Thieme

Measurements of Lung Size in Ultrasound and Magnetic Resonance Imaging in Congenital Diaphragmatic Hernia – A Comparison of Prenatal Imaging Techniques

Messung der Lungengröße mittels Ultraschall und Magnetresonanztomografie bei Kindern mit kongenitaler Zwerchfellhernie – ein Vergleich pränataler Bildgebungstechniken

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Keywords

Congenital diaphragmatic hernia, Prenatal diagnostics, Fetal magnetic resonance imaging

received 30.5.2024
accepted after revision 17.10.2024
published online 2025

Bibliography

Ultraschall in Med
DOI 10.1055/a-2525-6117
ISSN 0172-4614

Georg Thieme Verlag KG, Oswald-Hesse-Straße 50, 70469 Stuttgart, Germany

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Supplementary Material is available at https://doi.org/10.1055/a-2525-6117.

ABSTRACT

Purpose To investigate the correlation between different prenatal imaging techniques in congenital diaphragmatic hernia (CDH) and their prognostic value.

Materials and Methods 209 fetuses with CDH were enrolled in this retrospective cohort study. The prenatal ultrasound-based and MRI-based (MRI: magnetic resonance imaging) observed-to-expected lung-to-head ratio (o/e-LHR) and MRI-based relative fetal lung volume (rFLV) were evaluated and compared. Their prediction component with respect to clinical outcome was evaluated. Mean values were compared by two-sample t-tests or the Mann-Whitney U-test. The Chi-square or Fisher's exact test was used in order to compare qualitative parameters. Kappa coefficients, McNemar test, and Bowker's test were used to assess the degree of agreement.

Results The study population included 183 fetuses with left-sided and 26 fetuses with right-sided CDH. Survival did not differ significantly (74.3 % vs. 80.8 %, p = 0.053). For every imaging technique, incidences of extracorporeal membrane oxygenation (ECMO) and chronic lung disease decreased, and the probability of survival increased gradually reaching minima and maxima for o/e-LHR and rFLV above 35 %. Outcome improved if rFLV was above 35 % – compared to MRI-based measurement of o/e-LHR above 35 %.

Conclusion Our data confirm the predictive value of o/e-LHR for CDH – irrespective of the diagnostic modality. MRI evaluation of o/e-LHR was not superior compared to sonography. MRI evaluation of rFLV correlated with morbidity and mortality which can be beneficial for fetuses with an otherwise good prognosis based on higher o/e-LHR as 2 D imaging techniques can underestimate the fetuses' risk for pulmonary hypertension and ECMO.

ZUSAMMENFASSUNG

Ziel Die Korrelation unterschiedlicher pränataler Bildgebungsverfahren bei kongenitaler Zwerchfellhernie (CDH) zu untersuchen und einen Vergleich ihrer prognostischen Vorhersagekraft durchzuführen.

Material und Methoden 209 Feten mit CDH wurden in die Studie eingeschlossen. Die via Ultraschall und Magnetresonanztomografie (MRT) untersuchte relative Lung-to-head-Ratio (o/e-LHR) und das relative fetale Lungenvolumen (rFLV) wurden miteinander verglichen und ihre prognostische Wertigkeit evaluiert. Mittelwerte wurden mit Two-sample-t-Tests (Zwei-Stichproben-T-Tests) oder Mann-Whitney-U-Tests verglichen.

Ergebnisse Zwischen 183 Feten mit linksseitiger und 26 mit rechtsseitiger CDH bestand kein signifikanter Unterschied im Überleben (74.3 % vs. 80,8 %, p = 0.053). In MRT und Ultraschall nahmen mit steigendem o/e-LHR und rFLV die Rate der extrakorporalen Membran-Oxygenierung (ECMO) und chronischen Lungenerkrankung ab und das Gesamtüberleben zu. Minimal- und Maximalwerte wurden erreicht, wenn o/e-LHR und rFLV über 35 % betrugen. Das Outcome verbesserte sich, wenn das rFLV über 35 % betrug – verglichen mit jener Gruppe, bei der ein o/e-LHR von über 35 % prognostisch zugrunde lag.

Schlussfolgerungen Die Daten bestätigen den prognostischen Wert von o/e-LHR und rFLV bei CDH. Die MRT-Bestimmung von o/e-LHR war der Sonografie nicht überlegen. Das rFLV korreliert mit der Morbidität und Mortalität. Seine Bestimmung kann vorteilhaft sein, insbesondere für Kinder, die basierend auf höheren o/e-LHR-Werten gute Prognosen erhalten, denn 2 D-Messverfahren unterschätzen die Risiken für pulmonale Hypertonie und ECMO.

