Prenatal Prognostic Factors for Isolated Right Congenital Diaphragmatic Hernia: A Single Center's Experience

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Abstract

Background: Right-sided congenital diaphragmatic hernia (RCDH) is relatively rare. Clinical data of RCDH, especially with respect to antenatal prediction of neonatal outcome, are lacking. This study aimed to report the treatment outcome of newborn infants with RCDH and to identify prenatal prognostic indicators.

Methods: We retrospectively reviewed the medical records of newborn infants with isolated RCDH who were born at a gestational age of ≥35 weeks. We analyzed and compared the clinical and prenatal characteristics including the fetal lung volume, which was measured as the observed-to-expected lung area-to-head circumference ratio (O/E LHR), between the survivors and non-survivors.

Results: A total of 24 (70.6%) of 34 patients with isolated RCDH survived to discharge. The O/E LHR was significantly greater in survivors (67.0 ± 19.9) than in non-survivors (42.4 ± 25.0) ($P < .05$). In multivariate analysis, the O/E LHR was found to be a good predictor of mortality or requirement for extracorporeal membrane oxygenation (ECMO) support (area under the curve [AUC], 0.870; $P < .01$) and mortality (AUC, 0.789; $P < .05$). The best O/E LHR cut-off value for predicting mortality and mortality or requirement for ECMO support in isolated RCDH was 47.

Conclusions: The survival rate of patients with isolated RCDH was comparable to that of patients with left-sided CDH. The O/E LHR of the contralateral lung was a reliable predictor of short-term postnatal outcome in RCDH.

Introduction

Congenital diaphragmatic hernia (CDH) is a serious congenital anomaly with a high mortality rate. The incidence of CDH is 1 in 2500 to 4000 live births, with most cases being left-sided CDH.(1, 2) The key medical treatment strategy for CDH is the appropriate respiratory and hemodynamic support for pulmonary arterial hypertension during the early postnatal days. Unfortunately, some patients who are unresponsive to medical treatment eventually require extracorporeal membrane oxygenation (ECMO) support.(3) The survival rate of CDH has been reported to be higher in the ECMO centers than in non-ECMO centers.(4) Therefore, identifying prenatal risk factors to predict early postnatal outcome and determining the requirement for ECMO support in the fetus diagnosed with CDH are important.

Several antenatal parameters have been found to aid in predicting the outcome of CDH. Liver herniation into intrathoracic area and the degree of lung hypoplasia, as estimated by the observed-to-expected lung area-to-head circumference ratio (O/E LHR), have been suggested as prognostic indicators.(5–14) However, most of these parameters are detected in patients with left-sided CDH (LCDH). Whether these can be considered as risk factors for right-sided CDH (RCDH), which accounts for only 10–15% of all CDH cases, is unclear.(15) This study aimed to report the treatment outcomes of newborn infants with RCDH and to identify the prenatal prognostic indicators.

Methods

1. Study population and data selection

We reviewed the medical records of patients diagnosed with CDH who were born and hospitalized in the neonatal intensive care unit in Asan Medical Center, Seoul, Korea, between January 2006 and October 2020. The eligibility criterion for inclusion was prenatal diagnosis of RCDH. The exclusion criteria were as follows: (1) newborns with a gestational age of < 35+0 weeks and (2) newborns with additional congenital anomalies, such as major structural malformation, chromosomal, and/or single gene disorders (i.e., non-isolated CDH).(16) We analyzed the following demographic and clinical characteristics of all patients: gestational age at birth; body measurements such as birth weight; sex; mode of delivery; 1- and 5-min APGAR scores; total hospital days; maternal age; use of high frequency oscillatory ventilator (HFOV) and inhaled nitric oxide (iNO); associated major structural or chromosomal anomalies; repair operation; grade of defects(17); patch repair; requirement for ECMO support; and survival.(16) This study was approved by the Institutional Review Board (IRB) of Asan Medical Center, South Korea (IRB No. 2020-1916). No specific ethical consent was required for a retrospective analysis.

