


Observed/Expected Lung-To-Head Ratio and Total Lung Volumes That Identify Fetuses With Severe Congenital Diaphragmatic Hernia in a North American Fetal Center

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ABSTRACT

Objective: To define the ultrasound observed/expected lung-to-head ratio (O/E LHR) and magnetic resonance imaging (MRI) observed/expected total lung volume (O/E TLV) cut-offs associated with survival and lack of extracorporeal membrane oxygenation (ECMO) utilization to determine the most severe cohort that may benefit from fetal intervention.

Methods: Retrospective review of patients with a prenatal diagnosis of isolated left or right congenital diaphragmatic hernia (L CDH, R CDH) seen and delivered at our level III fetal center from January 2013–July 2023. Data were extracted from our clinical outcome database. Characteristics of survivors and non-survivors were compared for both the L CDH and R CDH groups. For both O/E LHR and O/E TLV, the Youden criteria were then used to determine a good sensitivity and specificity for predicting survival and ECMO utilization for L and R CDH, respectively, in Receiver Operator Characteristic (ROC) curve analysis.

Results: 340 patients were included in the study, including 283 (83.2%) with L CDH and 57 (16.8%) with R CDH. The median [interquartile range, IQR] O/E LHR for L and R CDH was 37.9 [28.7–47.3] and 49.0 [40.0–64.5], respectively. The median O/E TLV for L and R CDH was 36.0 [28.0–48.0] and 25.3 [23.6–29.8], respectively. For survival, an O/E LHR of 28.1% and O/E TLV of 34.0% and an O/E LHR of 46.8% and O/E TLV of 17.6% were the best cut-offs for L and R CDH, respectively. For ECMO utilization, an O/E LHR of 32.8% and O/E TLV of 35.3% and an O/E LHR of 47.0% and O/E TLV of 22.0% were the best cut-offs for L and R CDH, respectively.

Conclusion: We report the best ultrasound O/E LHR and MRI TLV cut-offs associated with survival and lack of ECMO utilization in our cohort.

1 | Introduction

Congenital diaphragmatic hernia (CDH) causes significant morbidity and mortality due to pulmonary hypoplasia,

pulmonary hypertension, and cardiac dysfunction [1]. Neonatal survival varies greatly among geographic location and center [2]. Since 22%–58% of cases occur with associated anomalies or genetic syndromes, the first determinant for survival is whether

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Summary

- What's already known about this topic?
 - Fetal endoluminal tracheal occlusion (FETO) improves survival and morbidity in a certain cohort of fetuses with severe congenital diaphragmatic hernia (CDH).
 - The TOTAL trial reported a survival benefit in fetuses that had FETO with left CDH and an observed/expected lung-to-head ratio (O/E LHR) < 25%, but the survival of both the FETO and expectantly managed cohorts was low compared to expectantly managed neonates in North American centers.
 - The cut-off to define fetuses with the most severe right CDH is unclear with previous studies suggesting an O/E LHR of < 45–65% be used to define the cohort that may benefit from fetal intervention.
- What does this study add?
 - Our data support using an O/E LHR cut-off of < 28.1–32.8% for L CDH and < 46.8–47.0% for R CDH to define the most severe groups that may benefit from fetal intervention in a North American center.
 - Our data also support using an MRI O/E TLV cut-off of < 32.8–34.0% for L CDH and < 17.6–22.0% for R CDH to define a similarly severe cohort by MRI.

the CDH is isolated/non-syndromic versus complex/syndromic [3–5]. When isolated, the next determinant of outcome is the size of the lungs and the position of the liver with worse outcomes in infants with small lungs and liver herniation.

Prenatal diagnosis allows for prognostication and preparation for delivery, and importantly, also provides a window for fetal intervention. Fetal lung size can be estimated by ultrasound using the lung-to-head ratio (LHR) and/or by magnetic resonance imaging (MRI) using total lung volumes (TLV) [6]. To account for gestational age at measurement, observed/expected LHR and TLV are used and have been correlated with neonatal outcomes including survival and respiratory morbidities [7, 8]. Several studies have demonstrated the usefulness of MRI in predicting CDH pulmonary and survival outcomes, but this usefulness is limited by a lack of availability in some centers [6, 9, 10].