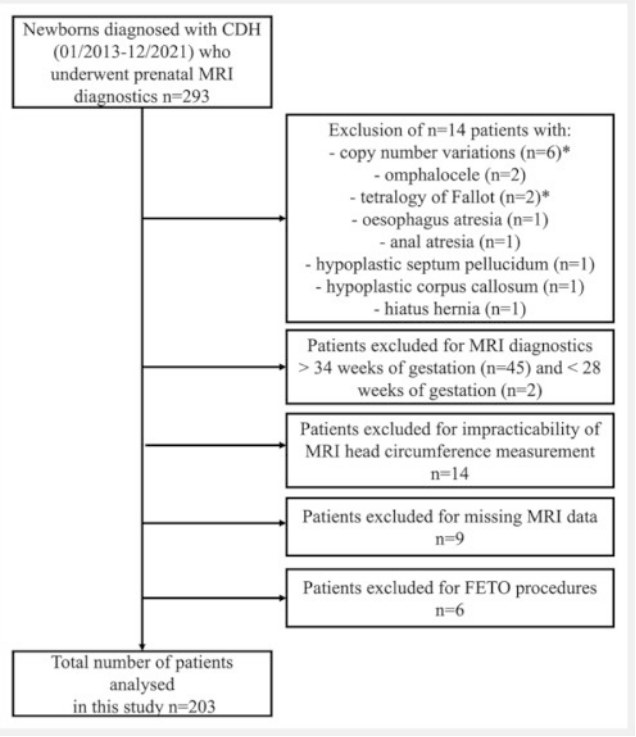
Introduction

Congenital diaphragmatic hernia (CDH) is a major birth defect accounting for 8 % of all congenital anomalies [1]. Upon defective diaphragm development, abdominal viscera within the thoracic cavity impair lung and heart development. As a result of respiratory failure due to lung hypoplasia and severe pulmonary hypertension which may result in heart failure, CDH-affected children face life-threatening cardiopulmonary conditions. Nevertheless, the survival of CDH-affected neonates has greatly improved, particularly if treated in specialized centers. Evidently, one of the main reasons for this is advances in postnatal care (e. g., improved ventilation strategies, extracorporeal membrane oxygenation [ECMO], and surgery). On the other hand, refined prenatal diagnostic imaging helps to establish an optimized environment for postnatal care. Due to the intrathoracic hernia, congenital diaphragm defects are usually determined reliably by prenatal ultrasound. Here, lower lung-to-head ratio (LHR) values and liver herniation were identified as predictors of the survival of CDH-affected neonates more than two decades ago [2]. Several years later, the observed-to-expected LHR (o/e-LHR) was measured to consider the inaccuracy of the LHR, since it depends on the gestational age. Henceforth, despite the lack of standardized prognostic parameters, the ultrasound-evaluated o/e-LHR persisted as the most validated predictor of morbidity and mortality in CDH [3, 4, 5]. It is noteworthy that there are different ways to assess the o/e-LHR value or lung volume: first, longest diameter; second, anteroposterior diameter; and third, tracing method [6]. With advances in fetal magnetic resonance imaging (MRI), this diagnostic imaging method holds great potential for more accurate measurements of the fetal lung and thus a more accurate prognosis. Consequently, MRI-evaluated fetal lung volume was suggested as an outcome predictor for CDH [7] and was hypothesized to correlate with the probability of chronic lung disease (CLD) [8]. Fetal MRI has therefore been implemented in standard prenatal care protocols at many centers. However, since prenatal risk assessment remains a pivotal issue, current scientific efforts try to identify the prognostic parameter best associated with morbidity and mortality. We therefore aimed to correlate the well-established ultrasound o/e-LHR representing the standard of prenatal diagnostic imaging with MRI-evaluated o/e-LHR values (the longest diameter method and tracing method) and relative fetal lung volume (rFLV) to investigate the possibilities and limitations of prenatal MRI imaging for the prediction CDH morbidity and mortality.

Materials and methods

Study cohort and design

We conducted a retrospective cohort study to compare prenatal imaging techniques for CDH. All newborns with CDH treated at our center between 01/2013 and 12/2021 who underwent prenatal MRI examination within 7 days after sonography were eligible. The exclusion criteria were syndromes, genetic alterations, and major additional congenital anomalies. Furthermore, all patients with MRI examinations before 28 and after 34 weeks of gestation



▶ **Fig. 1** Flowchart representing the composition of the study population. * One patient was diagnosed with tetralogy of Fallot and also exhibited a copy number variation. He therefore fulfilled both exclusion criteria and was listed twice.

were excluded for reasons of physiological lung growth and image quality. Incomplete datasets were also excluded from the study. Fetuses who underwent fetoscopic endoluminal tracheal occlusion (FETO) were ruled out. For details on the screening process, refer to ▶ **Fig. 1**. Concerning prenatal imaging, ultrasound-o/e-LHR, MRI-evaluated o/e-LHR, and relative fetal lung volume (rFLV) were evaluated and compared as the primary outcome. As secondary outcome parameters, the need for ECMO, the incidence and severity of chronic lung disease (CLD), and the survival to discharge were analyzed. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee.

