Peer Review File
Article information: https://dx.doi.org/10.21037/tp-23-14

Reviewer A
Comment 1: This is a retrospective study to evaluate long-term pulmonary morbidities in CDH patients. The authors found patients with large defects had more significant pulmonary comorbidities than those with small defects. Although it was not a new finding, the authors showed interesting data with pulmonary function testing. I suggest considering those in the revised manuscript.

Follow-up period should be shown.

Reply 1: We have extended the follow-up period for the entire study from 2012 to 2022. Patients managed at our children's hospital within the adult hospital system were followed up till discharge; a subset of these patients (n= 102) were further followed at a comprehensive multidisciplinary CDH clinic. We have modified the manuscript accordingly to reflect these changes in the methods section.
Changes in the text: Lines 45-48 "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.
Line 133-135 "Patients with Bochdalek CDH hernia (n=133) were seen between January 2012 and April 2022 at a single children's hospital within an adult hospital system and a subset seen at the comprehensive multidisciplinary CDH clinic (n=102) were enrolled

Comment 2: What is the difference between "athma" and "asthma-like" symptoms. Is athma in CDH patients deffrent from it in patients without CDH?

Reply 2: We have changed the term asthma to asthma-like symptoms and made this change consistent throughout the entire manuscript. CDH patients usually present with symptoms of mild dyspnea like asthma patients, at this time we are not certain if it is truly asthma but given the similar symptomatology, we are currently treating it in the same way and we will continue to monitor this.

Comment 3: The names LR and HR of the groups according to the defect sizse is not consistent with those in the tables. If LR and HR are abbreviations, those should be spelled out in the first appearence.

Reply 3: We have made the changes (methods section of abstract and introduction) in the current version of the manuscript.
Changes in the text: Lines 48-49 "CDH patients were stratified according to CDHSG stage, and then categorized as low risk (LR), defect size A and B, or high risk (HR), defect size C and D".

Line 120-121 “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”

Reviewer B
This is an interesting study describing the long-term pulmonary morbidity in CDH patients followed at a high-volume single center. I have the following suggestions for improvement:
Comment 1: HR and LR are not defined well in the manuscript. It took me awhile to determine that it was referring to high-risk and low risk. I suggest introducing in the introduction and/or abstract early for easier reading.

Reply 1: We have defined the HR and LR in the Abstract and Introduction sections of the manuscript based on your suggestion.
Changes in the text: Lines 48-49 “CDH patients were stratified according to CDHSG stage, and then categorized as low risk (LR); defect size A and B or high risk (HR); defect size C and D”
Lines 120-121 “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”

Comment 2: I only saw 2 figures (figure 1 had A and B) although the text eludes to figure 3&4. Not sure where those are?

Reply 2: We agree it is a mistake, we have modified the text to match the figure with the text and have included 3 figures in total.
Changes in the text: Lines 120-121. 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 (Fig.1)”
Lines 307-309 “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), $p<0.001$)) (Fig. 2)”.
Line 343-344 “the median Fres was 23.57 L/s in CDH vs 18.29 L/s in reference ($p=0.026$) (Fig.3)”.
Lines 348-350 “The median R5Hz was 12.95 kPa/(L/s) in CDH vs 9.8 kPa/(L/s) in the reference group ($p=0.010$), and the median Fres was 25.34 L/s in CDH vs 17.86 L/s in the reference group ($p=0.004$) (Fig.3)”.

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Comment 3: Frequency response is abbreviated Fres most of the time but did see fres (non-capitalized) at least once so would edit to ensure the same throughout.

Reply 3: We have modified fres to Fres and the change is reflected in a revised version of the manuscript.
Changes in the text: Lines 223-226 “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 5Hz and Fres. Patients with asthma have increased R5Hz and Fres, while the X5Hz is more negative"

Comment 4: The descriptions of R5Hz, X5Hz, and Fres are confusing and do not seem to match with the figures (the text says significant but there is no asterisk on the figure and sometimes the text says non-significant but there is an asterisk. The numbers don't seem to match between the text and the figure either. There is also a mention of figure 4 that compares HR vs LR groups and I don't see that.

Reply 4: We have modified the figure to accurately show asterisk with a significant difference. Agree, there is mention of figure 4 which is a mistake, as there is no figure 4 in the current version.

Changes in the text: Lines 120-121 "In this study defect size, A&B are categorized as low risk (LR) and defect size C&D as high risk (HR) to compare pulmonary outcomes (Fig. 1).
Lines 307-309 "Perfusion ratio on the ipsilateral side was significantly low in the HR CDH group (HR: 29 (IQR: 20-33) vs. LR:38 (IQR: 34-42), $p<0.001$)) (Fig. 2)"
Line 343-344 "The median Fres was 23.57 L/s in CDH vs 18.29 L/s in reference ($p=0.026$) (Fig.3)".
Lines 348-350" The median R5Hz was 12.95 kPa/(L/s) in CDH vs 9.8 kPa/(L/s) in the reference group ($p=0.010$), and the median Fres was 25.34 L/s in CDH vs 17.86 L/s in the reference group ($p=0.004$) (Fig.3)".

Comment 5: I found it interesting that there was no difference in the total number of admissions in the first year despite the increased hospital stay in the HR group. Any sense from the authors as to why this is? I would have assumed there would be less admissions in the LR group.

Reply 5: We recollected data to include all-cause hospitalizations in total (the majority of patients were recruited from our comprehensive multidisciplinary CDH clinic) and the number of rehospitalization was higher in the HR CDH group. As far as risk of hospitalization in the first year is concerned, believe that CDH is a medically complex patient with a high number of admissions regardless of cause.
Changes in the text: Lines 299-300 "Additionally, there was an increase in the average number of rehospitalizations in the HR group (LR: 0 (IQR:0-1) vs. (HR:1(IQR 0-2), $p=0.019$)".

Reviewer C
Comment 1: It is known that the prognosis of CDH is different depending on whether it is on the right side or the left side. There is no such analysis in this study. It is necessary to conduct an analysis of laterality or conduct research only in a specific group on the left or right side.

Reply 1: We agree that based on CDH laterality prognosis can vary; however, given a single-center study and with the majority of left-sided CDH patients (n=108), we have lumped right (n=24), left-sided, and bilateral (n=1) CDH together to derive meaning full data.

Abstract
Comment 2: 56-79 Abbreviations of CMHH, ANOVA, IOS, and ED in the abstract are unnecessary.

Reply 2: We have removed these abbreviations in the abstract and have included abbreviations in the body of the manuscript.

Comment 3: 58-59 You categorize A/B into LR and C/D into HR, but I think you need to explain LR and HR for readers. Low risk or high risk?