2. Imaging evaluation

The standard ultrasound imaging of the fetus suspected of CDH was performed at our center for a detailed evaluation to confirm the diagnosis and to exclude the presence of additional structural anomalies. Ultrasound measurements were performed using A30, WS80A (Samsung Medison Co., Ltd, Seoul, Korea), Voluson E8, or E10 Expert (General Electric Healthcare Austria GmbH & Co. OG, Zipf, Austria) with a 2–6-MHz transabdominal probe. Ultrasound measurements were performed in the second and third trimesters of pregnancy by two experienced obstetricians (MY Lee and HS Won) in our center.

The lung area contralateral (left) to RCDH was originally measured as the product of the two longest perpendicular linear measurements of the lung measured at the level of the four-chamber view of the heart on a transverse scan of the fetal thorax. The head circumference (mm) was retrieved from medical records. The lung area-to-head circumference ratio (LHR) was calculated as the lung area divided by the head circumference.(11, 18) The O/E LHR was calculated as described by Jani et al. and expressed as the percentage of the expected mean for the gestational age at the time of evaluation as the O/E LHR.(7) Herniated organs were identified by visual assessment on ultrasound images.

3. Management protocols for infants with RCDH

All infants who were prenatally diagnosed with CDH were intubated in the delivery room at birth and admitted to the neonatal intensive care unit. In all cases, immediate ventilator support was initiated and maintained according to the local protocol. HFOV was indicated if the target preductal saturation (85%–95%) or partial pressure of arterial carbon dioxide (45–60 mmHg) was not achieved by a conventional

ventilator with a high peak inspiratory pressure (up to 25 to 30 cmH_2O) and respiratory rate (> 40–60/min). ECMO support was indicated in the following cases: oxygenation index > 40, failure to wean from 100% oxygen, echocardiographic evidence of severe pulmonary hypertension with cardiac dysfunction or pressure resistant hypotension, and/or shock despite maximal cardiopulmonary support (i.e., iNO and inotropes).

4. Data analysis and statistics

We analyzed and compared the demographic and prenatal ultrasound findings, such as the lung volume measured as the O/E LHR between the survivors and non-survivors. The effect of the O/E LHR on neonatal mortality and requirement for ECMO support in RCDH was assessed using the Fisher's exact test and Mann–Whitney U test. Logistic regression analysis was performed to determine the association between the O/E LHR and mortality and requirement for ECMO support. Receiver operating characteristic (ROC) curves were used to determine the cut-off value of the O/E LHR for mortality or requirement for ECMO support. Data are presented as the area under the curve (AUC) and 95% confidence interval (CI). The cut-off value was calculated using the Youden index. Statistical analyses were performed using IBM SPSS statistics ver. 20.0 (IBM Co., Armonk, NY, USA). Categorical data are presented as numbers (percentages), and continuous data are presented as means ± standard deviations or medians. A *P* value of < .05 was considered statistically significant.

Results

A total of 45 patients with RCDH were found to be eligible for the study. However, 11 of 45 patients were excluded because of low gestational age (< 35 + 0 weeks, n = 5) and non-isolated CDH (n = 6). Thus, 34 patients were included in the analysis. The median gestational age and birth weight were 38 + 0 weeks (range: 35 + 1 to 40 + 1 weeks) and 3230 g (range: 2350–3587 g), respectively. Of the 34 patients, 24 (70.6%) patients survived to hospital discharge. Among the 10 patients (29.4%) who received ECMO support, 5 patients survived. In total, 29 (85.3%) patients underwent diaphragmatic repair. Almost all patients had liver herniation (n = 33, 97.1%) into the thorax. Other herniated organs were the bowel (n = 19, 55.9%), kidney (n = 3, 8.8%), gall bladder (n = 1, 2.9%), and spleen (n = 1, 2.9%).