Imaging Techniques

Sonography was performed on high-quality instruments (Voluson 750 Expert, Voluson E8 or E10, GE Healthcare ultrasound Systems, Germany). Each examination was carried out by one of three experienced ultrasound specialists. The o/e-LHR was determined using the freely available calculator according to perinatology (https://perinatology.com/calculators/LHR.htm). The fetal head circumference was measured on an axial plane image of the fetal head at the level of the paired thalami and third ventricle.

MRI-based evaluation of o/e-LHR was performed according to both the Longest Diameter and the Tracing method (example given in ▶ **Fig. 2**). Additionally, the relative fetal lung volume (rFLV) measured by MRI was considered a significant prognostic marker and the same cut-off values as for the o/e-LHR were evaluated. Fetal MRI was performed using a 1.5 Tesla MRI system (Magnetom Sonata or Avanto, Siemens Healthineers) without fetal sedation. Head circumference, o/e-LHR, and rFLV were measured by manual plotting using commercially available volume analysis software (Argus, Leonardo Workstation, version VB19A-SP1, Siemens Healthcare and Aycan OsiriX) in transverse planes with T2-weighted HASTE sequences applied using a 4 mm slice thickness. For each diagnostic modality, o/e-LHR values were calculated as published previously [9]. Considering the rFLV, lung tissue on both sides was included in the measurement only sparing the hilar region. rFLV was calculated as published previously [10]. Analysts measuring the lung sonographically or via MRI were blinded for clinical outcome.

ECMO initiation and diagnosis of CLD

ECMO was performed if criteria according to recommendations by the CDH EURO consortium were met [11]. At our center, the preferred ECMO mode was veno-arterial as reported by Rafat et al. [12]. CLD was diagnosed if there was an additional need for oxygen supplementation on day 28 after birth, as reported before [13].