Reply 3: Agree, we have defined High risk (HR) defect size C/D and Low risk (LR) defect size C/D in the abstract and later in the introduction.
Changes in the text: Lines 48-49 “CDH patients were stratified according to CDHSG stage, and then categorized as low risk (LR); defect size A and B or high risk (HR); defect size C and D”
Line 120-121 “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 (Fig. 1)”. .”

Introduction
Comment 4: 134-145 Readers are not familiar with the sudden appearance of HR and LR abbreviations.

Reply 4: We agree that high risk (HR) and low risk (LR) needs to be defined early in the introduction section. We have modified the introduction and defined HR and LR.
Changes in the text: Line 120-121: “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 (Fig. 1)”.

Methods
Comment 5: 156-157 LR (LR), HR (HR)?

Reply 5: We have rectified this mistake in the revised manuscript and introduced categorization in the introduction.
Changes in the text: Lines 120-123“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 (Fig. 1). We hypothesized that HR CDH survivors (C/D), as opposed to LR (A/B), experience more significant adverse pulmonary morbidities after discharge”.

Comment 6: 157 Figure 1 -> It is sufficient to present Figure 1a as an appendix.

Reply 6: We think the figure is fundamental for readers to understand the classification system. We have modified Figure 1 for a clear understanding of classification on the basis of defect size (Low risk vs high risk).

Comment 7: 208 Readers do not want to read review articles about IOS in methods. Please describe only the methods used in this study.

Reply 7: We have revised the methods section of the manuscript and have included only the IOS method used in this study.
Changes in the text: Lines 216-226 “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 (31, 32). 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” and moved IOS review in the discussion session “line 384-401”.

Discussion
Comment 8: 385-401 This paragraph is more of a review of CDH. How does it relate to this original research? Rather, it would be better to describe pulmonary hypoplasia according to DEFECT SIZE and subsequent poor long-term prognosis. The discussion of CDHSG's DEFECT SIZE, the main topic of this study, has only four lines (418-421), and that is also insufficient.

Reply8: We have added more content to the discussion section of the manuscript. We believe the size of the defect in congenital diaphragmatic hernia directly influences the severity of pulmonary hypoplasia, which in turn drives worse outcomes.
Changes in the text: Lines 450-462 “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”

Reviewer D

Comment 1: Emanuel and co-workers conducted a single-centre analysis of 127 infants with congenital diaphragmatic hernia that lived to discharge from the neonatal intensive care unit. They combined defects sizes A/B and C/D into two groups and analysed outcomes based on these dichotomisation. The authors found that various outcomes were associated to having a larger defect size and concluded that these were linked to negative long-term outcomes.

In the present version, the data do not support the conclusions. The manuscript requires substantial revision before its content might be appropriately judged. A non-exhaustive enumeration of points that need to be addressed:

It is frankly inappropriate to dichotomise the cohort based on defect size. The first issue with this approach is a statistical one: Dichotomisation of ordinal variables or, even worse, continuous variables, goes hand in hand with a substantial loss of information.

The second issue is the justification of this dichotomisation: The authors cite reference 14, 16, and 20 to support their dichotomisation. While this might deceive the unaware reader, those familiar with the literature might consider this actively misleading. Reference 14 includes defect size as a categorial variable in multivariate regression (Table 4). With respect to pulmonary morbidity in particular, one may not consider the groups similar: While defect size A is the reference category, defect size B has an odds ratio of almost 2, defect size C of ~8 and defect size D of ~15. Reference 16 describes the stages and defect sizes and reports on survival (Table 2). For the sake of argument, we might consider only those without major cardiac abnormality and a survival of 58% for defect size D is not similar to a survival of 78% in defect size C. Reference 20 does only include defect sizes A and B, because it aimed to assess factors that would be associated with a less favourable prognosis in these children with an anatomically less severe congenital diaphragmatic hernia.
Consequently, the line of argument of the author's does not withstand further scrutiny. Therefore, the authors will report the patients in their separate subgroup. Of note, in its present form, the reader is unaware of the distribution of defect sizes in the two groups, because it is not mentioned at all, even though these distinct groups are just lumped together for analysis.

Reply 1: Multiple studies have shown similar outcomes for defect size A & B (smaller defects) and defect size C & D (larger defects). In addition, given the single-center study with a limited number of patients and to derive meaningful data we have categorized A& B as the low-risk group and C&D as the high-risk group. *Chock VY, Danzer E, Chung S, Noh CY, Ebanks AH, Harting MT, Lally KP, Van Meurs KP; Congenital Diaphragmatic Hernia Study Group. In-Hospital Morbidities for Neonates with Congenital Diaphragmatic Hernia: The Impact of Defect Size and Laterality. J Pediatr. 2022 Jan;240:94-101.e6. doi: 10.1016/j.jpeds.2021.09.001. Epub 2021 Sep 7.*

PMID: 34506854. Putnam LR, Harting MT, Tsao K, Morini F, Yoder BA, Luco M, Lally PA, Lally KP; Congenital Diaphragmatic Hernia Study Group. Congenital Diaphragmatic Hernia Defect Size and Infant Morbidity at Discharge. Pediatrics. 2016 Nov;138(5):e20162043. doi: 10.1542/peds.2016-2043. PMID: 27940787.

Comment 2: During the manuscript, a control group magically appears that was not described or characterised in any way before (lines 341-345, 347-351, 353-357, and 364-367). The authors will clarify who these patients are, how many they are, and what makes them a suitable control.

Reply 2: We agree control group needs to be defined before introducing the control group in the results. For this study, the control group medians were calculated based on the predicted values of normal kids of the same age, height, race, and gender as patients in the CDH group. We have changed the "control group" to a "reference group" for clear and easier understanding for the readers.
Changes in the text: Lines 235-238. "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"

Comment 3: According to Table 3, 52 patients had a diagnosis of asthma, but only 41 had a lung function test. As far as I am informed, a lung function test also is a prerequiste of the diagnosis of asthma in the United States. Assuming that only patients above five years of age, as the authors did too (lines 195-197), might participate in these tests, the authors will clarify how these diagnoses in patients could be made without a lung function test.

Reply 3: Asthma diagnosis is challenging and is based on a combination of clinical symptoms, physical exams, and pulmonary function tests. We used validated screening tools such as asthma questionaries to identify asthma in patients not followed at a Comprehensive multidisciplinary CDH clinic. For patients seen at the comprehensive multidisciplinary CDH clinic who were not able to undergo pulmonary function testing due to age, inability to perform maneuvers, or pulmonary function testing not meeting American Thoracic Society, the diagnosis was based on a combination of clinical symptoms, physical exam, and pulmonologist assessment. We have modified our methods (asthma section) to reflect this change.
Changes in the text: Lines 198-206 "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 ”

Comment 4: The numbers according to Figure 1b do not add up: 64 patients were followed at the authors' clinic. 41 of them had a lung function test and 22 were excluded. As 41+22=63, there is one patient missing.

