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# Lung to thorax transverse area ratio as a predictor of neurodevelopmental outcomes in fetuses with congenital diaphragmatic hernia

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ABSTRACT

*Introduction:* Infants with congenital diaphragmatic hernia (CDH) are at risk of neurodevelopmental disabilities. This study aimed to investigate the association between lung to thorax transverse area ratio (LTR) and neurodevelopmental outcomes at 3 years of age in fetuses with CDH.

*Methods:* We performed a retrospective study of infants with prenatally diagnosed isolated left-sided CDH born in Kyushu University Hospital between 2008 and 2016. We examined the association between prenatal ultrasound findings including LTR and development quotient (DQ) at 36 to 42 months of chronological age.

*Results:* We identified 34 live-born fetuses with isolated left-sided CDH, of which 30 survived and four died before discharge. The median LTR in the survivors was higher than in the non-survivors ($p < 0.01$). Among the survivors, 26 had available data on LTR (median 0.12, range 0.08–0.18) and overall DQ at 3 years of age (93, 61–112). Their median gestational age and birth weight were 37.6 (range 34.4–39.1) weeks and 2716 (2.256–3494) grams, respectively. There was no significant difference in overall DQ scores between the two groups divided according to the median LTR values ($p = 0.62$). LTR values were not associated with overall DQ scores after adjusting for gestational age ($p = 0.39$). In addition, no association was observed between LTR values and any subscale DQ scores.

*Conclusion:* In fetuses with isolated left-sided CDH, prenatal LTR predicts the mortality but not neurodevelopmental outcomes at 3 years of age.

## 1. Introduction

Congenital diaphragmatic hernia (CDH) is a severe congenital abnormality characterized by a defect in the diaphragm that occurs in <5 cases in 10,000 births [1]. The primary causes of respiratory complications in CDH patients are abnormal lung development and compression of developing fetal lungs due to herniation of abdominal viscera into the thoracic cavity, resulting in pulmonary hypoplasia and pulmonary hypertension. These critical conditions are associated with high mortality [2]. Advances in neonatal care and surgical management for infants with CDH have led to improved survival over the past two decades [3,4]. With improvements in survival, however, neurocognitive disabilities and impaired functional outcomes are increasingly recognized in CDH survivors [5,6]. Prenatal risk estimation of both mortality and long-term neurodevelopmental outcomes is essential for families and professionals in neonatal care in making appropriate decisions for high-risk fetuses. Therefore, neurodevelopmental outcomes in CDH patients are of great clinical interest.

The prenatal prediction of severity of pulmonary hypoplasia and thus postnatal survival relies on imaging modalities that indirectly assess

*Abbreviations:* CA, Cognitive-adaptive; CDH, Congenital diaphragmatic hernia; DQ, Development quotient; ECMO, Extracorporeal membrane oxygenation; KSPD, Kyoto Scale of Psychological Development; LHR, Lung area to head circumference ratio; LS, Language-social; LTR, Lung to thorax transverse area ratio; NO, Nitric oxide; o/eLHR, Observed/expected lung area to head circumference ratio; PM, Postural-motor; PPHN, Persistent pulmonary hypertension of the newborn.

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fetal lung volume. Various parameters using prenatal ultrasonography have been proposed as predictors of postnatal survival. Lung area to head circumference ratio (LHR) and observed/expected LHR (o/e LHR) are commonly used worldwide [7,8]. Other indirect prenatal parameters include stomach position [9] and liver herniation [10,11]. In Japan, the lung to thorax transverse area ratio (LTR) has been widely used to assess pulmonary hypoplasia in fetal CDH patients [12–17]. As opposed to LHR, LTR has been reported not to be strongly influenced by the gestational age, and the LTR cut-off value of 0.08 has been significantly correlated with survival in isolated left-sided CDH patients [16,18]. However, it is unclear whether LTR can predict long-term morbidity outcomes in fetuses with CDH.

The present study examined this issue by focusing on whether objective measurements of fetal LTR, an indicator of lung hypoplasia, could accurately predict long-term neurodevelopmental outcomes in fetuses with isolated CDH.