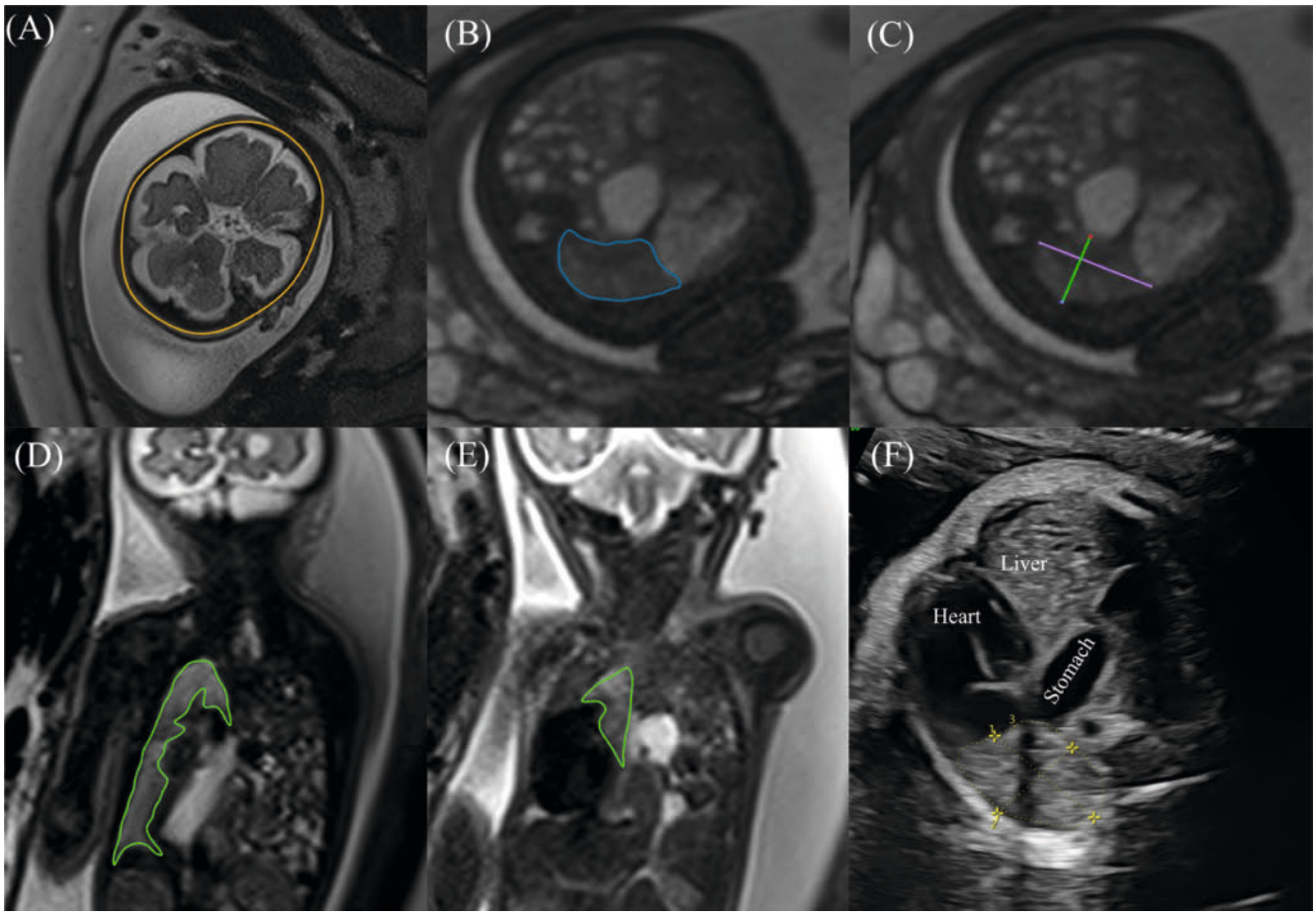
Data Analysis

Categorical variables are presented as percentages. Continuous variables are presented as mean ± standard deviation (SD). Statistical calculations were performed using SAS software, release 9.4 (SAS Institute Inc., Cary, NC, USA). The mean values of two groups were compared by two-sample t-tests (in the case of normally distributed data) or the Mann-Whitney U-test. To compare groups regarding qualitative parameters, Chi-square or Fisher's exact test were used, where appropriate. Kappa coefficients, the McNemar test, and Bowker's test were used to assess the degree of agreement. Cohen's Kappa was interpreted according to Kwiecien et al. [14]. Prediction of survival, CLD, and ECMO was performed using the SAS PROC LOGISTIC procedure for the different diagnostic methods. The area under the ROC curve (AUC) was assessed to quantify the predictive ability of the model. A p-value of <0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of the study cohort

A total of 293 fetuses with CDH underwent prenatal sonography and prenatal MRI examination within the following 7 days. 203 fetuses met the inclusion criteria. For an overview of the recruitment and the characteristics of the dropouts, please see ▶ **Fig. 1**. 177 neonates exhibited left-sided (LCDH) and 26 had right-sided (RCDH) diaphragm defects. ECMO was initiated in 96 cases of which 77 exhibited liver herniation and 19 did not ($p<0.0001$). Overall survival to discharge was 76.8 % and did not differ significantly between LCDH and RCDH (76.3 % vs. 80.8 %, $p=0.6446$). For a detailed overview of the study population, please refer to ▶ **Table 1**.



▶ **Fig. 2** MRI-assisted methods for o/e-LHR measurement (**A–E**) and ultrasound evaluation of o/e-LHR according to the longest diameter and area method (**F**). First, the fetal head circumference was evaluated (**A**). Then, o/e-LHR was assessed by both the MRI-Tracing Method (**B**) and the MRI-Longest Diameter Method (**C**) as described. The MRI-based relative fetal lung volume (**D–E**) was measured as described. The displayed MRI and ultrasound data were obtained from different individuals.

Comparison of imaging techniques

Each fetus was allocated to one of four groups based on o/e-LHR or rFLV values (<15%, 15–25%, 25–35%, >35%) for every diagnostic method individually (▶ **Table 2**). LCDH and RCDH are presented separately. With sonography, no o/e-LHR value <15% was determined. However, using MRI, o/e-LHR values <15% could indeed be detected. These individuals had low survival rates ranging from 0% to 50.0% – depending on the diagnostic method. For every diagnostic method, however, the incidences of ECMO and CLD decreased, and survival increased gradually, thus reaching a minimum and maximum, respectively, for o/e-LHR and rFLV values >35%.