Reply 4: We agree this is a mistake, 41 patients in total had pulmonary function test

Comment 5: Alpha inflation: Just Tables 1-5 consisted of 27 statistical comparisons with rather strange endpoints, e.g. days of rehospitalisation in Table 1, and there are even more reported in the results. As I assume these were not pre-specified, the authors will apply a method to tame the alpha inflation due to multiple testing. Just for the 27 comparisons in the Tables, the Bonferroni-corrected p-value would be 0.00185 instead of 0.05.

The authors seem to have lost track of their intense amount of abbreviations. For example, in the abstract HR and LR (lines 58-59) and NICU (line 67) are not defined at all, while the institution (line 56), analysis of variance (line 64), impulse oscillometry (line 75), and emergency department (line 79) are abbreviated, but not used afterwards. This continues within the manuscript with forced oscillation techniques (line 209) and receiver operator characteristics (line 244), whereas COPD (line 211) and ERS/ATS (line 252) are used without definition. Likewise, the abbreviation LR and HR are defined by itself (line 157). This journal does not employ word limits, consequently, restricting the use of abbreviations might be beneficial not only for the readability.
Reply 5: We have revised the manuscript.
Changes in the text: Lines 48-49 “CDH patients were stratified according to CDHSG stage, and then categorized as low risk (LR),defect size A and B, or high risk (HR),defect size C and Lines 45-48 “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”

We eliminated ER and IOS abbreviations in the abstract.
We have eliminated forced oscillation techniques abbreviations and receiver operator characteristic.
Changes in the text: Line 242 “following American Thoracic Society (ATS)/European respiratory society guidelines”

Comment 6: It is far from good practice to just report a p-value without accompanying data (lines 77-79 and 312-314).

Reply 6: We have removed that analysis as we recollected data to include more variables.

Comment 7: It is unclear to me why parts of the discussion (lines 233-249) are within the methods.

Reply 7: This has been moved to the discussion.

Comment 8: For all comparisons that the authors conducted, the statistical test that was utilised in the respective comparison is not reported at all. As I could not find any non-pairwise comparison, it also remains unclear when and why an analysis of variance was conducted and if any post-hoc tests were used.

In addition, I assume that Fisher's test was not used on continuous data, although it was claimed to be done (lines 282-283) as the result would be useless, because continuous data collide with the truncated hypergeometric distribution of Fisher's exact test. That said, some biostatistical guidance might be helpful during a revision.

The language the authors use is rather strong, although lung function tests are available for only a small subset of their cohort: Only 13% of patients had spirometry so far, which can still be considered to be the gold standard of lung function testing.

Reply 8: Asthma diagnosis is challenging and is based on a combination of clinical symptoms, physical exams, physician assessment, and/or pulmonary function tests. Pulmonary function tests are useful supplemental tools for asthma diagnosis to support the diagnosis of asthma.

Reviewer E
Comment 1: The authors do not define high risk and low risk (lines 58-59) prior to using the abbreviations.

Reply 1: We agreed this is a mistake. We have modified this in a revised version of the manuscript.
Changes in the text: Lines 48-49 “CDH patients were stratified according to CDHSG stage, and then categorized as low risk (LR), defect size A and B or high risk (HR), defect size C and D”

Comment 2: I would suggest presenting the frequency data in a different manner in the abstract and throughout the manuscript. (HR, 36%, n=46/127; LR, 64%, n=81/127) is not only cumbersome but also takes a moment to get through. I would suggest (HR 46 (36%) vs LR 81 (64%); p<0.001).

Reply 2: We have modified the results based on your suggestion.

Changes in the text: Lines 281-282.” HR CDH had a higher prevalence of pulmonary hypertension at discharge (HR: 16/54 (30%) vs. LR: 9/79 (12%), p=0.009)”

Comment 3: Line 71: please provide whether the metric was median [IQR] or mean +/- SD.

Reply 3: We modified the result section of the abstract.
Changes in the text: Lines 59-60 “the average number of mechanical ventilation days (HR: 17 days (IQR:12-27) vs. LR: 5 days, (IQR:2-9), p<0.001)”

Introduction
Comment 4: In the first paragraph, the authors briefly review the dual hit hypothesis. This is again reviewed in the discussion. In my opinion, their explanation was much better in the discussion and I would suggest moving it from that section to this and removing it from the discussion where it is currently not providing context to their findings.

Reply 4: We have modified the manuscript based on your suggestion and have removed the dual hit hypothesis from the discussion.

Comment 5: Lines 118-120: this sentence is quite confusing. Long-term or even post-discharge? I would rewrite this sentence or even potentially remove it. The authors introduce the idea of ongoing morbidity in the prior sentence and provide information regarding long term morbidities in the next sentence.

Reply 5: We have rewritten the sentence for better clarity and modified the manuscript accordingly.
Changes in the text: Lines 90-92 “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)”

Comment 6: The statement in lines 132-133 is incorrect. In both works published by Dao et al. published in the Journal of Pediatrics, the associations between CDHSG staging and long-term pulmonary outcomes (V/Q mismatching and pulmonary function by spirometry) was evaluated. The novelty of this study is the use of impulse oscillometry. I would recommend that the authors introduce that test in the introduction and highlight the novelty of this test and how this adds to the literature.

Reply 6: We agree there is previous data on these findings. We have modified the manuscript. We have introduced Impulse oscillometry in the introduction section.
Changes in the text: Lines 104-110 “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)"

Comment 7: Similarly, in lines 134-135, HR and LR abbreviations are used without being defined.

Reply 7: We have rectified this mistake in a revised version of the manuscript.
Changes in the text: Lines 121-123 "We hypothesized that HR CDH survivors (C/D), as opposed to LR (A/B), experience more significant adverse pulmonary morbidities after discharge"

Methods
Comment 8: Please move the inclusion and exclusion criteria (lines 163-166) further up in the methods. This should be likely the second sentence in the methods.

Reply 8: We have modified methods based on your suggestion.
Changes in the text: Lines 139-141 "CDH survivors with other primary chronic pulmonary conditions, such as cystic fibrosis, primary ciliary dyskinesia, and immunodeficiency disorders with pulmonary manifestations were excluded"
Comment 9: How did the authors identify if a patient had pulmonary hypertension? What criteria by echo did they utilize?