## 2. Methods

### 2.1. Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki and approved by the institutional review board at Kyushu University (#2019–531). Informed consent for parents was substituted with an opt-out process in the ethics committees' approval because all data were anonymized and this was a retrospective study. Parents of the patients were informed on our hospital's website of the planned study and were provided with an option to opt-out from their child's medical records being used in this research.

### 2.2. Study population and data collection

This is a single-center, retrospective, observational study. We reviewed the charts of all patients and their mothers who were referred to our hospital, a tertiary care center, during the gestational period. We included fetuses with prenatally diagnosed isolated left-sided CDH who were born alive at our hospital between April 2008 and April 2016. An isolated CDH was defined as a CDH without any life-threatening or major structural anomalies associated with factors that potentially could influence the LTR measurement or postnatal outcome. We excluded infants lost to follow-up and those without available follow-up data who were followed until age 3 years.

We collected the following prenatal ultrasound findings: the LTR, the o/e LHR, and the presence of intrathoracic stomach and liver. As the timing and number of these measurements differed depending mainly on the timing of referral to our hospital and the timing of delivery, we collected these parameters when they were measured at the first referral to our institution (median 31, range 23–37 weeks of gestational age). The LTR and the o/e LHR were measured at the transverse section containing the four-chamber view of the heart by ultrasonography. Freeze-frame capabilities were available, and on-screen calipers were used for manual measurements. We measured the area of the thorax, bounded by the inner border of bilateral ribs, the posterior edge of the sternum, and the center of the vertebra. The area of the contralateral lung was measured in the same way. The LTR was defined as the cross-sectional area of the contralateral lung divided by the cross-sectional area of the thorax [12]. The LHR was defined as the ratio of the contralateral lung area, which was the product of the longest two perpendicular linear measurements, to the head circumference [7]. The o/e LHR was defined as the observed LHR divided by the expected LHR. The expected LHR was obtained from the formula established by Dekonink et al. [8]. Stomach and liver herniation were defined as any visualization of stomach and liver in the left thoracic cavity, respectively [9–11]. We also reviewed the patient demographics including sex, gestational age at birth, birth weight, Apgar score at 5 min, the use of nitric oxide (NO) inhalation or extracorporeal membrane oxygenation (ECMO), and the surgical procedure performed.

### 2.3. Institutional strategy for management of infants with CDH

All patients were inborn and managed by immediate resuscitation followed by neonatal intensive care, including gentle ventilation mostly with high frequency oscillatory and preoperative stabilization. Inhaled NO was used in the patients with persistent pulmonary hypertension of the newborn (PPHN). PPHN was defined based on a combination of clinical and echocardiographic characteristics. We used ECMO support for patients with PPHN only when they showed clinical deterioration (inability to maintain preductal $SpO_2 > 85$ % or postductal $SpO_2 > 70$ % and/or oxygenation index $\geq$40 for >3 h) due to adverse respiratory events. After respiratory and circulatory stabilization was achieved, we performed primary or patch repair of the diaphragm [19]. The latter was selected if the defect size was not amenable to primary repair.

### 2.4. Neurodevelopmental assessments at 3 years of age

To determine neurodevelopmental outcomes in surviving children with CDH, certified psychologists assessed neurodevelopment using the Kyoto Scale of Psychological Development (KSPD) at 36 to 42 months of chronological age [20]. The KSPD is a standardized and validated developmental test for Japanese children. Through the standardized assessment and scoring procedure, the test can provide the examinee's developmental quotient (DQ). Each value is calculated by estimated developmental age divided by chronological age, and the mean and standard deviation of the DQ are 100.6 and 13.4, respectively [20]. The KSPD comprises three categories: postural-motor (PM), cognitive-adaptive (CA), and language-social (LS) domains. We calculated the overall DQ by averaging the DQ scores of the three categories. The KSPD is widely used in Japan to identify infants and young children at high risk for adverse neurodevelopmental outcome. For patients with CDH in our hospital, we developed a follow-up protocol that included the KSPD test at 3 years of age. In general, a developmental function was categorized as normal (DQ $\geq$ 85), subnormal (DQ 70–84), and delayed (DQ <70) in the KSPD. A DQ score of <70 with KSPD is equivalent to a cognitive score of <85 with Bayley III [20].