Cohen's Kappa (K) was evaluated to measure the degree of agreement between each of the diagnostic methods with regard to the sonographic method as the standard of perinatal care. Cohen's Kappa, therefore, allowed conclusion of how reliably one individuum was allocated to the same o/e-LHR or rFLV group, respectively, throughout different diagnostic methods. For the MRI longest diameter method compared to sonography, shifts within the diagnostic cohorts appeared to be insignificant ($p = 0.5233$) and a slight correlation was found ($K = 0.2413$) for each of the outcome parameters ECMO, CLD, and survival. Concerning the MRI-based o/e-LHR (Tracing method) or rFLV compared to ultrasound-evaluated o/e-LHR, correlation remained poor. Details are presented in **Supplementary Table 1**. When considering overall comparisons instead of intraindividual consistency, significant differences could be determined between groups in favor of the MRI-evaluated rFLV compared to the MRI Tracing method particularly in the o/e-LHR >35% and rFLV >35%, respectively. Both the incidences of ECMO (21.4% vs. 42.2%, $p < 0.05$) and CLD (31.4% vs. 47.2%, $p < 0.05$) were diminished, whereas survival to discharge further increased (97.1% vs. 83.4%, $p < 0.05$) if a fetus exhibited an rFLV >35% compared to a fetus who had only been evaluated with an o/e-LHR value >35% by MRI Tracing method.

Our ROC analyses indicate that each of the different diagnostic modalities is able to predict postnatal morbidity and mortality in cases of LCDH (▶ **Table 3**). The prediction of survival seems to work out best based on the MRI evaluation of rFLV (AUC = 0.80, $p < 0.0001$). Even for RCDH, CLD could be predicted by o/e-LHR evaluated by the MRI Longest Diameter method (AUC = 0.74, $p < 0.05$) and rFLV (AUC = 0.93, $p < 0.05$).

▶ **Table 1** Characterization of the study population.

	LCDH, *n* = 177	RCDH, *n* = 26	*p*-value
Birth weight [g]	2964 ± 542	3106 ± 502	ns
Liver-up, n (%)	102 (57.6)	26 (100)	<0.0001
Liver-down, n (%)	75 (42.4)	0 (0.00)	<0.0001
Severe PHT, n (%)	124 (70.1)	25 (96.2)	<0.01
Duration of NO in survivals [d]	16.2 ± 11.7	19.6 ± 7.33	ns
Patch closure, n (%)	136 (76.8)	21 (80.8)	ns
Boston Scale, n (%)			
▪ A	7 (3.95)	1 (3.85)	–
▪ B	49 (27.7)	2 (7.69)	–
▪ C	58 (32.8)	14 (53.8)	–
▪ D	17 (9.60)	3 (11.5)	–
Kitano score, n (%)			
▪ 0	19 (10.7)	26 (100)	–
▪ 1	55 (31.1)	0 (0.00)	–
▪ 2	66 (37.3)	0 (0.00)	–
▪ 3	37 (20.9)	0 (0.00)	–
Survival, n (%)	135 (76.3)	21 (80.8)	Ns

LCDH = left-sided congenital diaphragmatic hernia, RCDH = right-sided congenital diaphragmatic hernia, PHT = pulmonary hypertension, NO = nitric oxide. *p*-values were calculated only where appropriate.

Incidences of liver-up

In our study, 57.6 % of LCDH cases and 100 % of RCDH cases were diagnosed with liver-up ($p < 0.0001$). For every diagnostic method, incidences of liver-up gradually decreased with growing o/e-LHR and rFLV values, respectively. Among the groups of highest o/e-LHR and rFLV, liver-up occurred most frequently in the MRI Tracing method (57.1 %) and was minimal if the rFLV was above 35 % (37.1 %). Details are presented in ▶ **Table 4**. Notably, liver-up accounted for 80.2 % of all required ECMO interventions as compared to liver-down (19.8 %, $p < 0.0001$; data not shown).

Discussion

The ultrasound-evaluated o/e-LHR is one of the oldest prognostic parameters for CDH and since sonography is the standard of prenatal care, the ultrasound-evaluated o/e-LHR is most commonly used. Meanwhile, both total fetal lung volume and the o/e-LHR evaluated on MRI were shown to be equally valuable prognostic tools [7, 15]. For the o/e-LHR, cut-off values as applied herein are generally accepted to classify the severity of CDH as suggested before [16]. Since such consensus for rFLV is not yet available, we used the same cut-off values as for the o/e-LHR to investigate its prognostic value. For every imaging technique, the incidences of ECMO and CLD decreased, whereas the probability of survival increased gradually, reaching a minimum and maximum respectively for o/e-LHR values and rFLV > 35 %. Yet, the outcome parameters significantly improved if rFLV was above 35 % compared to MRI-based measurement of o/e-LHR values > 35 %. Our study shows that different diagnostic modalities measuring o/e-LHR either via ultrasound or via two different MRI-based calculations do not correlate well. Also, the rFLV data seem to be distributed more equally across the different groups (15–25 %, 25–35 %, > 35 %) compared to the other diagnostic modalities where a shift towards the best prognostic group (o/e-LHR > 35 %) occurred. A possible explanation could be the inherent differences between sonographic o/e-LHR and MRI-derived rFLV measurement, which might explain why 3 D-MRI measurement and thus evaluation of rFLV may be the superior diagnostic tool to predict morbidity and mortality: Ultrasound analysis only considers the lung contralateral to the diaphragm defect whereas MRI evaluated rFLV includes the lung on the contralateral side and on the ipsilateral side. This ipsilateral lung tissue if measured on a complementary basis may allow for more precise prognosis concerning the need for ECMO and survival.