Reply 9: Pulmonary hypertension was based on echocardiogram findings of indirect signs of pulmonary hypertension, such as increased TR jet, elevated RVSP, and/or interventricular septal flattening at discharge. In addition, for the purpose of this study, only patients with evidence of pulmonary hypertension on echocardiogram and on pulmonary hypertension treatment such as O2, sildenafil, and/or bosentan were included. We have modified the methods section to reflect this change.
Changes in the text: Lines 166-171 "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 O2, sildenafil, and/or bosentan were included"

Comment 10: To better understand the study cohort, please elaborate on the criteria for being followed at the high risk comprehensive CDH clinic. Does this suggest that patients with very mild CDH were not followed at this clinic?

Reply 10: All patients with CDH are considered eligible for the comprehensive multidisciplinary clinic.

Comment 11: I really enjoyed the IOS section of the methods. This was likely my favorite part of the paper. Please correct the names of the statistical tests used in the Data analysis portion. Mann-Whitney U test. Analysis of Variance (ANOVA). Fisher's exact test. Please move frequencies with percentages to the beginning of this paragraph.

Reply 11: We have modified the manuscript based on your suggestion.
Changes in the text: Lines 266-270 "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"

Results
Comment 12: The patient characteristics used to compare the HR and LR CDH patients were age, gender, and race. Regarding race, please provide more granularity. Typically, one presents this data as Non-Hispanic (NH) white, NH-Black, Hispanic, Asian, and other. Further, I feel that there are many critical characteristics that are missing from the Table 1. Please consider the evaluation of the following: birth weight, gestational age, laterality of CDH, prenatal diagnosis, presence of an intrathoracic liver, length of NICU hospitalization, type of surgical repair. These characteristics have been previously associated with both short-term and long-term outcomes in the CDH cohort and would provide important information to help understand the cohort (ex: Wigen et al Eur J Pediatric Surg 2019). Further, there needs to be a greater understanding of the co-morbidities of this cohort. How many patients had tracheobronchomalacia, BPD, CCAM, pulmonary sequestration? How many required a trach/vent or were discharged on oxygen?

Reply 12: We have included the baseline characteristics of birth weight, gestational age, laterality of CDH, prenatal diagnosis, presence of an intrathoracic liver, length of NICU hospitalization, and type of surgical repair in Table 1 ad Table 2. We have not collected data on comorbidities, although we agree that CDH patient can present with these comorbidities, but aim of this study was to look at outcomes by defect size in patients with CDH without additional comorbidities. We have included the patient discharged on oxygen in Table 2.

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 (%) Hispanic, n (%) Black, n (%)	 59 (44) 42 (32) 15 (11)	 34 (43) 24 (30) 9 (11)	 25 (46) 18 (33) 6 (11)	0.447

Asian, n (%) Other, n (%)	8 (6) 9 (7)	4 (5) 8 (10)	4 (7) 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 (%) Right, n (%) Bilateral, n (%)	 108 (81) 24 (18) 1 (1)	 70 (88) 9 (12) 0 (0)	 38 (70) 15 (28) 1 (2)	 0.023*
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 (33-52.4)	45.8 (36.5-53.4)	39.3 (25.4-47.4)	0.175
Surgical repair Primary, n (%) Patch, n (%)	 48 (36) 85 (64)	 48 (61) 31 (39)	 0 (0) 54 (100)	 <0.001*

IQR= interquartile range, o/e LHR= observed/expected lung head circumference ratio

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 (%) Vent, n (%) Nasal cannula, n (%) Room air, n (%)	 18 (14) 3 (2) 15 (11) 115 (87)	 2 (3) 0 (0) 2 (3) 77 (97)	 16 (30) 3 (6) 13 (24) 38 (70)	 <0.001*
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*

ECLS = extracorporeal life support, IQR = interquartile range

Comment 13: The prevalence of PH at the discharge echo reported in this study would be significantly higher than many other institutions. They report 59%, while the estimated prevalence of PH at time of NICU discharge is closer to ~30% (Lusk et al J

of Peds 2015). If there was this high prevalence of PH, please provide severity (mild, moderate, or severe) and the therapies that these patients were discharged on. It would also be interesting to see if the history of PH at discharge is associated with abnormal pulmonary function.

Reply 13: We have recollected the data and looked at patients with evidence of pulmonary hypertension based on echocardiogram findings of indirect signs of pulmonary hypertension, such as increased TR jet, elevated RVSP, and/or interventricular septal flattening at discharge. In addition, for the purpose of this study, only patients with evidence of pulmonary hypertension on echocardiogram and on pulmonary hypertension treatment such as O2, sildenafil, and/or bosentan were included. We have modified the methods section to reflect this change. Pulmonary hypertension prevalence was reported to be 19 % in our cohort based on the above criteria.
Changes in the text: Lines 166-171" 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 O2, sildenafil, and/or bosentan were included"
Lines 281-282 "HR CDH had a higher prevalence of pulmonary hypertension at discharge (HR: 16/54 (30%) vs. LR: 9/79 (12%), p=0.009)"

Comment 14: As in the abstract, please strongly consider changing how frequency data is presented. I find it very confusing.

Reply 14: We have made changes to the frequency data based on your suggestion.
Changes in the text: Lines 57-58 "During NICU stay, the prevalence of pulmonary hypertension (HR: 16/54 ((30%) vs. LR: 9/79 (12%), p=0.009"

Comment 15: Please provide more information on the duration of follow-up in this cohort to help us understand the prevalence of asthma.

Reply 15: This is a cross-sectional study, PFTs were recorded at only one given time.

a. Of note, this prevalence of asthma is quite high. I would recommend discussing this further in the discussion by providing relevant prior studies reported prevalence of asthma in their CDH Cohorts and perhaps exploring reasons why the cohort at this institution has a high rate.

Author reply a: We have recollected data and our reported prevalence is 28% which is in range of previously reported literature.
Changes in the text: Lines 293--296 "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 persistent pulmonary hypertension and all these patients belonged to the HR group".
Line 375-377- 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)"

b. What other characteristics were associated with the presence of asthma other than size of defect? Duration of ventilation? Gestational age? Pulmonary co-morbidities?

Author reply b: Unfortunately, for the purpose of this study, we have done an analysis to look at only the presence of asthma with defect size.

c. How many were being treated for asthma?

Author reply c: Unfortunately, for the purpose of this study, we have not collected data on patients being treated for asthma as our aim is to only report the prevalence of asthma by defect size.

Comment 16: Please provide a brief summary of the indications for hospitalization within the first year of life – were these related to viral illnesses, feeding intolerance, or more serious infections? If so, was there a difference in defect size?