### 2.5. Statistical analyses

Continuous and categorical variables were compared using Wilcoxon rank-sum test and Fisher exact test, respectively. Spearman rank-sum test was used to examine the association between continuous variables. We evaluated the relationship between prenatal ultrasound findings and the overall DQ or the DQ of each of the three KSPD domains by performing linear regression analysis. Results with a two-sided $p$-value of <0.05 were considered significant. All analyses were conducted using R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria).

## 3. Results

During the study period, we identified 50 fetuses with prenatally diagnosed left-sided CDH born alive in our hospital. Of these, we excluded 16 infants with congenital heart disease (large ventricular septal defect, double-outlet right ventricle, transposition of the great arteries, tetralogy of Fallot [$n = 3$], hypoplastic left heart syndrome [n = 3], single ventricle, total anomalous pulmonary venous connection), congenital respiratory disease (tracheal agenesis, pulmonary sequestration), brain malformation (Dandy-Walker malformation, microgyria), or chromosomal abnormality (12p duplication). Thus, we identified 34 infants with isolated left-sided CDH. Four infants had died during the neonatal intensive care unit stay, and consequently, 30 infants survived to discharge home. We first compared the perinatal characteristics between surviving ($n = 30$) and non-surviving infants ($n = 4$) were

**Table 1**
Clinical characteristics of the infants with isolated left-sided congenital diaphragmatic hernia.

| | Total | Survivors | Non-survivors | P-value |
|---|---|---|---|---|
| | *n* = 34 | *n* = 30 | n = 4 | |
| Male | 21 (62) | 17 (57) | 4 (100) | 0.14 |
| Prenatal information | | | | |
| LTR | 0.12, 0.04–0.18 | 0.13, 0.08–0.18 | 0.06, 0.04–0.08 | <0.01 |
| o/e LHR, % | 32.4, 12.4–69.8 | 33.9, 22.0–69.8 | 17.1, 12.4–32.2 | <0.01 |
| Stomach herniation | 24 (71) | 20 (67) | 4 (100) | 0.55 |
| Liver herniation | 15 (44) | 11 (37) | 4 (100) | 0.03 |
| Postnatal information | | | | |
| Gestational age at birth, weeks | 37.6, 34.4–39.1 | 37.6, 34.4–39.1 | 37.9, 34.4–38.0 | 0.75 |
| Birth weight, grams | 2674, 2256–3494 | 2674, 2256–3494 | 2795, 1958–3010 | 0.61 |
| Apgar score at 5 min | 7, 3–9 | 7, 3–9 | 5, 4–6 | 0.08 |
| Inhaled nitric oxide | 26 (76) | 23 (77) | 3 (75) | >0.99 |
| ECMO | 2 (6) | 0 (0) | 2 (50) | 0.01 |
| Primary diaphragmatic repair | 20(59) | 20 (67) | 0 (0) | 0.02 |

Values are the number (%) or the median and range. *P*-values were obtained from Wilcoxon rank-sum test for continuous variables and Fisher exact test for dichotomous variables.
LTR: lung to thorax transverse area ratio, n: number, o/e LHR: observed per expected lung to head circumference ratio, ECMO: extracorporeal membrane oxygenation.

(Table 1). The median LTR (0.13 [range, 0.08–0.18] *vs.* 0.06 [0.04–0.08], $p < 0.01$) and o/e LHR (33.9 % [22.0 %–69.8 %] *vs.* 17.1 % [12.4 %–32.2 %], $p < 0.01$) in the survivors were higher than in the non-survivors. When we divided the patients into two groups based on an LTR of 0.08, a previously reported cut-off value [14], the proportion of infants surviving until discharge was 0 % (0/3) for infants with an LTR of <0.08, as compared with 97 % (30/31) for those with an LTR of ≥0.08 ($p < 0.01$).