The tracheal occlusion to accelerate lung growth (TOTAL) trial, a randomized controlled trial comparing fetuses with left CDH (L CDH) that underwent fetal endoscopic tracheal occlusion (FETO) to those that were expectantly managed, showed a decrease in mortality with FETO in fetuses with a severe L CDH but not in those with a moderate L CDH [11, 12]. Severe L CDH was defined as fetuses with O/E LHR less than 25% while moderate L CDH was defined as those with an O/E LHR between 25% and 34.9% irrespective of liver position or 35%–44.9% with liver herniation. Post hoc analysis of pooled data suggested that FETO increased survival in both the moderate and severe groups and the authors hypothesized that the lack of statistically significant survival benefit in the moderate arm may be due to later balloon insertion in this cohort [13]. Additionally, follow-up studies demonstrated that despite comparable survival, there is a benefit of FETO on respiratory outcomes and

resolution of pulmonary hypertension in the moderate group [14, 15].

A criticism of the TOTAL trial is that the survival of 15% with expectant care and 40% with FETO is much lower than the survival rate among patients with severe L CDH expectantly managed in many high-volume centers, particularly in North America [2]. Subsequent studies have shown that populations with higher baseline survival may not have a survival benefit from FETO, but may have a decrease in respiratory morbidities, including decreased extracorporeal membrane oxygenation (ECMO) utilization and decreased persistent pulmonary hypertension [16, 17]. Furthermore, one study suggested that FETO may be associated with an improvement in neurodevelopmental outcomes despite an earlier gestational age at delivery [18].

Although many centers offer FETO for both L and right CDH (R CDH), there is a debate on the cut-off to use for fetuses with the most severe R CDH that would benefit from fetal intervention. R CDH patients are traditionally thought to be more severe than L CDH patients due to liver herniation in virtually all patients. Additionally, there is some evidence that O/E LHR and TLV are less predictive for R CDH than they are for L CDH [19]. Studies from Europe have shown that an O/E LHR cut-off of < 45–50% is the best to predict survival, whereas a study from Latin America reported a cut-off of < 65% [7, 8, 20, 21]. Practically, FETO has been shown to have benefit in fetuses with R CDH and many centers use an LHR O/E cut-off of < 45–50% to identify the cohort that may benefit [20].

The downside of FETO is that it is associated with higher rates of preterm premature rupture of membranes (PPROM) and preterm delivery (PTD) as well as tracheal morbidities [17, 22–25]. It also presents an airway emergency in cases that deliver urgently prior to balloon removal. This necessitates the ability to identify the optimal population to benefit from the intervention to optimize the risk-to-benefit ratio.

Given the differences in survival outcomes in North America and the uncertain cut-off to identify fetuses with the most severe R CDH, we sought to determine the O/E LHR and TLV cut-offs that best differentiated survival and ECMO utilization among fetuses with L and R CDH at our center.

2 | Methods

After institutional review board approval (IRB# 21-018553), we conducted a retrospective cohort study of fetuses prenatally diagnosed with isolated L or R CDH that were followed and delivered at our level III fetal care center between January 2013–July 2023 [26]. Data was extracted from our clinical outcomes database archive (CODA) and included maternal demographic characteristics, pregnancy details, antenatal/delivery course, and postnatal outcomes [27]. Patients with known genetic conditions, perinatal palliative care decision, severe congenital heart disease, bilateral CDH, and those who underwent FETO were excluded.

Ultrasound imaging was performed with Philips EPIQ Elite 7G machines (Philips Medical Systems, Andover, Massachusetts, USA) using 9-2 and 5-1 MHz curvilinear array probes as well as an eL 18-4 MHz linear array probe. A detailed fetal anatomic survey was performed to identify associated abnormalities. Assessment of the fetal thorax then included measurement of the lung contralateral to the side of the hernia in a transverse thoracic image at the level of the cardiac four-chamber view. The LHR and the observed/expected LHR were calculated [21]. When available, the trace method was preferentially used due to its superior reproducibility compared to the anterior/posterior (AP) method [28].

MRI examinations were performed on 1.5- or 3-T scanners and interpreted by pediatric radiologists with subspecialty expertise in fetal imaging. Motion-free fast spin echo T2-weighted or steady-state free precession sequences were used to obtain trace areas of the right and left lungs in either the axial or coronal planes. The sum of the trace areas was multiplied by image slice thickness to obtain the TLV. To calculate the observed/expected TLV, the TLV was divided by the gestational age-based normal lung volume [29, 30].

Pregnancy management occurred in our center and included regular prenatal care, serial growth scans, antenatal testing beginning at 34 weeks, and amnioreduction in cases of symptomatic polyhydramnios. Delivery care and postnatal management were carried out by a multi-disciplinary specialized team with published protocols detailing optimal care for CDH neonates [31–33].