Reply 16: For the purpose of this study, we have not looked into causes of rehospitalization as our main objective is to high light increased burden of morbidity in this population by defect size. We believe the CDH population is a high-risk medically complex pediatric population with high rates of complications, irrespective of defect size leading to increased hospitalizations, and all cause of re-hospitalization.
.
Comment 17: Please define persistent pulmonary hypertension, specifically at what age. Does this represent pulmonary hypertension at any point after discharge during the follow-up period? If so, that is an incredibly high number and would be very different from the current literature (Miles et al. Ped Pulm 2023, Critser et al. AHA abstract). How many are being treated at most recent follow-up for PH? If this is a true prevalence rate, please consider discussing this in the discussion and provide reasons for why the rate of PPHN is so high in this cohort.

Reply 17: Persistent pulmonary hypertension post-discharge was defined as the presence of pulmonary hypertension requiring treatment at the most recent clinical encounter during our data collection. Only 4% (n=5/133) of CDH patients had persistent pulmonary hypertension and all these patients belonged to the HR group line. The overall prevalence of pulmonary hypertension in our cohort at discharge was 19% with a higher percentage in the HR group

Comment 18: The statement in lines 312-314 is not supported by the data presented in Table 3. Please remove this sentence or add relevant supporting data to the tables.

Reply 18: We have eliminated the comparison of CDH patients to children with asthma without CDH. 8% is referring to the prevalence of asthma in the general pediatric population from the result section.

Comment 19: Please reference the flow diagram (1B) to line 316) and add information regarding the 63 patients who were not followed at the clinic. Were they not followed due to the family moving, were they lost to follow-up, did they experience a serious complication or death? Additionally, please consider comparing the baseline characteristics of the patients who were and were not followed at the comprehensive CDH clinic.

Reply 19: We have removed Figure IB from the current version of the manuscript. As for patients not followed at the clinic, it was based on the family's decision, insurance limitations, as well patients not qualifying for the clinic (rare).

Changes in the text: Lines 179-181"A subset of 102 patients (77%) surviving hospital discharge whose families decided to continue to care at the dedicated comprehensive multidisciplinary CDH clinic were followed longitudinally"

Comment 20: If I am understanding the data correctly, the data presented in sentences 318-319 are incorrect. It should read "In this clinic, HR CDH was associated with an increased prevalence of asthma, HR: 19/23 (83%) vs. LR: 17/41 (41%), p=0.0017).". Similarly, the sentences of 320-322 are confusing and may benefit from re-writing."

Reply 20: This reflects the overall prevalence in CDH survivors following NICU discharge including the patients not followed at the clinic.

Changes in the text: Lines 291-296"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)".

Comment 21: Please provide patient characteristics for the patients who underwent spirometry and IOS. At a minimum, please provide the age, sex, and size of the patients performing the test and please indicate if they had a history of any pulmonary co-morbidities and whether they were on any pulmonary medications at the time of this therapy.

Reply 21: Unfortunately for the purpose of the study, we haven't collected baseline characteristics of patients' spirometry and IOS as the main aim was to highlight the ability of IOS to detect subtle changes in lung function, especially in high-risk CDH.

Medication history is not recorded, as a diagnosis of asthma was based on initial PFTs (for patients who underwent testing) while patients were not on medications.

Discussion

Comment 22: Line 369: It is difficult to agree with their statement of "long-term" outcomes if they do not provide the time course for their outcomes (i.e. length of follow-up, age at testing, etc.).

Reply 22: We have modified the manuscript

Changes in the text: Lines 363-370 "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"

Comment 23: Lines 372-374: Please make these a separate sentence. These outcomes are unrelated to the first half of this sentence. Consider rewriting sentence to "As in prior studies, higher CDHSG stage was associated with pulmonary hypertension at discharge, need for ECMO, and prolonged mechanical ventilation in the NICU (studies XYZ). Further, higher CDHSG staging was associated with a substantial burden of pulmonary morbidity in this study, including ***". The outcomes listed in this original sentence "pulmonary hypertension, asthma, and rehospitalization" may be true but they are not the most important part of this study. Please highlight the use of oscillometry, which is the real novel aspect of this work.

Reply 23: We have modified the manuscript.

Changes in the text: Lines 363-370 "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"

".

Comment 24: As part of the second paragraph of the discussion, could you please specify what were the differences between IOS and spirometry assessment of the patients? Higher rates of obstructive lung disease? What is the clinical relevance of this finding and where does your team envision the use of IOS being in the future? What

would be the benefit of incorporation across other institutions? This would be the true meat of this discussion and would be most interesting to a reader.

Reply 24: We have included para to reflect the increased sensitivity of IOS especially in high-risk CDH.
Changes in the text: Lines 403-416 "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)"

Comment 25: Please consider removing the third paragraph, which focuses too much on basic biology which would be better suited in the introduction.

Reply 25: We have made changes to the manuscript and removed the third paragraph.

Comment 26: Please review the literature for the many studies that have demonstrated long-term pulmonary morbidities in the CDH population and adequately provide context for the novelty of this study. Did your study find anything different from the others in terms of prevalence of disease?

Reply 26: We have introduced IOS in the discussion section of the manuscript as this has not been reported before in CDH patients.

Comment 27: Lines 418-421: This statement is not true. You demonstrate that defect size is associated with increased prevalence of asthma, but you do not demonstrate in any of your testing that this is due to pulmonary hypoplasia. Further, you do not provide information on severity of asthma.

Reply 27: We believe that CDH leads to the arrest of pulmonary parenchymal growth versus evolving emphysema, a degree of which correlates with defect size. The size of the defect in congenital diaphragmatic hernia directly influences the severity of

pulmonary hypoplasia, which in turn drives worse outcomes as in HR CDHSG including lung function.
Changes in the text: Lines 456-462 “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”

Comment 28: Line 425: it is difficult to make any strong conclusions based on the data from 22 patients who underwent lung perfusion testing and specifically 8 patients who had decreased perfusion. It is interesting that, by chance, all patients with C/D defect sizes and perfusion <30% to that lung had asthma, but it certainly isn’t conclusive. For example, decreased lung perfusion is likely reflective of worse vascular and parenchymal disease, of which asthma may be sequelae. Dao et al studied this extensively.

Reply 28: Agree, this finding isn’t certainly conclusive, our purpose was to report our findings of the association of <30% perfusion on the affected side in the HR CDH group. We speculate it is due to a greater degree of shunt resulting in reduced ventilation which may contribute to asthma.

Comment 29: The discussion in lines 431-436 is a stretch. Without understanding the reasons for frequent hospitalizations, it is very difficult to understand if asthma/pulmonary co-morbidities played a role when there are other good reasons for kids to be hospitalized in the CHD survivor cohort (ex: feeding intolerance).