Among the survivors, we excluded the following infants: one who was lost during the follow-up period and three who were not assessed by the KSPD at 3 years of age because of acute gastroenteritis, not visiting our hospital, and hyperactivity and inattention. The study populations finally consisted of 26 children who had recorded data of the KSPD at 3 years of age. Table 2 shows the clinical characteristics of the study population. The median gestational age and birth weight were 37.6 (range 34.4–39.1) weeks and 2716 (2256–3494) grams, respectively.

To determine whether the measured LTR values could be predictive of neurodevelopmental outcomes, we divided the study population according to the median value of LTR (0.12) and compared the clinical data between children with LTR ≥ 0.12 ($n = 15$) and LTR < 0.12 ($n = 11$) groups (Table 2). The median o/e LHR was higher in LTR ≥ 0.12 group than in LTR < 0.12 group. The other prenatal and postnatal variables did not differ between the two groups. At 3 years of age, the medians of the overall DQ, PM DQ, CA DQ, and LS DQ were 93 (range 61–112), 100 (55–128), 96 (49–110), and 92 (59–117), respectively. There were no differences in the overall DQ and the three KSPD domains at 3 years of age between the two groups.

We investigated the relationship between prenatal ultrasound findings and the overall DQ or each DQ of the three KSPD domains. The overall DQ, PM DQ, CA DQ, and LS DQ were not associated with LTR (Fig. 1A and B), o/e LHR (Fig. 1C and D), or the presence or absence of stomach herniation (Fig. 1E and F) (Table 3). The median of LS DQ was significantly lower in patients with liver herniation than in those without liver herniation (Fig. 1H, rightmost panel); however, the overall DQ, PM DQ, and CA DQ did not differ between patients with and without liver herniation (Fig. 1G and H) (Table 3). Similar findings were observed in linear regression analyses (Table 4). The presence of liver herniation showed a negative impact on LS DQ in the univariate analysis; however, there was no association between liver herniation and LS DQ after adjustment for gestational age at birth. We checked hearing-impaired children at 3 years of age *via* an interview with their parents and found no children with decreased hearing requiring a hearing aid.

**Table 2**
Clinical characteristics of the study population and comparison according to LTR.

| | Total | LTR ≥ 0.12* | LTR < 0.12* | *P*-value |
|---|---|---|---|---|
| | *n* = 26 | n = 15 | n = 11 | |
| Male | 15 (58) | 11 (73) | 4 (36) | 0.11 |
| Prenatal information | | | | |
| LTR | 0.12, 0.08–0.18 | – | – | – |
| o/e LHR, % | 34.0, 22.0–69.8 | 44.9, 24.3–69.8 | 30.2, 22.0–41.1 | <0.01 |
| Stomach herniation | 18 (69) | 10 (67) | 8 (73) | >0.99 |
| Liver herniation | 10 (38) | 4 (27) | 6(55) | 0.22 |
| Postnatal information | | | | |
| Gestational age at birth, weeks | 37.6, 34.4–39. | 37.7, 36.7–39.1 | 37.6, 34.4–38.3 | 0.75 |
| Birth weight, grams | 2716, 2256–3494 | 2644, 2506–3494 | 2762, 2256–3236 | 0.61 |
| Apgar score at 5 min | 7 (3–9) | 8 (3–9) | 6 (3–9) | 0.10 |
| Inhaled nitric oxide | 20 (77) | 11 (73) | 9 (82) | >0.99 |
| ECMO | 0 (0) | 0 (0) | 0 (0) | >0.99 |
| Primary diaphragmatic repair | 18 (69) | 12 (80) | 6 (55) | 0.22 |
| Outcomes at 3 years of age | | | | |
| Overall DQ | 93, 61–112 | 97, 61–112 | 92, 70–103 | 0.62 |
| ≥85 | 21 (81) | 12 (80) | 9 (82) | >0.99 |
| Postural-motor DQ† | 100, 55–128 | 100, 55–128 | 88, 76–107 | 0.22 |
| ≥85 | 19 (76) | 13 (93) | 6 (55) | 0.09 |
| Cognitive-adaptive DQ | 96, 49–110 | 97, 49–106 | 94, 78–111 | 0.68 |
| ≥85 | 20 (77) | 11 (73) | 9 (82) | >0.99 |
| Language-social DQ | 92, 59–117 | 95, 59–117 | 92, 64–100 | 0.31 |
| ≥85 | 19 (73) | 11 (73) | 8 (73) | >0.99 |