Since we expected L and R CDH to have different risk profiles for survival, we conducted a separate analysis for each group. Continuous demographic and clinical characteristic data were summarized as median [IQR], and categorical data were reported as frequencies. Continuous variables were compared between survivors and non-survivors using the Wilcoxon rank sum test. Similarly, the Chi-squared test was used to evaluate the association between categorical variables and the survival outcome. The ability of the O/E LHR to discriminate between the survivors and non-survivors and the ECMO utilizers and ECMO non-utilizers was assessed by receiver operating curve (ROC) analysis, and the best cut-off was selected by maximizing the Youden criteria. Since the gestational age at ultrasound was hypothesized to affect the O/E LHR and TLV values as well as the outcome, we also assessed the covariate-adjusted ROC curve using the frequentist approach detailed in the ROCnReg package in R. Statistical analysis was performed using R version 4.4.0 on Rstudio 2024.04.0 (Vienna, Austria). Results were considered statistically significant for p -values less than 0.05.

3 | Results

A total of 340 patients, including 283 (83.2%) with L CDH and 57 (16.8%) with R CDH, met the inclusion criteria for the study. Of the complete cohort, 188 (55.3%) had O/E LHR calculated using the trace method, 130 (38.2%) had O/E LHR calculated using the AP method, and 22 (6.5%) were missing O/E LHR data. The median [IQR] GA at calculation of O/E LHR was 24.1

[22.1–27.9] weeks. Two hundred eighty-six patients (84.1%) had MRI in addition to ultrasound. The median GA for the calculation of MRI O/E TLV was 24.2 [22.2–27.9] weeks.

Comparison of prenatal, delivery, and outcome characteristics between survivors and non-survivors with L and R CDH are detailed in Tables 1 and 2. For L CDH, non-survivors were more likely to be non-white race, have liver and stomach herniation, and have lower O/E LHR and O/E TLV. Survivors were less likely to have amnioreduction compared with non-survivors and delivered at a later GA with larger birthweight and younger age at CDH repair. They had longer neonatal intensive care unit (NICU) length of stay because the non-survivors did not survive long enough for prolonged NICU care. ECMO use was higher in the non-survivor group. For R CDH, there was no difference in demographics, pregnancy, and outcome characteristics between survivors and non-survivors except that survivors delivered at a slightly later GA and had longer NICU length of stay, again because many non-survivors did not survive long enough for prolonged NICU care. Of note, the median GA in weeks at calculation of O/E LHR for L and R CDH was lower in the non-survivors compared to survivors (L CDH: 22.8 [21.0–25.7] vs. 23.8 [22.1–28.3], $p = 0.005$; R CDH: 21.9 [21.5–25.5] vs. 25.7 [23.8–30.4], $p = 0.02$).

For L CDH, the median O/E LHR was 38.5 [30.7–48.1] for survivors compared to 30.0 [25.1–43.1] for non-survivors ($p = 0.002$). For R CDH, the median O/E LHR was 51.9 [42.0–67.0] for survivors compared to 42.6 [33.8–52.3] for non-survivors ($p = 0.206$). O/E LHR values of 28.1% and 46.8% were estimated as the best cut-offs to classify survivors and non-survivors for L and R CDH, respectively. For left CDH, 181 (88%) of fetuses with O/E LHR $\geq 28\%$ survived compared with 38 (67%) fetuses with O/E LHR $< 28\%$ (Table 3). For right CDH, 26 (90%) fetuses with O/E LHR $\geq 47\%$ survived compared with 19 (73%) fetuses with O/E LHR $< 47\%$ (Table 4). The area under the ROC curve (AUC) for L CDH was 0.65, with sensitivity and specificity of 0.82 and 0.45. For R CDH, the AUC was 0.63, with sensitivity and specificity of 0.60 and 0.70 (Figure 1). The AUC from covariate-adjusted (adjusted for GA at O/E LHR measurement) ROC curves for L and R CDH to discriminate between survivors and non-survivors were 0.66 and 0.69, respectively.

Similarly, O/E LHR values of 32.8% and 47.0% were estimated as the best cut-offs to discriminate ECMO utilization in L and R CDHs, respectively. The AUC for L CDH was 0.71, with sensitivity and specificity of 0.76 and 0.62. For R CDH, the AUC was 0.79, with sensitivity and specificity of 0.71 and 0.75 (Figure 2). The AUC from covariate-adjusted (adjusted for GA at O/E LHR measurement) ROC curves for L and R CDH to discriminate between ECMO utilization and non-utilization were 0.65 and 0.78, respectively.

