 respiratory cycles with the patient in the supine position. Imaging was preferably performed in the upright position to increase chest cavity size and minimize diaphragmatic motion. Supine and decubitus images were obtained when upright images could not be obtained. A value of less than 30% perfusion ratio on the affected side was chosen as the threshold for severe perfusion compromise, based on previous literature (35).

Data analysis

Frequencies (with percentages) were used to describe the categorical variables. Descriptive statistics of the median and interquartile range were used for continuous variables. Mann–Whitney U test and Fisher's exact test were used for continuous data as needed. All statistical testing was performed in Stata/IC v.13.1 (Stata Corp, College Station, TX, USA) and statistical significance was assumed at a two-sided alpha of 0.05.

Results

NICU outcomes among CDH survivors

One hundred and thirty-three total patients were discharged from the NICU and 102 (77%) of these patients were seen in the comprehensive multidisciplinary CDH clinic. There were no statistically significant differences in demographics (age, gender, and race), birth weight, or gestational age; however, baseline characteristics such as prenatal diagnosis, intrathoracic liver, laterality, o/e LHR, and surgical repair varied significantly between LR CDH [n=79, defect A: n=25/79 (32%), defect B: n=54/79 (68%)] and HR CDH [n=54, defect C: n=45/54 (83%), defect D: n=9/54 (17%)]

Table 1 Characteristics of CDH patients

Characteristics	All patients, n=133	LR (defect type A/B), n=79	HR (defect C/D), n=54	P value
Age (months), median (IQR)	91 (53–128)	88 (54–123)	97 (53–141)	0.348
Male gender, n (%)	66 (50)	41 (52)	25 (46)	0.526
Race				
Caucasian, n (%)	59 (44)	34 (43)	25 (46)	0.447
Hispanic, n (%)	42 (32)	24 (30)	18 (33)	
Black, n (%)	15 (11)	9 (11)	6 (11)	
Asian, n (%)	8 (6)	4 (5)	4 (7)	
Other, n (%)	9 (7)	8 (10)	1 (2)	
Birth weight (kg), median (IQR)	2.98 (2.61–3.35)	3.03 (2.69–3.40)	2.94 (2.56–3.18)	0.135
Gestational age (weeks), median (IQR)	38 (37–39)	38 (37–39)	38 (37–39)	0.440
Laterality of CDH				
Left, n (%)	108 (81)	70 (88)	38 (70)	0.023*
Right, n (%)	24 (18)	9 (12)	15 (28)	
Bilateral, n (%)	1 (1)	0 (0)	1 (2)	
Prenatal diagnosis, n (%)	76 (57)	39 (49)	37 (69)	0.028*
Liver intrathoracic, n (%)	44 (33)	13 (17)	31 (57)	<0.001*
o/e LHR, median (IQR)	41.6 (33.0–52.4)	45.8 (36.5–53.4)	39.3 (25.4–47.4)	0.175
Surgical repair				
Primary, n (%)	48 (36)	48 (61)	0 (0)	<0.001*
Patch, n (%)	85 (64)	31 (39)	54 (100)	

*, P<0.05. CDH, congenital diaphragmatic hernia; LR, low-risk; HR, high-risk; IQR, interquartile range; o/e LHR, observed/expected lung head circumference ratio.

(*Table 1*). The overall prevalence of pulmonary hypertension at discharge was 19% (n=25/133). HR CDH had a higher prevalence of pulmonary hypertension at discharge [HR: 16/54 (30%) *vs.* LR: 9/79 (12%), P=0.009]. Similarly, ECLS utilization [HR: 19/54 (35%) *vs.* LR: 4/79 (5%), P<0.001] was higher in HR CDH. HR CDH patients required a longer median period of ventilation compared with LR CDH [HR: 17 days (IQR: 12–27) *vs.* LR: 5 days (IQR: 2–9), P<0.001] (*Table 2*). The total length of NICU stay was also significantly higher in HR CDH [HR: 59 days (IQR: 31–91) *vs.* LR: 17 days (IQR: 12–31), P<0.001]. A significantly higher number of HR patients were discharged on oxygen [HR: 16/54 (30%) *vs.* LR: 2/79 (3%), P<0.001] (*Table 2*).