Reply 29: The purpose of including all-cause hospitalizations was to highlight a greater number of HR CDHs. We believe that CDH is a medically complex patient with a high number of admissions regardless of cause. We have removed this paragraph in the discussion section but have kept it in the results section to highlight the different outcomes between HR and LR

Comment 30: Regarding the limitations, please discuss further what your group did to address the limitations. For example, if you’re able to address concerns of selection bias, that would be pertinent.

Rely 30: Selection bias was unlikely given the lack of difference in demographic features between HR and LR, and our study population's similar distribution by defect size as reported previously in the literature.

Conclusions

Comment 31: Please add the novelty of IOS to the conclusion as this is one piece that truly adds something to the current literature. The rest of the findings have been previously reported.

Reply 31: We have added IOS to the conclusion.

Comment 32: After the above comment, please consider: This study supports prior literature that patients with high risk CDHSG staging are at increased risk for long-term pulmonary morbidities. While long-term management of CDH survivors remain poorly understood, this data provides relevant information for risk-stratified pulmonary follow-up in CDH survivors.

Reply 32: We have modified the conclusion based on your suggestions.
Changes in the text: Lines 481--487 " 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"

Reviewer F
Comment 1: The clinical implications of the demonstrated results should be explained more clearly in the discussion. To this reviewer, it is not clear how these data can be used in clinical practice. Especially, what do the authors mean with the options mentioned in line 449? In line 138-139 the authors mention 'comprehensive pulmonary management' – however, this is not explained further.

Reply 1: Comprehensive pulmonary management is provided with in an enhanced medical home with open access for acute respiratory conditions to the clinic Monday to Friday with 24/7 direct access via cell phone to primary care physicians who can schedule same/next day visits or call ED as needed on nights & weekends. In addition, this medical home has a low patient-provider ratio ($\leq$1:100) and has weekly meetings to discuss all ED visits, hospital, and PICU admissions. We have explained this in the methods sections of the revised manuscript.
Changes in the text: Lines 184-189 "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""

Comment 2: The discussion could also be improved by a better focus on the main aim mentioned in the introduction. For example, the first paragraph of the discussion could be rewritten. Other than that, the discussion includes information that is more suitable for the introduction (line 385-401); if the authors decide to leave this section in the discussion, please write more concise and provide a rationale for including it. Also, lines 414-416 repeat 381-383. Several paragraphs of the discussion lack a conclusion/referral to the current data (line 431-436). Finally, could the authors elaborate more on the small sample sizes in certain analyses and the potential bias induced by this?

Reply 2: We have modified the discussion.
Changes in the text: Lines 363-370 "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"

We have moved dual hit hypothesis and physiology to the introduction (lines 381-383 in the previous version). Furthermore, we have added para to demonstrate that size of the defect in congenital diaphragmatic hernia directly influences the severity of pulmonary hypoplasia, which in turn drives worse outcomes as shown by worse outcomes in HR CDHSG
Changes in the text: Lines 457-462 "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."

We agree that small sample sizes for some analyses such as PFTs and V/Q scans have the risk of bias and are one of the limitations of our study; however, we believe selection bias is unlikely given the absence of significant differences in demographic data, defect-sized based protocolized management and our population's similar distribution by defect size as reported previously in the literature.

Comment 3: The population of infants with CDH is heterogeneous, for example as a result of factors such as laterality. Therefore, it is favorable to add data to the baseline characteristics table, such as o/e LHR, laterality, and liver position. Other than that, the first paragraph of the Results section could be added to the baseline table instead of being reported as outcomes (combining Tables 1 and 2).

Reply 3: We agree; however, we think it would be helpful to separate baseline characteristics from morbidities as sequelae of CDH

Comment 4: In this reviewer's opinion, the paper should be written more concisely. Suggestions to do so:
a. Methods section: the paragraph on IOS is very long and should be written more concisely.
Author reply a: Method section is modified with no review of previous studies in IOS section

b. Results section:
i. Both the text and tables mention the exact same data; please report data in either of both.
Author reply i: We have reported baseline characteristics in table 1 only and PFTs (IOS and spirometry in text).

ii. Do not repeat what is already mentioned in the methods (e.g. line 299-300).
iii. Unfortunately, the text includes several wrong references to tables (line 314: information not to be found in table 3) and (non-existing) figures (line 319, 323, 367).
Author reply iii: We have modified the manuscript and include only 3 tables and 3 figures
iv. Impulse Oscillometry: consider to only report the LR vs HR group outcomes, as this answers the research question. Also, errors in the data are present in these paragraphs, as the medians and IQRs mentioned in lines 360-363 were first mentioned as belonging to controls, whereas afterwards mentioned as belonging to CDH infants. This should be corrected in both text, tables and figures.
Given the low number of patients in each group and to derive meaningful data we compared the CDH group (LR and HR) to their age, sex, height, and weight predicted values.

Author reply iv: We corrected the results section HR vs LR.

Changes in the text: HR vs LR CDH Group

Lines 353-360 "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) - (-2.42)) in the HR group vs -2.23(IQR: (-4.07) - (-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 – (-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)"

.

c. Discussion section: in the discussion, certain statements are similar to what is mentioned in the methods. Please remover these lines from the discussion and focus

on the main results, historical literature, limitations, and further clinical/research perspectives.
Author reply c: We have modified discussion to include historical literature, and limitations.

Comment 5: Lines 153-155: the surgical categorization only includes three categories in contrast to the A-D categorization.

Reply 5: We have included all four defect types
Changes in the text: Line 145-151 " '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."

Comment 6: Line 160: please add the definition used to categorize pulmonary hypertension.
Reply 6: We did not categorize pulmonary hypertension in this study, our purpose was to highlight the prevalence of pulmonary hypertension in the CDH patient population at discharge by defect size and persistence at the most recent follow-up.

Comment 7: Lines 163-165: could the authors add the number of cases per exclusion criteria or add this to the flowchart?

Reply 7: Unfortunately, we did not collect that data on participants not included in the study, although we understand it may have helped to understand outcomes in the CDH population with additional pulmonary morbidity.

Comment 8: Line 173: why did the authors choose to include 'all-cause' rehospitalisation? Could it be that infants with larger defects are at higher risk for rehospitalisation due to for example gastro-intestinal, neurological, or re-CDH problems, thereby biasing the results? This outcome would be stronger if only including pulmonary reasons for readmission.

Reply 8: We believe the CDH population is a high-risk medically complex pediatric population with high rates of complications, irrespective of defect size leading to increased hospitalizations irrespective of defect size, and cause of re-hospitalization.

Comment 9: Line 202: change reference 22 to right format.

Reply 9: We have corrected this mistake.

Comment 10: Line 208-further: please use either Ax or AX as abbreviation. Also, please consistently use abbreviations in the manuscript after having mentioned the abbreviation (e.g. line 347).