In line with previous results, our data confirm the predictive value of o/e-LHR and rFLV in CDH with regard to the need for ECMO, the incidence of CLD, and survival to discharge irrespective of the diagnostic modality. Concerning rFLV, there is also a meta-analysis available confirming that higher observed-to-expected total fetal lung volume is associated with higher chances of survival [17]. Health care providers should be aware of the fact that sonography can hardly discriminate between the lowest o/e-LHR value groups and can even be unable to detect any o/e-LHR below

▶ **Table 2** Different methods to measure o/e-LHR. Comparison of ultrasound and MRI (lung area vs. longest diameter).

		Ultrasound				MRI Tracing				MRI Longest Diameter				MRI rFLV		
		o/e-LHR <15%, *n=0*				**o/e-LHR <15%, *n=1***				**o/e-LHR <15%, *n=2***				**rFLV <15%, *n=3***		
						ECMO	CLD	Survival		ECMO	CLD	Survival		ECMO	CLD	Survival
Overall, *n (%)*						0 (0.00)	0 (0.00)	0 (0.00)		1 (50.0)	0 (0.00)	1 (50.0)		3 (100)	1 (33.3)	1 (33.3)
LCDH					1 (100)	0 (0.00)	0 (0.00)	0 (0.00)	2 (100)	1 (50.0)	0 (0.00)	1 (50.0)	2 (66.6)	2 (100)	0 (0.00)	0 (0.00)
RCDH					0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (33.3)	1 (100)	1 (100)	1 (100)
		o/e-LHR 15–25%, *n=21*				**o/e-LHR 15–25%, *n=2***				**MRI o/e-LHR 15–25%, *n=22***				**rFLV 15–25%, *n=50***		
		ECMO	CLD	Survival		ECMO	CLD	Survival		ECMO	CLD	Survival		ECMO	CLD	Survival
Overall, *n (%)*		15 (71.4)	14 (66.7)	10 (47.6)		2 (100)	1 (50.0)	1 (50.0)		16 (72.7)	13 (59.1)	12 (54.5)		35 (70.0)	31 (62.0)	33 (66.0)
LCDH	17 (81.0)	11 (64.7)	10 (58.8)	7 (41.6)	2 (100)	2 (100)	1 (50.0)	1 (50.0)	21 (95.5)	15 (71.4)	12 (57.1)	11 (52.4)	40 (80.0)	26 (65.0)	22 (55.0)	25 (62.5)
RCDH	4 (19.0)	4 (100)	4 (100)	3 (75.0)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (4.55)	1 (100)	1 (100)	1 (100)	10 (20.0)	9 (90.0)	9 (90.0)	8 (80.0)
		o/e-LHR 25–35%, *n=58*				**o/e-LHR 25–35%, *n=39***				**MRI o/e-LHR 25–35%, *n=48***				**rFLV 25–35%, *n=77***		
		ECMO	CLD	Survival		ECMO	CLD	Survival		ECMO	CLD	Survival		ECMO	CLD	Survival
Overall, *n (%)*		35 (60.3)	30 (51.7)	36 (62.1)		26 (66.7)	24 (61.5)	25 (64.1)		27 (56.3)	29 (60.4)	32 (66.7)		42 (54.5)	45 (58.4)	53 (68.8)
LCDH	54 (93.1)	33 (61.1)	29 (53.7)	35 (64.8)	38 (97.4)	25 (65.8)	23 (60.5)	24 (63.2)	48 (100)	27 (56.3)	29 (60.4)	32 (66.7)	64 (83.1)	34 (53.1)	37 (57.8)	44 (68.8)
RCDH	4 (6.90)	2 (50.0)	1 (25.0)	1 (25.0)	1 (2.56)	1 (100)	1 (100)	1 (100)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	13 (16.9)	8 (61.5)	8 (61.5)	9 (69.2)
		o/e-LHR >35%, *n=116*				**o/e-LHR >35%, *n=161***				**MRI o/e-LHR >35%, *n=131***				**rFLV >35%, *n=70***		
		ECMO	CLD	Survival		ECMO	CLD	Survival		ECMO	CLD	Survival		ECMO	CLD	Survival
Overall, *n (%)*		42 (36.2)	54 (46.6)	102 (87.9)		**68 (42.2)***	**76 (47.2)**$^{\Delta}$	**131 (83.4)**$^{\Delta\Delta}$		49 (37.4)	58 (44.3)	112 (85.5)		**15 (21.4)***	**22 (31.4)**$^{\Delta}$	**68 (97.1)**$^{\Delta\Delta}$
LCDH	99 (85.3)	30 (30.3)	41 (41.4)	86 (86.9)	136 (84.5)	50 (36.8)	59 (43.4)	111 (81.6)	106 (80.9)	31 (29.2)	41 (38.7)	92 (86.8)	68 (97.1)	14 (20.6)	22 (32.4)	66 (97.1)
RCDH	17 (14.7)	12 (70.6)	13 (76.5)	16 (94.1)	25 (15.5)	18 (72.0)	17 (68.0)	20 (80.0)	25 (19.1)	18 (72.0)	17 (68.0)	20 (80.0)	2 (2.86)	1 (50.0)	0 (0.00)	2 (100)