Outcomes among CDH survivors following NICU discharge

Pulmonary outcomes, such as asthma, pulmonary hypertension, and health care utilization were determined in our complete cohort of patients surviving NICU discharge (n=133) and who were seen in the comprehensive multidisciplinary CDH clinic (n=102). The prevalence of asthma in CDH patients was n=37/133 (28%) and it was significantly higher in the HR group [HR: 20/54 (37%) *vs.* LR: 17/79 (22%), P=0.05]. Only 4% (n=5/133) of CDH patients had CDH-associated pulmonary hypertension, and all these patients belonged to the HR group. There was a higher percentage of patients with rehospitalizations

Table 2 NICU outcomes among CDH patients

Outcomes	All patients, n=133	LR (defect type A/B), n=79	HR (defect C/D), n=54	P value
Pulmonary hypertension at discharge, n (%)	25 (19)	9 (12)	16 (30)	0.009*
Receipt of ECLS, n (%)	23 (18)	4 (5)	19 (35)	<0.001*
Mechanical ventilation days, median (IQR)	8.5 (4–17)	5 (2–9)	17 (12–27)	<0.001*
Discharged on oxygen				
Overall, n (%)	18 (14)	2 (3)	16 (30)	<0.001*
Vent, n (%)	3 (2)	0 (0)	3 (6)	
Nasal cannula, n (%)	15 (11)	2 (3)	13 (24)	
Room air, n (%)	115 (87)	77 (97)	38 (70)	
Length of NICU stay (days), median (IQR)	28.5 (15–59)	17 (12–31)	59 (31–91)	<0.001*
Age at discharge (weeks), median (IQR)	4.8 (2.9–9.7)	3.4 (2.0–6.7)	8.4 (4.7–13.0)	<0.001*

*, P<0.05. NICU, neonatal intensive care unit; CDH, congenital diaphragmatic hernia; LR, low-risk; HR, high-risk; ECLS, extracorporeal life support; IQR, interquartile range.

Table 3 Outcomes among CDH patients following NICU discharge

Outcomes	All patients, n=133	LR (defect type A/B), n=79	HR (defect C/D), n=54	P value
Asthma, n (%)	37 (28)	17 (22)	20 (37)	0.050*
CDH associated pulmonary hypertension, n (%)	5 (4)	0 (0)	5 (9)	0.006*
Patients that had rehospitalizations, n (%)	65 (49)	33 (42)	32 (59)	0.050*
Number of rehospitalizations, median (IQR)	1 (0–1)	0 (0–1)	1 (0–2)	0.019*
Average days of rehospitalization, median (IQR)	5 (2–15)	4 (1–8)	9 (2–27)	0.035*
Patients that had ER visits, n (%)	66 (50)	37 (47)	29 (54)	0.472
Number of ER visits, median (IQR)	1 (0–3)	0.5 (0–2)	1 (0–3)	0.245

*, P<0.05. CDH, congenital diaphragmatic hernia; NICU, neonatal intensive care unit; LR, low-risk; HR, high-risk; IQR, interquartile range; ER, emergency room.

in the HR group (HR: 32/54 (59%) *vs.* LR: 33/79 (42%), P=0.019). Patients in the HR group had a significantly longer duration of hospital stay [HR: 9 (IQR: 2–27) *vs.* LR: 4 (IQR: 1–8), P=0.035]. Additionally, there was an increase in the average number of rehospitalizations in the HR group [HR: 1 (IQR: 0–2) *vs.* LR: 0 (IQR: 0–1), P=0.019]. There was no difference in the number of ER visits between the HR and LR groups [HR: 1 (IQR: 0–3) *vs.* LR: 0.5 (IQR: 0–2), P=0.245] (*Table 3*).

Outcomes among CDH survivors at comprehensive multidisciplinary CDH clinic

Of the 133 CDH patients, a total of 102 patients were followed at the comprehensive multidisciplinary CDH clinic. Of those, 42% were HR (n=43/102) and 58% were LR (n=59/102). A lung perfusion scan was performed in 38% (n=39/102) of CDH patients. Perfusion ratio on the ipsilateral side was significantly lower in the HR CDH group [HR: 29 (IQR: 20–33) *vs.* LR: 38 (IQR: 34–42),

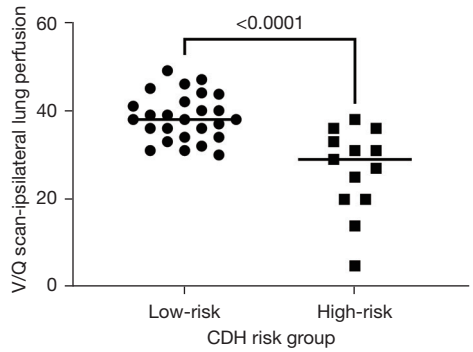

Figure 2 Perfusion ratio of the ipsilateral lung in low-risk (CDHSG defects A/B) and high-risk (CDHSG defects C/D) patients. CDH, congenital diaphragmatic hernia; CDHSG, Congenital Diaphragmatic Hernia Study Group.