The 5-min APGAR score was higher and the incidence of mediastinal shifting and use of HFOV and iNO were lower in survivors than in non-survivors. The intraoperative findings of the defect size and the rate of patch repair did not differ between survivors and non-survivors (Table). The O/E LHRs of 21 patients were available. The O/E LHR was significantly greater in survivors (67.0 ± 19.9) than in non-survivors (42.4 ± 25.0; *P* = .028) (Fig. 1A). In addition, the O/E LHR was greater in survivors who did not receive ECMO support (72.7 ± 16.8) than non-survivors or those who received ECMO support (43.0 ± 21.4; *P* = .002; Fig. 1B).

Table

Perinatal characteristics and clinical outcomes in survivors and non-survivors

	Survivors (n = 24)	Non-survivors (n = 10)	*P* value
Male sex	17 (70.8)	6 (60.0)	.692
Cesarean section	16 (66.7)	8 (80.0)	.683
Gestational age, week	37.8 ± 1.2	37.5 ± 1.1	.455
Birth weight, g	3095.3 ± 338.6	3223.8 ± 193.1	.174
1-min APGAR score	5 (3-8)	5 (0-8)	.060
5-min APGAR score	7 (6-9)	7 (3-8)	.031
Total hospital days	32.2 ± 13.1	48.5 ± 73.8	.504
Maternal age, year	31.3 ± 4.3	31.8 ± 3.2	.740
Head circumference, cm	33.7 ± 6.2	35.8 ± 1.3	.312
Chest circumference, cm	32.4 ± 1.9	32.4 ± 1.3	.954
Abdominal circumference, cm	28.8 ± 2.5	28.5 ± 1.9	.774
Polyhydramnios	12 (50.0)	6 (60.0)	.715
Pleural effusion	4 (16.7)	4 (40.0)	.195
Mediastinal shifting	14 (58.3)	10 (100)	.017
High frequency ventilator use	12 (50.0)	10 (100)	.006
Inhaled nitric oxide use	9 (37.5)	10 (100)	.001
Patch repair*	13 (54.2)	4 (80)	.370
Defect size* A/B/C/D	2 / 5 / 14 / 2	0 / 1 / 2 / 2	.194

Values are presented as means ± standard deviations or numbers with percentages or ranges in parentheses.
APGAR, Appearance, Pulse, Grimace, Activity, and Respiration

* Data on the defect size were not available for some patients who did not undergo repair.

We performed logistic regression analysis to determine the association between independent prenatal indicators and short-term postnatal outcomes in survivors with RCDH who did not receive ECMO support and non-survivors with RCDH or those with RCDH who received ECMO support. The model was adjusted for body weight, the O/E LHR, and mediastinal shifting. After adjusting for body weight and mediastinal

shifting, the O/E LHR (odds ratio [OR], 0.918; 95% CI 0.847–0.996; *P* = .039) alone was significantly associated with mortality or requirement for ECMO support.

To determine whether the O/E LHR, a well described prenatal prognostic indicator of LCDH, can be considered a prognostic indicator of RCDH, patients were divided into two groups: patients with an O/E LHR of < 45 (n = 8) and those with an O/E LHR of ≥ 45 (n = 13). The mortality was significantly higher in patients with an O/E LHR of < 45 (5/8, 62.5%) than in those with an O/E LHR of ≥ 45 (1/13, 7.7%; OR, 20.000; 95% CI 1.655–241.723; *P* = .014). In addition, the incidence of death or ECMO use was significantly greater in patients with an O/E LHR of < 45 (7/9, 87.5%) than in those with an O/E LHR of ≥ 45 (2/13, 15.4%; OR, 38.500; 95% CI 2.915–508.463; *P* = .002). The area under the ROC curve of the O/E LHR for predicting mortality and requirement for ECMO support in RCDH was 0.870, which was statistically significant (Fig. 2). The best O/E LHR cut-off value for predicting mortality (sensitivity: 92% and specificity: 78%) and mortality or requirement for ECMO support (sensitivity: 80% and specificity: 83%) in isolated RCDH with a Youden index of 0.694 was 47.