For overall cases of ECMO, CLD, and survival per group, the denominator is the total number of study participants for each group. When divided by LCDH and RCDH, the denominator is the total count of cases of LCDH and RCDH per group.

CDH = congenital diaphragmatic hernia, o/e-LHR = observed-to-expected lung-to-head ratio, MRI = magnetic resonance imaging, ECMO = extracorporeal membrane oxygenation, CLD = chronic lung disease, rFLV = relative fetal lung volume, RCDH = right-sided CDH, LCDH = left-sided CDH. $^{*}p<0.05$, $^{\Delta}p<0.05$, $^{\Delta\Delta}p<0.05$.

▶ **Table 3** Predictive ability of different diagnostic methods.

		LCDH		RCDH	
Method	**Prediction of**	**AUC**	***p*-value**	**AUC**	***p*-value**
Sonography o/e-LHR	Survival	0.74	<0.0001	0.75	ns
	CLD	0.74	<0.0001	0.85	ns
	ECMO	0.70	<0.0001	0.67	ns
MRI tracing o/e-LHR	Survival	0.71	0.0002	0.56	ns
	CLD	0.82	<0.0001	0.82	ns
	ECMO	0.72	<0.0001	0.65	ns
MRI LD o/e-LHR	Survival	0.72	0.0002	0.46	ns
	CLD	0.78	<0.0001	0.74	<0.05
	ECMO	0.71	<0.0001	0.58	ns
MRI rFLV	Survival	0.80	<0.0001	0.64	ns
	CLD	0.79	<0.0001	0.93	<0.05
	ECMO	0.71	<0.0001	0.77	Ns

LCDH = left-sided congenital diaphragmatic hernia, RCDH = right-sided congenital diaphragmatic hernia, o/e-LHR = observed-to-expected lung-to-head ratio, MRI = magnetic resonance imaging, LD = longest diameter method, rFLV = relative fetal lung volume, AUC = area under the curve, ns = not significant

▶ **Table 4** Incidences of liver-up among groups divided by method.

o/e-LHR	**Sonography**	**Tracing**	**LD**	**rFLV**
<15%	–	2 (100)	2 (100)	2 (66.6)
15–25%	18 (85.7)	2 (100)	20 (90.9)	46 (92.0)
25–35%	45 (77.6)	33 (84.6)	38 (79.2)	52 (67.5)
>35%	56 (48.3)	92 (57.1)	68 (51.9)	26 (37.1)

o/e-LHR = observed-to-expected lung-to-head ratio. LD = longest diameter method, rFLV = relative fetal lung volume. For ultrasound, area and LD, percentages refer to the o/e-LHR value. Regarding rFLV, percentages refer to the actual rFLV.