The median MRI O/E TLV for L CDH was 37.0 [29.1–49.5] for survivors compared to 28.0 [22.0–34.7] for non-survivors ($p < 0.001$). For R CDH, the median MRI O/E TLV was 24.6 [19.4–33.5] for survivors compared to 23.7 [17.0–30.6] for non-survivors ($p = 0.928$). O/E TLV values of 34.0% and 17.6% were estimated as the best cut-offs to discriminate survival for L and R CDH, respectively. The AUC for L CDH was 0.70, with

TABLE 1 | Comparison of demographic, pregnancy and outcome factors in survivors versus non-survivors with left CDH.

	Survivors <i>n</i> = 239	Non-survivors <i>n</i> = 44	<i>p</i>-value
Maternal age	31.4 [27.4–34.5]	31.4 [25.6–37.1]	0.989
Maternal Race			0.001
White	157 (65.7%)	20 (45.5%)	
Black	17 (7.1%)	7 (15.9%)	
Asian/Indian/Hawaiian/PI	18 (7.5%)	0	
Multiracial/other	47 (19.7%)	17 (38.6%)	
Maternal ethnicity			> 0.990
Not Hispanic	198 (82.8%)	36 (81.8%)	
Hispanic	41 (17.2%)	7 (15.9%)	
Missing	0	1 (2.3%)	
Parity			0.960
Nulliparous	114 (47.7%)	20 (45.5%)	
1	77 (32.2%)	15 (34.1%)	
2+	48 (20.1%)	9 (20.5%)	
Liver herniation			< 0.001
No	119 (49.8%)	4 (9.1%)	
Yes	120 (50.2%)	40 (90.9%)	
Stomach herniation			0.006
No	66 (27.6%)	3 (6.8%)	
Yes	173 (72.4%)	41 (93.2%)	
GA at O/E LHR			
Median [IQR]	23.8 [22.1–28.3]	22.8 [21.0–25.7]	0.005
O/E LHR			
Median [IQR]	38.5 [30.7–48.1]	30.0 [25.1–43.1]	0.002
Missing	20 (8.4%)	0	
GA at O/E TLV			
Median [IQR]	23.9 [22.2–28.1]	23.5 [21.9–26.5]	0.079
O/E TLV			
Median [IQR]	37.0 [29.1–49.5]	28.0 [22.0–34.7]	< 0.001
Missing	20 (8.4%)	6 (13.6%)	
Polyhydramnios	139 (58.2%)	28 (63.6%)	0.609
Amnioreduction	6 (2.5%)	5 (11.4%)	0.016
Male/female ratio	1.63	0.83	0.060
Gestational age at delivery			
Median [IQR]	39.1 [38.0–39.5]	38.2 [35.8–39.2]	< 0.001
Birthweight			
Median [IQR]	3110 [2780–3420]	2800 [2420–3280]	0.001
Missing	3 (1.3%)	1 (2.3%)	
ECMO utilization	40 (16.7%)	31 (70.5%)	< 0.001
Neonatal age at CDH repair (weeks)			
Median	1.5 [0.7–2.6]	3.6 [2.1–4.9]	0.001
Missing	0	22 (50%)	
NICU length of stay (days)	58.0 [33.0–95.0]	24.0 [4.8–60.8]	< 0.001

(Continues)

TABLE 1 | (Continued)

	Survivors <i>n</i> = 239	Non-survivors <i>n</i> = 44	<i>p</i>-value
Ventilatory support (days)	23.0 [14.0–40.0]	23.0 [8.0–53.0]	0.964
Pulmonary hypertension medications at discharge	37 (15.5%)	b	a
Missing	1 (0.4%)		

^aAnalysis not possible.

^bNo values as all deceased.

TABLE 2 | Comparison of demographic, pregnancy and outcome factors in survivors versus non-survivors with right CDH.