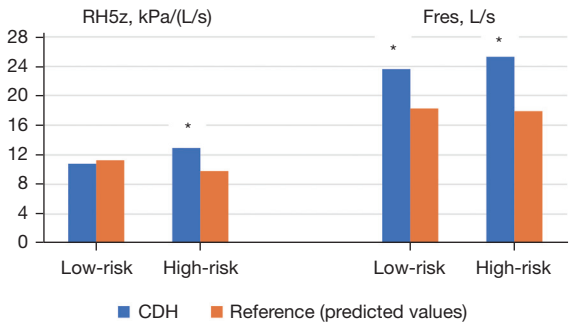

Figure 3 Abnormal impedance (peripheral airway obstruction) by IOS in patients with high-risk CDH. Increase airway resistance at 5Hz in high-risk CDH patients compared with the reference group (predicted values). No difference in low-risk CDH patients. Fres (resonant frequency) increased in high- and low-risk CDH patients compared with the reference group (predicted values). *, P value <0.05. IOS, impulse oscillometry; CDH, congenital diaphragmatic hernia.

P<0.001] (*Figure 2*). A perfusion ratio of less than 30% on the CDH ipsilateral side was seen in 13% (n=5/39) of patients with a V/Q scan; all 5 patients belonged to the HR group. All HR CDH patients with a perfusion ratio of less than 30% developed asthma [HR: 5/13 (38%), (P=0.002)].

Pulmonary function tests

Spirometry

A total of 17 patients underwent spirometry [forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and FEV1/FVC] at their baseline (waiting at least 4 weeks after a pulmonary infection). The median values were FVC 92% predicted (1.6 L), FEV1 86% predicted (1.3 L), FEV1/FVC 92% predicted (86%), and FEF 25–75% was 66% predicted (1.5 L). Of these, 3 patients (17%) had an obstructive pattern; 3 patients (18%) had a restrictive pattern, and 11 patients (65%) had normal spirometry. There was no significant difference in expiratory flows between HR and LR CDH patients. The FVC median was 88.8% predicted (IQR: 85–117) in the HR group *vs.* 87% predicted (IQR: 79.5–99.5) in the LR group (P=0.441). The FEV1 median was 79% predicted (IQR: 67.4–102) in the HR group *vs.* 89% predicted (IQR: 77–94) in the LR group (P=0.885). The FEV1/FVC median was 85% (IQR: 79–96) in the HR group *vs.* 96.5% (92.5–103) in the LR group (P=0.111). The FEF 25–75% median was 58% predicted (IQR: 38–70) in the HR group *vs.* 74.5% predicted (IQR: 63–93.5) in the LR group (P=0.149).

Impulse oscillometry

All IOS participants

IOS was performed in 24 patients measuring resistance at 5Hz (R5Hz), reactance at 5Hz (X5Hz), and resonant frequency (Fres). The median R5Hz for the CDH group was 10.37 (IQR: 8.6–12.2) kPa/(L/s) *vs.* 11.62 (IQR: 8.2–13.4) kPa/(L/s) in the reference group (P=0.07); the median X5Hz for CDH group was –3.57 [IQR: (–3.9) to (–2.63)] kPa/(L/s) *vs.* –2.84 [IQR: (–3.6) to (–1.095)] kPa/(L/s) in the reference group (P=0.02); the median Fres was 18.19 (IQR: 17.1–20.4) *vs.* 25.15 (IQR: 21.1–29.1) L/s in the reference group (P=0.001).

LR Group

The resistance, reactance, and resonant frequency were similar compared to the reference group. Specifically, the median R5Hz was 10.72 kPa/(L/s) in LR CDH *vs.* 11.3 kPa/(L/s) in LR reference (P=0.134); the median X5Hz was –2.23 kPa/(L/s) in LR CDH *vs.* –3.62 kPa/(L/s) in LR reference (P=0.012); the median Fres was 23.57 L/s in LR CDH *vs.* 18.29 L/s in LR reference (P=0.026) (*Figure 3*).

HR group

The resistance and Fres were increased in the CDH group compared to the reference group. Specifically, the median R5Hz was 12.95 kPa/(L/s) in HR CDH *vs.* 9.8 kPa/(L/s) in the HR reference group (P=0.010), and the median Fres was 25.34 L/s in HR CDH *vs.* 17.86 L/s in the HR reference group (P=0.004) (*Figure 3*). However, the reactance was

similar in both groups. The median X5Hz was –3.16 kPa/(L/s) for the HR CDH *vs.* –3.15 kPa/(L/s) in the HR reference group (P=0.735).