Reply 10: We have eliminated the abbreviation for the area of reactance in the manuscript as the following.
Changes in the text: Lines 223-226 "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 5Hz and Fres. Patients with asthma have increased R5Hz and Fres, while the X5Hz is more negative (28, 29)"

Comment 11: Line 230: 'increased sensitivity' in comparison to what? IOS has increased sensitivity in comparison to spirometry".

Reply 11: Yes, we have added it to the manuscript (discussion section).
Changes in the text: Lines 388-390 "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"

Comment 12: Line 297: p-value 0.042 does not correspond to p<0.001 in table 2.

Reply 12: We have modified the tables and data in order to collect more variables. Please refer to new tables.

Comment 13: Results: please report LR vs HR ór HR vs LR in text.

Reply 13: We have modified the results based on suggestions.
Changes in the text: Lines 281-288 "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)"

Comment 14: Line 306: number of readmissions cannot be expressed as percentage. Please correct this and make sure that methods and results correspond ('number of days of rehospitalization' vs 'number of hospitalizations'). The same for: ED (table) vs ER (text) as abbreviations for emergency room.

Reply 14: Agree, we have modified our results section.
Changes in the text: Lines 299-300 “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)”

Comment 15: Line 323: what is evaluated with the mentioned p-value? We have eliminated that analysis in our current version of the manuscript and have not looked into the association of pulmonary hypertension and asthma with ER visits
Line 324: table 5 should be referenced in this paragraph.

Reply 15: We have modified the tables and data in order to collect more variables. Please refer to new tables.

Comment 16: Line 347-351: multiple p-values <0.05, hence not similar? Line 371: the name for the CDH clinic is not consistent in the manuscript, please use one name for increased readability.
Reply 16: We agree it is a mistake, we have changed the comprehensive CDH clinic to a” comprehensive multidisciplinary CDH clinic” and this change is consistent throughout the manuscript.

Comment 17: Line 385: factors OF pulmonary morbidities.
Reply 17: We have modified the discussion and eliminated that para as it refers to basic physiology.

Comment 18: Line 403: please mention in which subgroup of CDH infants the percentages are reported

Reply 18: We have modified the discussion section, please refer to the discussion in the current version of the manuscript.

Comment 19: Line 424: only one reference while ‘studies’ are mentioned.

Reply 19: We have modified the discussion section, please refer to the discussion in the current version of the manuscript.

Reviewer G
Comment 1: Was the cohort just newborns or neonates with Bochdalek CDH? I assume yes but not stated.

Reply 1: Yes, the cohort was neonates with Bochdalek CDH. We have modified the draft to reflect these changes.

Changes in the text: Line 133-135. “Patients with Bochdalek CDH hernia (n=133) were seen between 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”

Comment 2: The authors never define HR and LR which I assume mean high risk and low risk. Please add to abstract and manuscript.

Reply 2: Agree, this is a mistake. We have made changes in the revised manuscript.
Changes in the text: Lines 48-49 “CDH patients were stratified according to CDHSG stage, and then categorized as low risk (LR), defect size A and B, or high risk (HR), defect size C and D”
Line 120-21. “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 (Fig. 1)”.

Comment 3: Line 59. Please clarify the pHTN as virtually all have pHTN at birth. Is this defined as at index hospital DC? If so, how is it defined? ECHO concern, or on treatment with sildenafil, oxygen etc. Please adjust the analogous sections in the paper to match your definition.

Reply 3: For the purpose of this study, we included infants with pulmonary hypertension at discharge; however, in the revised manuscript in order to better define pulmonary hypertension and not solely rely on echocardiogram findings we have included patients with echocardiogram findings indicative of pulmonary hypertension and warranting treatment for pulmonary hypertension (O2, sildenafil and/or bosentan)
Changes in the text: Lines 167-171 “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 O2, sildenafil, and/or bosentan were included

Comment 4: I am not confident that ave length of readmission and ER visits are pertinent to pulmonary morbidity only. Did you count readmission for elective operations, or just count admissions for pulmonary morbidities, such as infections, etc. The latter would be more instructive.

Reply 4: We understand that collecting data on an average length of readmission and ER visits secondary to pulmonary morbidity would be helpful, but we believe the CDH population is a high-risk medically complex pediatric population with high rates of complications, leading to increased hospitalizations irrespective of the causes of re-hospitalizations.

Comment 5: Please include use of oxygen at DC and subsequent clinic visits as a metric of pulmonary morbidity.

Reply 5: We have added both variables (oxygen at DC) in the revised manuscript; however, we did not collect data on oxygen dependency on subsequent visits.

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 (%) Vent, n (%) Nasal cannula, n (%) Room air, n (%)	 18 (14) 3 (2) 15 (11) 115 (87)	 2 (3) 0 (0) 2 (3) 77 (97)	 16 (30) 3 (6) 13 (24) 38 (70)	 <0.001*
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*

ECLS = extracorporeal life support, IQR = interquartile range

Comment 6: The diagnosis of asthma (line 72) is challenging in this cohort and seems to be from testing IOS then later spirometry. Is the dx also used when on inhalers, etc.

Reply 6: Asthma diagnosis was made based on a screening asthma questionnaire in CDH patients who were not followed at the CDH comprehensive clinic. Pulmonary function testing was done for patients who were followed at the CDH clinic and met the eligibility criteria for spirometry and IOS i.e., age, ability to perform maneuvers and follow commands. Asthma diagnosis for patients followed at clinic who were unable to undergo spirometry and IOS due to factors such as age, unable to follow commands, and maneuvers required for pulmonary function testing, unacceptable test as per ATS guideliens was based on a screening asthma questionnaire alongside pulmonologist assessment. Patients seen at the clinic were started on inhalers after assessment in the clinic (Pulmonologist and pulmonary function test), and were not on inhalers at time of pulmonary function test collection.

Comment 7: IOS is not commonly used and many readers (including this reviewer) are unfamiliar with its use. I would keep your high-level overview of the testing; tell the reader at what age it is validated (? infants), and how it complements later spirometry

testing which is not typically initiated until "compliance" with testing is age-appropriate, typically around age 5.

Reply 7: We have made changes in the manuscript to reflect these changes.
Changes in the text: Lines 216-226 “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)"”.

Comment 8: Line 78. PHTN at DC? See above question.
Reply 8: Yes

Comment 9: Line 123. How are you defining ventilator lung injury in the contemporary "gentle ventilation" era?

Reply 9: We believe that despite “gentle ventilation” small residual lung injury remains secondary to prolonged ventilation due to areas of over and underinflated aeration in settings of arrested early lung growth

Comment 10: Line 127. Mortality not part of this study. Would either clarify if mortality in your cohort, or eliminate.