	Survivors <i>n</i> = 46	Non-survivors <i>n</i> = 11	<i>p</i>-value
Maternal age	28.8 [23.8–35.1]	31.5 [26.8–36.6]	0.298
Maternal Race			0.083
White	30 (65.2%)	11 (100%)	
Black	3 (6.5%)	0	
Asian/Indian/Hawaiian/PI	0	0	
Multiracial/other	12 (26.15)	0	
Missing	1 (2.2%)	0	
Maternal ethnicity			> 0.990
Not Hispanic	37 (80.4%)	9 (81.8%)	
Hispanic	8 (17.4%)	2 (18.2%)	
Missing	1 (2.2%)	0	
Parity			0.894
Nulliparous	28 (60.9%)	7 (63.6%)	
1	12 (26.1%)	2 (18.2%)	
2+	6 (13.0%)	2 (18.2%)	
Liver herniation			> 0.990
No	1 (2.2%)	0	
Yes	45 (97.8%)	11 (100%)	
Stomach herniation			a
No	45 (97.8%)	11 (100%)	
Yes	0	0	
Missing	1 (2.2%)	0	
GA at O/E LHR			
Median [IQR]	25.7 [23.8–30.4]	21.9 [21.5–25.5]	0.020
O/E LHR			
Median [IQR]	51.9 [42.0–67.0]	42.6 [33.8–52.3]	0.206
Missing	1 (2.2%)	1 (9.1%)	
GA at O/E TLV			
Median [IQR]	26.2 [24.1–29.9]	23.7 [22.0–25.4]	0.150
O/E TLV			
Median [IQR]	24.6 [19.4–33.5]	23.7 [17.0–30.6]	0.928
Missing	6 (13.0%)	2 (18.2%)	
Polyhydramnios	29 (63%)	8 (72.7%)	0.730
Amnioreduction	3 (6.5%)	0	> 0.990
Male/female ratio	1.1	1.2	> 0.990

(Continues)

TABLE 2 | (Continued)

	Survivors <i>n</i> = 46	Non-survivors <i>n</i> = 11	<i>p</i> -value
Gestational age at delivery			
Median [IQR]	39.0 [38.3–39.4]	38.1 [37.5–39.0]	0.039
Birthweight			0.706
Median [IQR]	3170 [2920–3360]	3320 [2700–3480]	
ECMO utilization	17 (37.0%)	7 (63.3%)	0.173
Neonatal age at CDH repair (weeks)			
Median	1.6 [1.1–2.7]	2.8 [0.6–3.6]	0.727
Missing	0	6 (54.5%)	
NICU length of stay (days)	69.0 [48.0–113.0]	21.0 [4.8–34.2]	< 0.001
Ventilatory support (days)			
Median	31.0 [21.0–37.0]	21.0 [4.75–34.3]	0.176
Missing	0	1 (9.1%)	
Pulmonary hypertension medications at discharge	10 (21.7%)	b	a

^aAnalysis not possible.

^bNo values as all deceased.

TABLE 3 | Survival in fetuses with left CDH based on LHR O/E categories.

	<i>n</i>	Survivors (<i>n</i> (%))
LHR O/E categories		
O/E ≥ 25	229	196 (86%)
O/E < 25	34	23 (68%)
LHR O/E categories		
O/E ≥ 28	206	181 (88%)
O/E < 28	57	38 (67%)
LHR O/E categories		
O/E ≥ 30	190	168 (88%)
O/E < 30	73	51 (70%)

Abbreviations: LHR = lung head ratio; O/E = observed/expected.

TABLE 4 | Survival in fetuses with right CDH based on LHR O/E categories.

	<i>n</i>	Survivors (<i>n</i> (%))
LHR O/E categories		
O/E ≥ 45	31	27 (87%)
O/E < 45	24	18 (75%)
LHR O/E categories		
O/E ≥ 47	29	26 (90%)
O/E < 47	26	19 (73%)

Abbreviations: LHR = lung head ratio; O/E = observed/expected.

sensitivity and specificity of 0.63 and 0.74. For R CDH, the AUC was 0.51, with sensitivity and specificity of 0.80 and 0.33 (Figure 3). The AUC from covariate-adjusted (adjusted for GA at O/E TLV measurement) ROC curves for L and R CDH to discriminate between survivors and non-survivors were 0.69 and 0.40, respectively.

Similarly, O/E TLV values of 35.7% and 22.0% were estimated as the best cut-offs to discriminate ECMO utilization for L and R CDHs, respectively. The area under the ROC curve for L CDH was 0.71, with sensitivity and specificity of 0.59 and 0.74. For R CDH, the AUC was 0.72, with sensitivity and specificity of 0.81 and 0.59 (Figure 4). The AUC from covariate-adjusted (adjusted for GA at O/E TLV measurement) ROC curves for L and R CDH to discriminate between ECMO utilization and non-utilization were 0.69 and 0.68, respectively.

4 | Discussion

In this study, we define the best ultrasound O/E LHR and MRI O/E TLV cut-offs to discriminate between patients who survived and did not, as well as those who utilized ECMO and did not, in our North American cohort of fetuses with prenatally diagnosed CDH. Our results are useful in determining the group of patients that may most benefit from fetal intervention in similar settings.