Values are the number (%) or the median and range. *P*-values are obtained from Wilcoxon rank-sum test for continuous variables and Fisher exact test for dichotomous variables between children with LTR ≥ 0.12 and with LTR < 0.12.
LTR: lung to thorax transverse area ratio, n: number, o/e LHR: observed per expected lung to head circumference ratio, ECMO: extracorporeal membrane oxygenation, DQ: developmental quotient.
* The cut-off values are set at the median values of LTR.
† Data are not obtained from one infant.

## 4. Discussion

This study first investigated the association between the prenatal LTR and neurodevelopmental outcomes at 3 years of age in fetuses with isolated left-sided CDH. Our study demonstrated that measurements of LTR did not predict long-term neurodevelopmental outcomes in these patients. We also found that, as a group, isolated left-sided CDH survivors had favorable neurodevelopmental outcomes at 3 years of age. As also shown in this study, a cut-off value of LTR of 0.08 or more has been reported to be a reliable predictor of postnatal survival [16,18]. These results have implications when counseling parents regarding expected short- and long-term outcomes of their fetuses.

The ability to accurately determine the prognosis of fetuses with CDH is essential for counseling their families and potential management strategies. To assist with these tasks, several studies investigated the association between neurodevelopmental outcomes in CDH survivors and the severity of pulmonary hypoplasia during the fetal period, that is,