Reply 10: We have eliminated mortality as we agree it is not a focus of our study

Comment 11: Line 145/157. Fig1a is not referenced in the text of article. Same for 1b. Please adjust.

Reply 11: We agree it is a mistake, we have adjusted the figure to match the text in the body of the manuscript
Changes in the text: Lines 120-121 “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 (Fig. 1)”.

Comment 12: Line 164-166. Regarding inclusion criteria: How many had those conditions at DC? Fascinating as these are rare. How did you define CLD, and why use

it as an exclusion criteria when the premise of your findings suggest most survivors have pulmonary impact.

Reply 12: We have revised our manuscript to include infants with oxygen at discharge but not specifically looked at the age at the time of discharge with reference to gestational age and oxygen dependency.

Comment 13: Why exclude premiees as they are few overall, and tend to have less pHTN. I would include them unless very compelling reason as would be instructive.

Reply 13: Our study population had median gestation age in weeks 38 (37-39)

Comment 14: Line 176. Seems that PFT/IOS were not done in all pts? How is testing chosen if not for all? Patient seen in clinic Eligibility criteria, CDH criteria
Reply 14: Asthma diagnosis was made based on a screening asthma questionnaire in CDH patients who were not followed at the CDH comprehensive clinic. Pulmonary function testing was done for patients who were followed at the CDH clinic and met the eligibility criteria for spirometry and IOS i.e., age, ability to perform maneuvers and follow commands. Asthma diagnosis for patients followed at the clinic who were unable to undergo spirometry and IOS due to factors such as age, unable to follow commands, unacceptable test measures by ATS guidelines and maneuvers required for pulmonary function testing was based on the pulmonologist's clinical assessment, considering clinical history, and physical examination findings.

Changes in the text: Line 198-206 "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"

Comment 15: Can IOS can be done at an earlier age than standard PFT's? Yes.
16. Line 208. The section on IOS is very technical and I would greatly tone down and reference another paper if the reader wants more detail.... the average reader gets lost with all of the technical terminology.

Reply 15: The manuscript has been modified to reflect these changes.
Changes in the text: Line 216-226 "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)"

Comment 16: Line 298. It seems in this paragraph you are suggesting a 40% asthma rate at DC? If you mean overall, would eliminate the "following NICU DC" in the subtitle.

Reply 16: This statement refers to the overall prevalence of asthma in CDH survivors following NICU discharge. Our study population is from NICU.
Changes in the text: Lines 291-296 "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."

Comment 17: Again, need clarification that readmissions are relevant to pulm function.

Reply 17: We have included all cause of rehospitalization as we believe the CDH population is a high-risk medically complex pediatric population with high rates of complications, irrespective of defect size leading to increased hospitalizations irrespective of the causes of re-hospitalizations.

Comment 18: If a pulmonologist called pts to determine if they have asthma that were not followed in the clinic? I was confused and would suspect this would require a consent?

Reply 18: Yes, Verbal phone consent was taken, and this was approved by IRB as well.
Changes in the text: Lines 203-206 "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"

Comment 19: How were pts chosen to receive a VQ scan?

Reply 19: VQ scans were done as part of our defect size-based protocol implemented in our Comprehensive multidisciplinary CDH clinic. VQ scan for low risk (defect size A/B) was done at 12 months and 3 years of age. High-risk (defect size C/D) patients had V/Q scans at 12 months, 3, 4, and 5 years of age, depending on findings and clinical presentation.

Comment 20: Line 325. Only 17 of over 100 discharged patients had PFT's. It seems statistical testing was not possible due to the low numbers? How were they chosen and do they reflect the overall population? If 65% were normal this appears to not align with the high prevalence of asthma? Just need more clarity as not sure you can be definitive with reporting on this small number.

Reply 20: Agree, a low number makes statistical analysis difficult. The overall prevalence of asthma was based on a screening asthma questionnaire in CDH patients who were not followed at the CDH comprehensive clinic.

Pulmonary function testing was done for patients (a small proportion of patients) who were followed at the multidisciplinary CDH clinic and met the eligibility criteria for spirometry and IOS i.e., age, ability to perform maneuvers and follow commands.

Asthma diagnosis for patients followed at the clinic who were unable to undergo spirometry and IOS due to factors such as age, unable to follow commands, and maneuvers required for pulmonary function testing was based on history, clinical examination, and pulmonologist assessment.

Comment 21: Lines 340-450. The details on IOS testing are not well known by the average reader, so maybe better to tell us what all the numbers mean and consider a table if important to include.IOS

Reply 21: We have modified the IOS section.
Changes in the text: Lines 216-226 “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)”

Comment 22: Line 364-7. If IOS documents asthma in a relatively high number, but not correlated on spirometry, what are the clinical implications? Are these kids on meds, and is this IOS testing clinically relevant?

Reply 22: We believe that IOS can detect subtle changes in lung function and can perhaps lead to earlier detection of asthma in at-risk young populations as it is not effort dependent and does not require patient cooperation.
Changes in the text: Lines 402-415 “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)”

Comment 23: Line 431. I suggest that health care utilization was not studied with enough granularity to make significant conclusions; this is also perhaps your conclusion as this paragraph is not too instuctive. Please consider a deeper dive into pulmonary readmissions or eliminate.

Reply 23: Our purpose was to highlight the higher risk number of readmission in the CDH patient population by defect size. We believe medically complex high-risk patient population with an increased number of rehospitalizations irrespective of defect size

Comment 24: Table 1. It would appear no one in the cohort is older than 8 years? Would consider putting that into the text as kids would only be eligible for standard PFT's after age 5ish or so. Consider telling us the % of eligible patients.

Reply 24: We recorded the age for the first encounter at the time of collection of data which was not indicative of the actual date of the pulmonary function test.

Comment 25: Table 2. pHTN at DC? Not sure this table adds much as not the focus of the study and is in the body of the manuscript.

Reply 25: We agree; however, we think it would be helpful to separate baseline characteristics from morbidities as sequelae of CDH.

Comment 26: Table 3. Definition of asthma still is a struggle for me if cohort is this young. Based on IOS? Table 5 seeks to address this, but i am mystified by the great disparity in prevalence on IOS vs. PFT testing. I see this a major concern I need help understanding.

Reply 26: Asthma diagnosis in younger patients not eligible for pulmonary function tests was based on the pulmonologist's clinical assessment, considering clinical history, and physical examination findings for patients seen in the clinic. For patients not seen in the clinic, asthma diagnosis was based on the validated asthma screening questionnaire over the phone after verbal consent. IOS was done on a limited number of patients in clinic who were able to follow commands and were over 3 years of age.