For L CDH, our cut-offs for survival and ECMO utilization were < 28.1 and 32.8%, respectively, which are higher than the < 25% cut-off currently used to define the most severe L CDH group [21]. For R CDH, our cut-offs were < 46.8 and 47.0% for survival and ECMO use, respectively, which are similar to those of DeKoninck et al. and Russo et al. who reported cut-offs to define severe right CDH of < 45% and < 50%, respectively [8, 20]. They differ from those of Cruz-Martinez et al. who reported a cut-off of < 65% likely due to lower baseline survival in Latin America [7].

In terms of MRI, our L CDH O/E TLV cut-offs of < 34.0 and < 35.7% for survival and ECMO utilization, respectively, are similar to prior studies that identified an O/E TLV cut-off of < 35% to identify fetuses at highest risk for mortality and chronic lung disease [34, 35]. Our additional finding of cut-offs of < 17.6% and < 22.0% for survival and ECMO utilization, respectively, in R CDH patients is new information given that prior studies did not analyze R CDH patients separately from L CDH

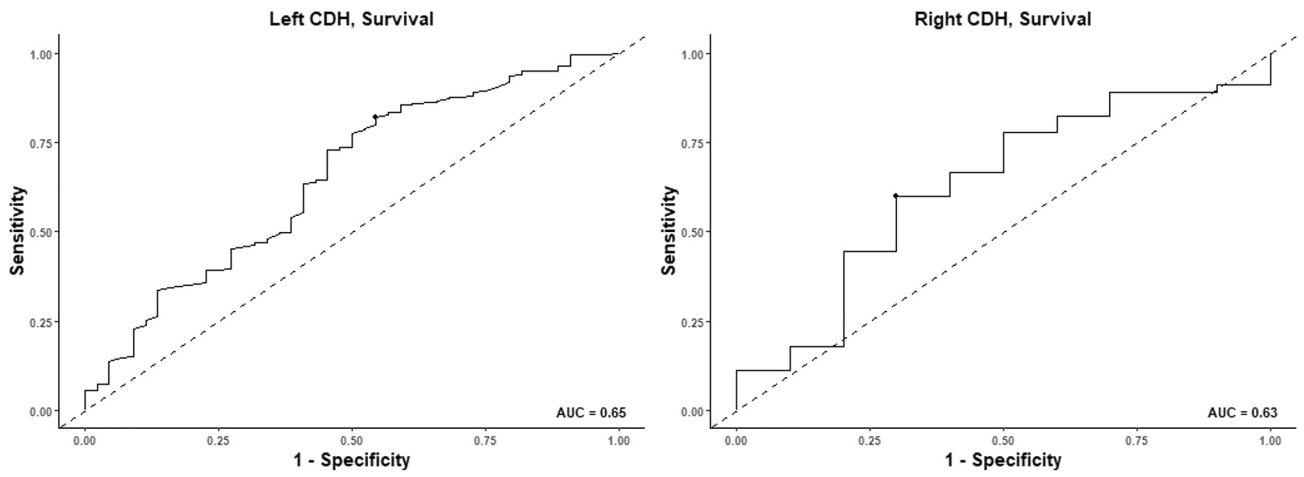


FIGURE 1 | ROC analysis for the observed/expected lung-to-head ratio in the prediction of survival for both left and right CDH. The cut-point for left CDH was 28.1% and for right was 46.8%.