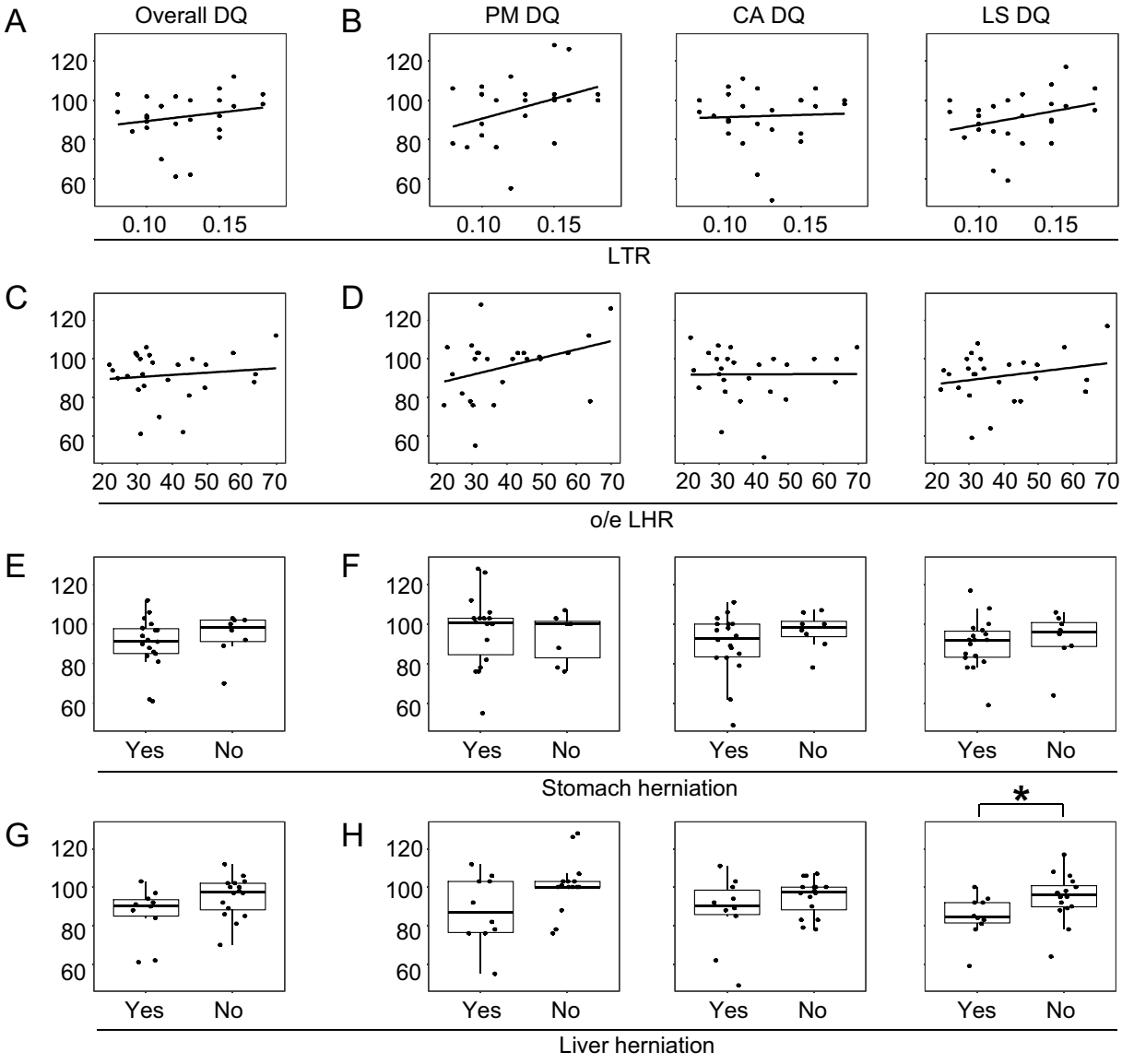


**Fig. 1.** The relationship between prenatal parameters and neurodevelopmental outcomes.
A) LTR and overall DQ, B) LTR and PM DQ, CA DQ, and LS DQ. C) o/e LHR and overall DQ, D) o/e LHR and PM DQ, CA DQ, and LS DQ. E) stomach herniation and overall DQ, F) stomach herniation and PM DQ, CA DQ, and LS DQ. G) liver herniation and overall DQ, H) liver herniation and PM DQ, CA DQ, and LS DQ.
LTR: lung to thorax transverse area ratio, DQ: development quotient, CC: Spearman's correlation coefficient, PM: postural-motor, CA: cognitive-adaptive, LS: language-social, o/e LHR: observed per expected lung area to head circumference ratio. *: $p < 0.05$.

**Table 3**
The relationship between prenatal parameters and neurodevelopmental outcomes.

| | Overall DQ | | Postural-motor DQ | | Cognitive-adaptive DQ | | Language-social DQ | |
|---|---|---|---|---|---|---|---|---|
| | CC | P-value | CC | P-value | CC | P-value | CC | P-value |
| LTR | 0.23 | 0.26 | 0.25 | 0.24 | 0.06 | 0.76 | 0.30 | 0.14 |
| o/e LHR | 0.01 | 0.94 | 0.32 | 0.12 | −0.11 | 0.60 | 0.11 | 0.58 |
| | Score | P-value | Score | P-value | Score | P-value | Score | P-value |
| Stomach herniation | | | | | | | | |
| Yes | 92, 61–112 | 0.31 | 101, 55–128 | 0.54 | 93, 49–111 | 0.30 | 92, 59–117 | 0.37 |
| No | 99, 70–103 | | 100, 76–107 | | 99, 78–107 | | 96, 64–106 | |
| Liver herniation | | | | | | | | |
| Yes | 91, 61–103 | 0.10 | 87, 55–112 | 0.24 | 91, 49–111 | 0.35 | 85, 59–100 | 0.03 |
| No | 98, 70–112 | | 100, 76–128 | | 98, 78–107 | | 96, 64–117 | |

Values are Spearman's correlation coefficients or the median and range. P-values are obtained from Spearman rank-sum test or Wilcoxon rank-sum test.
LTR: lung to thorax transverse area ratio, o/e LHR: observed per expected lung to head circumference ratio, DQ; developmental quotient, CC: Spearman's correlation coefficient.