Discussion

In the present study, the overall survival rate of isolated RCDH was 70.6%. The survival rate of RCDH in our study is similar to the range (29% – 78%) reported in previous large studies.(18–25) Moreover, the survival rate in our present study is comparable to that in our previous study of 27-year single-center data of patients with CDH, of which 85% patients had LCDH.(26) Controversy continues on whether the laterality of CDH affects mortality.(21–25, 27–29) The uncertainty regarding the effect of laterality might be because of the small sample size, relative difficulty in prenatal diagnosis of RCDH, and postnatal management policies such as the timing of surgical repair. However, two recent large-scale studies in the United States found no difference in the overall mortality rates of RCDH and LCDH.(27, 30) Although the closure of the right pleuroperitoneal canal occurs before that of the left pleuroperitoneal canal, the mechanism of abdominal viscera herniation into the thoracic cavity resulting in the compression of the fetal lungs and leading to pulmonary hypoplasia is less likely to differ by the side.(31) Although a lower survival rate of RCDH (67%) versus LCDH (72%) was reported in a large international registry, the difference disappeared after controlling the diaphragmatic defect size.(28) The defect size, which could be observed only in patients who underwent surgical repair, did not differ between the survivors and non-survivors in our study. Overall, our results suggest that the defect laterality per se is not associated with mortality in isolated CDH.

In our study, the O/E LHR was a significant risk factor for isolated RCDH. The prognostic predictability of the O/E LHR was quite favorable, and the best O/E LHR cut-off value for mortality and mortality or requirement for ECMO support was 47%. This is consistent with the range of the predictive O/E LHR cut-off value (45–50%) in LCDH proposed by CDH EURO Consortium Consensus and antenatal CDH registry.(32, 33) The degree of pulmonary hypoplasia, as estimated by the LHR or O/E LHR, is known to be the most important determinant in predicting the outcome in infants with CDH. A recent meta-analysis indicated that the LHR and O/E LHR were significantly related to ECMO support requirement in isolated

LCDH.(34) However, whether the O/E LHR can predict survival in RCDH is debatable because the number of RCDH cases is less, as it is relatively rare. Jani et al. demonstrated that the O/E LHR is useful for predicting subsequent survival in both LCDH and RCDH, in which no survival has been reported for an O/E LHR of < 25%.(7) DeKoninck et al. reported that after expectant in utero management, the survival rates in patients with RCDH and an O/E LHR of < 45% and < 30% were 17% and 0%, respectively.(21) In contrast, Victoria et al. raised questions regarding the reliability of the O/E LHR as a predictor of RCDH.(20) In this single-center study, the survival rate of RCDH was relatively high (up to 60%) even in patients with an O/E LHR of < 45%, probably because the results were derived from only five cases. In the registry of isolated LCDH, the survival rate was reported based on the O/E LHR interval (15%, 25%, 35%, and 45%) along with the presence of liver herniation.(32) A recent ECMO guideline for CDH proposed a prenatal risk stratification system, which includes an O/E LHR cut-off value of < 25%, liver herniation, and the O/E total lung volume.(35) However, it remains unclear whether such a graded classification can be used for RCDH. To the best of our knowledge, no study has investigated whether a dose–response relationship exists between the O/E LHR value and mortality or ECMO support requirement in RCDH with an O/E LHR of < 45%.

A well-known predictor of outcome in LCDH is the intrathoracic position of the liver.(15, 33, 36) However, the anatomical difference between left and right CDH makes the application of the liver status irrelevant because the liver is almost always up in every case of RCDH. Similar to previous reports, liver herniation was observed in almost all patients with RCDH.(15, 20) The degree of liver herniation, manifested by the percentage of the herniated liver and measured by fetal magnetic resonance imaging (MRI), was suggested as a prenatal indicator of LCDH(37); however, the volume of the herniated liver was not found to be predictive of survival in a recent study on RCDH.(20) We had no data on the herniated liver volume because fetal MRI data were unavailable. Other fetal ultrasound findings, such as mediastinal shifting and polyhydramnios, were not associated with neonatal outcome in RCDH.(38)

This study has some limitations. First, because of the rarity of RCDH, the sample size was relatively small albeit it included all patients examined during a 15-year time period. Second, although prenatal ultrasound data of all patients were available, the O/E LHR was available for relatively recently diagnosed cases alone. However, our single-center study is strengthened by the uniformity of antenatal diagnosis and postnatal management. We expect to report more data in the near future and intend to provide a graded O/E LHR cut-off criteria.