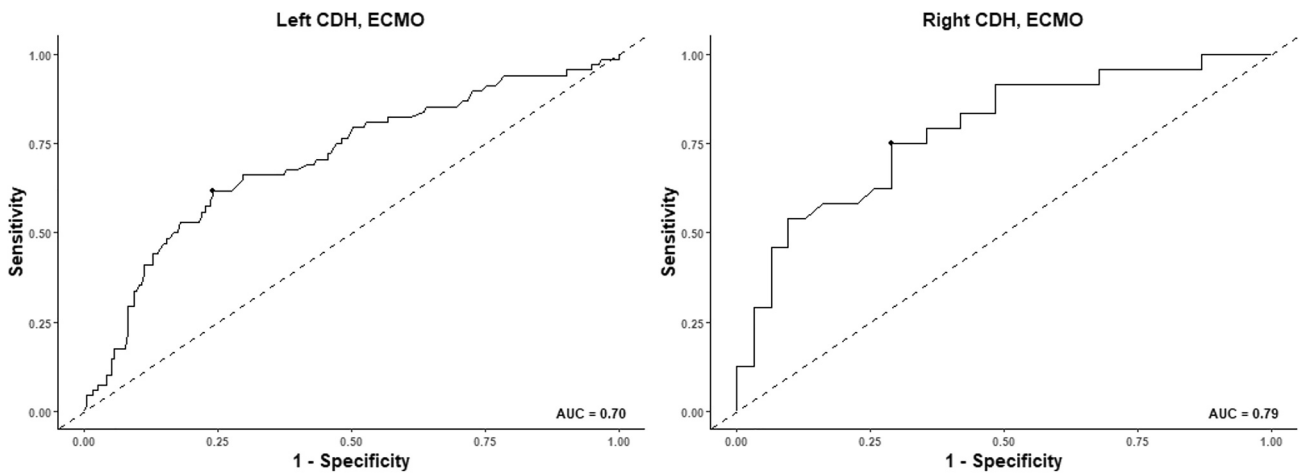


FIGURE 2 | ROC analysis for the observed/expected lung-to-head ratio in the prediction of ECMO use for both left and right CDH. The cut-point for left CDH was 32.8% and for right CDH was 47.0%.

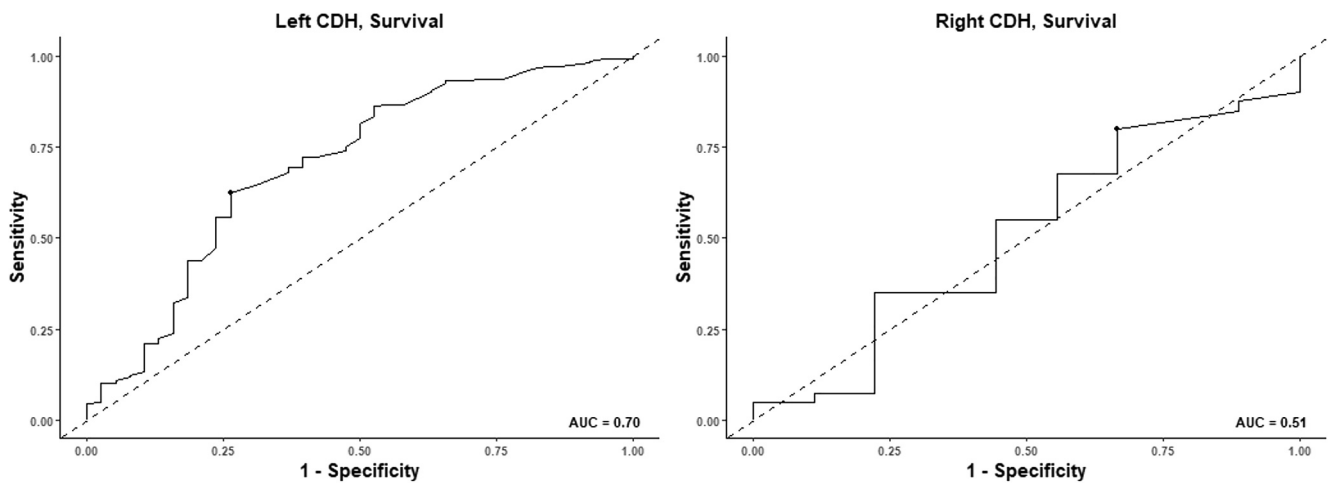


FIGURE 3 | ROC analysis for MRI observed/expected total lung volumes in the prediction of survival for both left and right CDH. The cut-point for left CDH was 34.0% and for right CDH was 17.6%.