15% at all as can be seen in our study. Despite this diagnostic uncertainty in the lower o/e-LHR groups, it appeared that among the MRI-based modalities the Longest Diameter method and the Tracing method are not superior to sonography and classification of CDH according to o/e-LHR. Therefore, CDH severity could be easily assessed by every clinician by measuring o/e-LHR in MRI data. All of the modalities tend to put many fetuses in the best prognostic group based upon o/e-LHR evaluation. Hence for routine assessment of CDH-affected fetuses, sonography is an adequate diagnostic tool and remains the standard of care. However, sonography is an error-prone technique as it depends perhaps more than any other technique on the experience and skills of the examiner. Additionally, prenatal sonography can be difficult as visualization might be compromised by the fetus's position. These challenges can cause low measurement reliability and reproducibility and justify efforts to standardize prenatal sonographic examination for CDH [6, 9]. Unsurprisingly, high reproducibility is a strength of MRI in the context of CDH [8, 10, 18]. On the other hand, our data also indicate that the better a fetus is evaluated based upon two-dimensional imaging (o/e-LHR >35%), the more likely this screening method is inferior to a three-dimensional MRI evaluation of rFLV. It seems all the other diagnostic methods tend to underestimate the morbidity of these fetuses as could be concluded from the significant differences in the incidences of ECMO and CLD and in the probability of survival to discharge with respect to the MRI Tracing method compared to the rFLV in the clinically best fetuses (>35% o/e-LHR and rFLV, respectively). Even though the prognostic accuracy for CDH morbidity and mortality based on ultrasound-evaluated o/e-LHR increases if the position of the liver is taken into account [16], rFLV remains a promising prognostic tool.

Traditionally, o/e-LHR values above the cut-off of 35 % are considered prognostically favorable. In our cohort, the risk for ECMO among these fetuses still ranged between 36.2 % and 42.2 % and it was only reduced to 21.4 % if rFLV also exceeded 35 %. These findings justify recommending fetal MRI to support or to challenge a relatively good prognosis based upon sonography in order to plan conditions of delivery. However, interestingly, even if the rFLV reached values of 35 % and beyond, ECMO remained a commonly used therapeutic intervention within our postnatal intensive care unit (21.4 %). This observation was also valid, if only liver-down neonates were considered. In this subset, ECMO was used in 18.2 % of cases. This may be due to severe pulmonary hypertension that can also occur in patients with a good prognosis based on o/e-LHR. ECMO availability and readiness may, therefore, be an important criterion when planning delivery of CDH-affected children because, in our opinion, the rate of ECMO interventions in this study may be the main reason for the high survival rates as suggested previously [19].

FETO holds an established position in the management of CDH ever since the TOTAL trial attested a superior outcome in neonates with severe left-sided CDH treated with FETO [20]. However, there is also evidence that survival might be even better if neonates with severe LCDH receive ECMO instead of FETO [19]. Due to these promising data, in our very experienced ECMO center, FETO was reserved for fetuses suffering from severe LCDH and exhibiting rFLV < 25 %.

Our prognostic abilities to predict morbidity and mortality of CDH-affected neonates based on prenatal imaging involving sonography, prenatal MRI, and genetic testing have developed immensely throughout recent years [21, 22]. Interestingly, the lung-to-liver signal intensity ratio as evaluated by fetal MRI was introduced as a novel prognostic tool to predict postnatal survival [23]. Today, rFLV values above 35 % can predict survival in as much as 97 % of all cases. Yet, we do not know why the same cohort still suffers from chronic lung disease in 31.4 % of cases or depends on ECMO in 21.4 %. Therefore, we argue that it is necessary to expand our view for future research and consider other prognostic parameters in order to become more accurate in predicting morbidity. Especially prenatal predictability of pulmonary hypertension could be a possible aim of future studies.

As one of the largest regional neonatal critical care centers, we are able to base our studies on large case numbers. However, our analyses were restricted to MRI datasets of inborn fetuses for methodologic reasons. Although MRI is considered the more reproducible and objective diagnostic tool, our MRI dataset was also slightly incomplete due to unfavorable positioning of the fetal head which prevented accurate measurements of the head circumference. Results drawn from our study are limited due to the retrospective design. Moreover, RCDH is a relatively rare condition compared to LCDH. Consequently, the small number of RCDH cases did not allow for separate analysis of LCDH and RCDH. Hence, we can only presume that our results are valid for both LCDH and RCDH.

Our data confirm the predictive value of o/e-LHR in fetuses with CDH irrespective of the diagnostic method. MRI evaluation of o/e-LHR was not superior compared to sonographic evaluation. Yet, MRI seemed to be beneficial with respect to the measurement of rFLV particularly in fetuses who were otherwise classified with high o/e-LHR values as two-dimensional evaluation methods tended to underestimate morbidity of the fetuses. In our opinion, due to an unacceptable risk for ECMO, an external delivery cannot be recommended even in such cases where prenatal diagnostic imaging would suggest good prognosis based on rFLV > 35 % and absent liver herniation. Hence, we recommend that every fetus with CDH requires a tertiary neonatal care unit with ECMO expertise and readiness.

Acknowledgement

The authors thank the parents for their consent to publish some of the MRI and ultrasound data of their children.

Conflict of Interest

The authors declare that they have no conflict of interest.

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