Conclusion

The O/E LHR is a useful indicator for predicting mortality and requirement for ECMO support in patients with isolated RCDH. Further large studies are warranted for standard prenatal risk stratification for RCDH.

Abbreviations

CDH: Congenital diaphragmatic hernia; RCDH: Right-sided congenital diaphragmatic hernia; LCDH: Left-sided congenital diaphragmatic hernia; ECMO: extracorporeal membrane oxygenation; LHR: lung area-to-head circumference ratio; O/E LHR: Observed-to-expected lung area-to-head circumference ratio; HFOV: High frequency oscillatory ventilator; iNO: Inhaled nitric oxide; ROC: Receiver operating characteristic; AUC: area under the curve; CI: confidence interval; MRI: magnetic resonance imaging.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of Asan Medical Center, South Korea (IRB No. 2020-1916). No specific ethical consent was required for a retrospective analysis.

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors have no conflicting financial interests.

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Author’s contributions

J Jeong and BS Lee designed the study. DY Kim, S-C Kim and J-M Namgoong provided clinical data. T Cha, M-Y Lee, H-S Won, BS Lee, K-S Kim, and Ellen A-R Kim collected clinical data along with patient care. J Jeong and BS Lee analyzed the clinical data and wrote the manuscript. All authors have read and approved the final manuscript.

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Figures

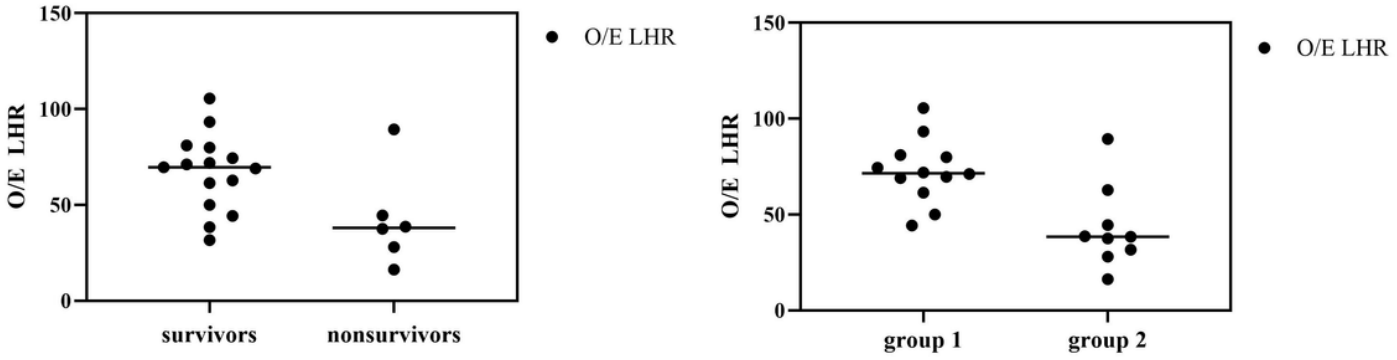

Figure 1

A. The O/E LHR and clinical outcomes: survivors versus non-survivors. B. The O/E LHR and clinical outcomes: group 1 versus group 2 Group 1, survivors who did not receive ECMO support; Group 2, non-survivors or those who received ECMO support. ECMO, extracorporeal membrane oxygenation; O/E LHR, observed-to-expected lung area-to-head circumference ratio