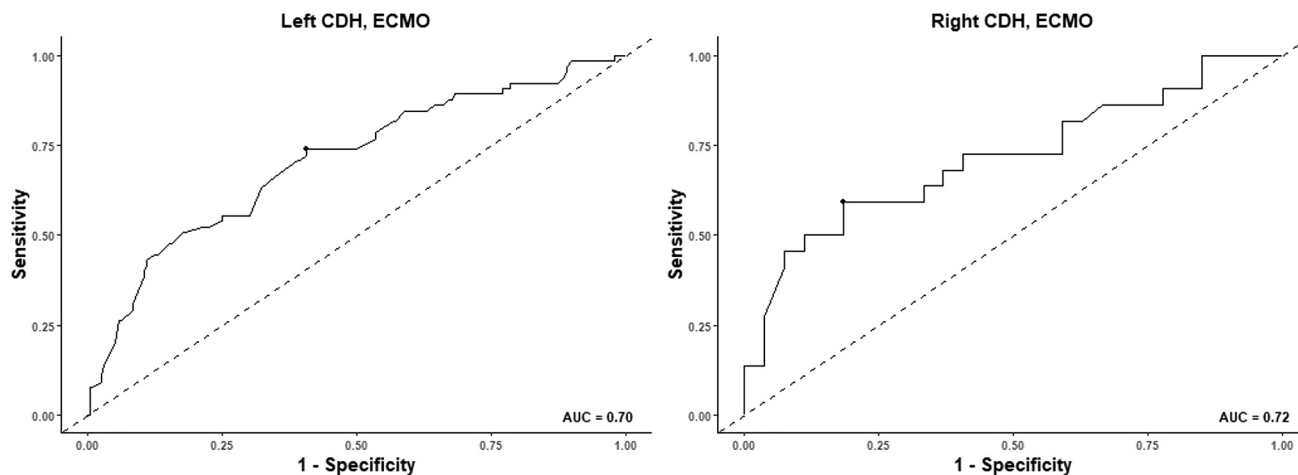


FIGURE 4 | ROC analysis for MRI observed/expected total lung volumes in the prediction of ECMO use for both left and right CDH. The cut-point for left CDH was 35.3% and for right CDH was 22.0%.

ones [9, 10, 34, 35]. These cut-offs are particularly interesting given that the cut-offs to define severe R CDH by O/E LHR are higher than those for L CDH, while the O/E TLV that define severe R CDH are much lower.

Notably, neither O/E LHR nor O/E TLV were highly sensitive or specific, suggesting that defining the highest risk group for both death and ECMO utilization may require a combination of factors. In larger cohorts, adding factors such as stomach position/volume (distension), percent liver herniation, and/or novel MRI lung measurements may improve the ability to predict morbidities and mortality [34, 36–38]. Similar to the findings of Jani et al, MRI O/E TLV did not appear superior in predicting survival compared with ultrasound LHR O/E in our cohort [10]. We therefore focused on the ultrasound parameters since these are more widely available.

It must be noted that given the higher baseline survival in our population, FETO may not improve survival but may improve morbidities. Morbidities have a large impact on quality of life; therefore, this is also an important outcome. Additionally, adoption of the smart balloon for tracheal occlusion will likely decrease some of the risks associated with FETO by eliminating the need for a second fetal surgical procedure for balloon removal and decreasing the chance of an urgent delivery with an inflated balloon [39, 40]. It will also, and perhaps most importantly, ameliorate the logistical challenges related to providing 24 h per day 7 days per week availability of staff to remove the balloon. This may further shift the risk-benefit ratio to performing FETO not only to improve survival, but also to decrease morbidities, such as those incurred with ECMO use.

Although the strength of our study is the relatively large cohort from one North American level III fetal center, the study is not without limitations. One limitation is that given the retrospective nature, the O/E LHR and TLV measurements were taken based on when the patients presented and not at a pre-determined gestational age. This could limit the overall sensitivity and specificity of the measurements by including measurements at gestational ages which are likely to be less predictive of outcomes [41]. For this reason, we adjusted the analysis for gestational age at O/E LHR measurement with similar results in the adjusted and non-adjusted analyses.

Additionally, because of the retrospective nature of the study, only 55% of patients had LHR measured using the preferred trace method, while the others had LHR calculated using the AP method [28, 42]. If all patients had the tracing method, the sensitivity and specificity of O/E LHR may have been higher, but we did not perform this analysis because it would have excluded a large portion of our cohort. A third limitation is that although our cohort for R CDH is relatively large, the numbers remain small compared to L CDH and therefore limit interpretation. Finally, the decision of whether to go on ECMO is a complex one even in a single center, which limits our analysis but also highlights the importance of delivery in a center with an expert postnatal team that specializes in CDH [31, 43, 44].

Despite these limitations, we believe that our data are important in guiding which groups might most benefit from fetal intervention in North American centers. Our results support the use of an O/E LHR cut-off of < 28.1–32.8% for L CDH and < 46.8–47.0% for R CDH to define the more severe population that is likely to most benefit from FETO to improve survival and decrease ECMO utilization. Our results show that the MRI O/E TLV can support ultrasound findings when available but may not greatly improve discriminatory performance at this point. We encourage ongoing research in this area as well as consideration of both parameters when there are large discrepancies between what would be expected.

5 | Conclusion

Our data supports the use of an ultrasound O/E LHR of < 28.1–32.8% for L CDH and < 46.8–47.0% for R CDH to define the population with the most severe CDH that may benefit from fetal intervention in our North American cohort. MRI O/E TLV can be used as an adjunct, but more studies are needed to fully determine its role.

Acknowledgments

The authors have nothing to report.

Ethics Statement

The study was reviewed and approved by the Children's Hospital of Philadelphia Institutional Review Board, IRB#21-018553. The study was deemed exempt from the patient consent process due to the retrospective nature of the data collection and review. The research complies with the guidelines for human studies and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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