HR *vs.* LR CDH groups

The R5Hz median was 12.95 (IQR: 7.59–11.7) in the HR group *vs.* 10.72 (IQR: 9.9–12.74) in the LR group (P=0.111). The X5Hz median was –3.16 [IQR: (–3.97) to (–2.42)] in the HR group *vs.* –2.23 [IQR: (–4.07) to (–3.11)] in the LR group (P=0.385). The Fres median was 25.34 (IQR: 16.27–19.51) in the HR group *vs.* 23.57 [IQR: 17.56 to (–23.13)] in the LR group (P=0.622). HR CDH patients had an increased prevalence of asthma by IOS measurements compared with LR CDH patients (8 *vs.* 2, P=0.038), but spirometry did not detect this difference (LR 0 *vs.* HR 2 patients, P=0.471).

Discussion

In this single-center study, we demonstrated that infants with HR CDH (CDHSG defects: C/D) have a higher likelihood of experiencing significant morbidities such as asthma, pulmonary hypertension, need for ECLS, and prolonged ventilator dependency in NICU compared to those with LR CDH (CDHSG defects: A/B). These findings are consistent with previous literature (21,36,37). Specifically, there was a twofold increase in the risk of asthma and pulmonary hypertension at discharge in HR CDH. Our study highlights the usefulness of IOS in monitoring lung function in CDH patients, revealing a higher prevalence of asthma in HR CDH when compared to spirometry.

Approximately 75% of CDH patients experience a post-discharge pulmonary morbidity (13) including asthma, and pulmonary hypertension, resulting from pulmonary hypoplasia, ventilator therapy, diaphragm dysfunction, and mechanical changes in the chest wall and spine (38). Previous literature has shown impaired lung function in CDH patients (39-42), with reported asthma prevalence ranging from 23.6% to 30%, which aligns with our study's finding of 28% prevalence (43-45). The process of bronchioles and blood vessels branching impediment during the embryonic phase can result in acinar hypoplasia (46,47). Pulmonary hypoplasia and prolonged ventilator support in early life could set the stage for structural and functional pulmonary vascular alterations, resulting in synaptic airway growth leading to asthma and obstructive ventilatory impairment (48,49).

While spirometry has traditionally been employed to identify ventilatory impairment in CDH patients (40,44), IOS is now being utilized to study several disease states, including asthma, chronic pulmonary obstructive disease, and interstitial lung diseases. Although most of the studies have been done in children with asthma and are focused on monitoring disease progress and elucidating the effect of bronchodilators, research on IOS implementation in CDH remains limited. When compared to baseline measurements, a 20% decrease in FEV is equivalent to a 50% decrease in X5Hz, and this has demonstrated increased sensitivity for identifying bronchial hyperreactivity compared to spirometry; a feature of asthma (50). Schulze *et al.* revealed that even at lower doses of methacholine, there were significant changes in IOS parameters compared to baseline, reflecting the sensitivity of the procedure. This allows bronchoprovocation tests to be performed with smaller doses of bronchoconstriction agents (51). Shi *et al.* compared baseline spirometry and IOS parameters between children with well-controlled asthma and those subsequently presenting with acute exacerbations of asthma (52). Spirometry only detected small differences in the FEV1/forced vital capacity (FVC) ratio between the groups and did not reach statistical significance. However, IOS parameters, including R5Hz, and the frequency dependence of resistance (R5–R20), were significantly different between the two groups (52). Similarly, Gonem *et al.* showed that entropy of impedance measured over time can differentiate the patients with more frequent exacerbations compared to those with less frequent exacerbations (53).

Severe CDH with large defect sizes represents a population at risk for worsening lung function at an early age (41). In the HR CDH population, IOS measures of R5Hz and Fres were notably higher compared to predicted values of healthy children. A higher proportion of patients in the HR group were diagnosed with asthma based on IOS compared to spirometry. It has been shown that average pulmonary function declines with age relative to the expected population norm. This reflects an arrest of pulmonary parenchymal growth versus evolving emphysema, which predisposes these patients to the future development of obstructive lung disease (54). The increased prevalence of asthma in HR CDH detected by IOS compared to spirometry can be attributed to the ability of IOS to capture subtle changes in lung function by measuring airway resistance and reactance in the central and peripheral airways during tidal breathing. This enables the

identification of obstructive changes and declines in asthma control prior to the spirometry (52). This finding may be associated with the limited effectiveness of spirometry in the younger patient population, making tidal breathing techniques an acceptable alternative option (55-57).