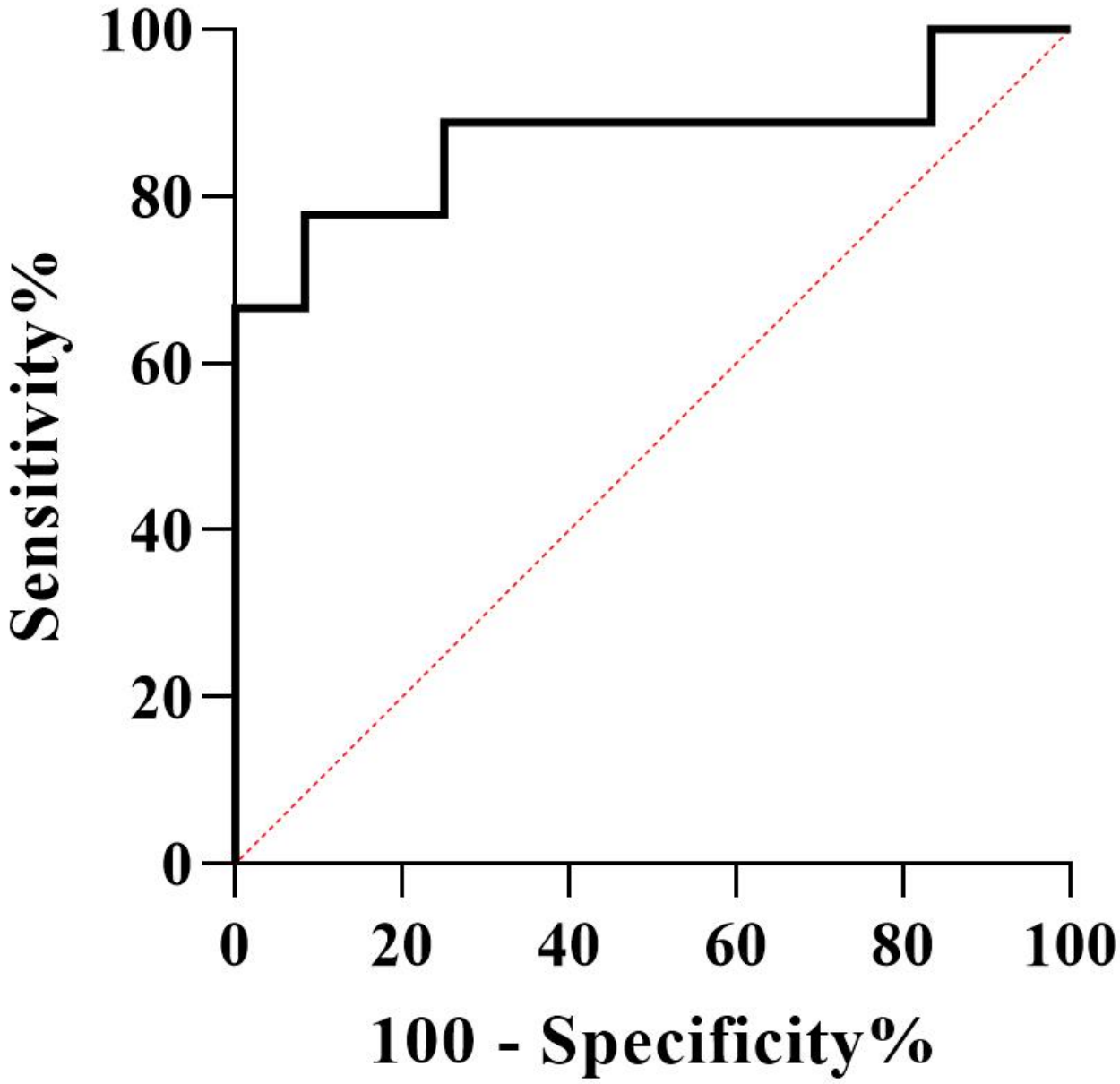

Figure 2

The ROC curve for predicting mortality or ECMO in RCDH according to O/E LHR. The ROC curve for predicting mortality or requirement for ECMO support in neonates with RCDH according to the O/E LHR. The dashed line is the reference line (AUC = 0.870). AUC, area under the curve; ECMO, extracorporeal membrane oxygenation; O/E LHR, observed-to-expected lung area-to-head circumference ratio; ROC, receiver operating characteristic.