An early embryogenic alteration affects the development of pulmonary vasculature, lung parenchyma, and diaphragm. Pulmonary hypertension in CDH survivors may be caused by a combination of factors, including external compression from herniated intra-abdominal contents, persistent poorly perfused ventilated areas representing dead space, and subsequent increased intrapulmonary shunting and hypoxemia, especially in large-size defects (58). The overall prevalence of pulmonary hypertension in our cohort at discharge was 19% with a higher percentage in the HR group. The prevalence of CDH-associated pulmonary hypertension was only 4%. This finding supports existing data that the tendency to develop pulmonary hypertension decreases with time (59). However, previous data reports that the time it takes for these changes to occur is longer because of the current limitations of invasive support measures, like ECLS (59). The prevalence of pulmonary hypertension has been reported between 11–17% for patients on all kinds of treatment including intravenous and oral medications; other studies have reported a range of 4.5–38% (60-62). Despite our cohort consisting of medically complex patients from a comprehensive multidisciplinary CDH clinic, the prevalence of pulmonary hypertension falls within the range reported in previous studies. This likely reflects the effectiveness of our comprehensive pulmonary management approach, which includes round-the-clock access to healthcare providers, integrated within our comprehensive multidisciplinary CDH clinic.

It is well-accepted that capillary growth and alveolar growth are intricately connected. Previous work has shown a worse V/Q ratio based on ECLS requirements and patch repair (larger defect) correlating the severity of defect size. This supports our findings of low perfusion on the affected side in the HR group (35). The requirement for ECLS and patch repair was higher in our HR CDH group. These perinatal variables like patch repair could be surrogates marker for a greater degree of pulmonary hypoplasia present at birth (63). Interestingly in our study, a perfusion ratio of less than 30% on the affected side was associated with asthma specifically in the HR group. These findings could be interpreted as either a greater degree of shunt across distal airways resulting in reduced ventilation, or inherent structural defects in pulmonary vasculature in large-size defects related to pulmonary hypoplasia. It is possible that a V/Q scan serves as an adjunct to a pulmonary function test. This close relationship between asthma and perfusion can help identify a subset of patients at risk for poor long-term functional outcomes.

Fetal lung volume measurement by magnetic resonance imaging (MRI) is a potential predictor of pulmonary hypoplasia (64). Perrone *et al.* demonstrated that prenatal ultrasound and MRI measurements of lung volume correlate with postnatal outcomes, including survival, ECLS use, defect size, and liver position (19,65). However, it has also been shown that radiological methods to assess the degree of pulmonary hypoplasia are not that reliable (66). Data on predictors for outcomes in the CDH population such as birth weight, Apgar scores, associated anomalies, presence of moderate-to-severe CDH-related pulmonary hypertension, need for higher ventilatory settings, ECLS, and shock is not disease-specific (67-70). The size of the diaphragm defect is disease-specific and correlates with morbidity in liveborn infants with CDH. Furthermore, animal models suggest that a large defect is associated with much smaller lungs (36). Based on our findings we posit that the size of the defect in CDH has a direct impact on the severity of pulmonary hypoplasia. This, in turn, contributes to worse outcomes, as evidenced by adverse events in HR CDH patients.

The current study is subject to limitations typically associated with single-center studies including lower volume, potential care evolution over the time examined, and the potential for non-universal generalizability. However, it is important to note that selection bias was unlikely given the no significant difference in demographic features between HR and LR groups. Furthermore, similarity in the distribution of the CDH population by defect size compared to previous literature add to the generalizability of our findings (37). Further, we did not have non-CDH controls to estimate the prevalence of asthma, hence we used published data on the prevalence of asthma in the general pediatric population (8% of children 0–17 years of age) (71,72) compared to 28% which we identified in the CDH group. The number of CDH survivors who underwent objective assessment for asthma via both spirometry and IOS was limited due to age and technical challenges associated with performing these maneuvers. Moreover, collection during the pandemic was limited for a myriad of reasons. Finally, our comprehensive multidisciplinary CDH clinic was launched in 2016, limiting follow-up for patients discharged 2012–2015.

Conclusions

This study reinforces existing literature that patients with large defect size are at increased risk for long-term pulmonary morbidities. These data provide valuable insight for risk-stratified pulmonary follow-up in CDH survivors and are helpful in developing screening tools, protocolized management, and guidance for families regarding outcomes in CDH-related long-term morbidities in accordance with diaphragm defect size. In addition, our study reports the application of IOS in the CDH patient population underscoring the importance of early detection and monitoring of lung disease, particularly in the HR CDH group.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of The University of Texas Health Science Center at Houston of Institutional Review Board approval (No. HCS-MS-18-1036) and individual consent for this retrospective analysis was waived.

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