**Table 4**
The influence of prenatal predictors on the neurodevelopmental outcome at 3 years of age.

| | Crude | | Adjusted* | |
|---|---|---|---|---|
| | β | *P*-value | β | P-value |
| LTR, per 0.01-point increase | | | | |
| Overall DQ | 0.86 ± 0.87 | 0.33 | 0.81 ± 0.92 | 0.39 |
| Postural-motor DQ† | 2.0 ± 1.1 | 0.08 | 1.86 ± 1.15 | 0.12 |
| Cognitive-adaptive DQ | 0.21 ± 0.98 | 0.83 | 0.21 ± 1.04 | 0.84 |
| Language-social DQ | 1.36 ± 0.85 | 0.13 | 1.29 ± 0.90 | 0.16 |
| o/e LHR, per 1 %-point increase | | | | |
| Overall DQ | 0.11 ± 0.19 | 0.56 | 0.10 ± 0.20 | 0.64 |
| Postural-motor DQ† | 0.43 ± 0.24 | 0.08 | 0.40 ± 0.26 | 0.14 |
| Cognitive-adaptive DQ | 0.007 ± 0.22 | 0.98 | 0.003 ± 0.23 | 0.99 |
| Language-social DQ | 0.22 ± 0.19 | 0.26 | 0.20 ± 0.20 | 0.33 |
| Stomach herniation | | | | |
| Overall DQ | −4.0 ± 5.3 | 0.47 | −3.6 ± 5.6 | 0.53 |
| Postural-motor DQ† | 3.7 ± 7.5 | 0.62 | 5.2 ± 7.6 | 0.50 |
| Cognitive-adaptive DQ | −6.7 ± 5.9 | 0.27 | −7.0 ± 6.2 | 0.27 |
| Language-social DQ | −2.6 ± 5.5 | 0.64 | −1.8 ± 5.7 | 0.75 |
| Liver herniation | | | | |
| Overall DQ | −8.8 ± 4.8 | 0.08 | −8.8 ± 5.1 | 0.10 |
| Postural-motor DQ† | −12.6 ± 6.4 | 0.06 | −11.6 ± 6.7 | 0.09 |
| Cognitive-adaptive DQ | −7.6 ± 5.5 | 0.18 | −8.1 ± 5.8 | 0.18 |
| Language-social DQ | −10.0 ± 4.8 | 0.048 | −9.8 ± 5.1 | 0.07 |

β values are mean ± standard error. β and p-values are obtained from linear regression analysis.
LTR: lung to thorax transverse area ratio, o/e LHR: observed per expected lung to head circumference ratio, DQ; developmental quotient.
* The values are adjusted for gestational age at birth.
† Data are not obtained from one infant.

LHR and liver position. Some studies reported adverse neurodevelopmental outcomes in fetuses with CDH who had a low LHR [21–23] or intrathoracic liver position [24,25], whereas others showed a null association between neurodevelopmental outcomes and LHR [6,26] or liver position [6,22,26]. Our study showed a positive correlation between LTR and o/e LHR (Spearman's correlation coefficient = 0.68, $p < 0.01$), as also previously reported [17], and no association between neurodevelopmental outcome and o/e LHR (Table 4, Fig. 1C and D). These results suggest that measurements of LTR during the fetal period may not predict neurodevelopmental outcomes in isolated left-sided CDH. However, there are variations among these studies in the timing of ultrasound assessment during the prenatal period, the method and age of neurological assessments, the number of participants, and the statistical modeling techniques. This heterogeneity has limited the direct comparison of data on prenatal parameters and neurodevelopmental outcomes across studies. Further studies should be designed to better predict neurodevelopmental outcomes in CDH fetuses.

Multiple studies over the past decade have drawn attention to long-term neurodevelopmental outcomes in CDH survivors [5,6,27]. CDH survivors are at significant risk for neurodevelopmental impairment [6,22,27]. The current study demonstrated that most CDH survivors performed well within the normal range, with the median scores of our children slightly lower than the expected score of 100 for the overall and subscale scores on the KSPD (Table 2). The incidences of adverse neurodevelopmental outcomes in our study are somewhat lower than in the previous reports [6,22,27], with one-fifth of all survivors demonstrating subnormal or delayed development on the KSPD test (Table 2). Several risk factors associated with an adverse neurodevelopmental outcome in CDH survivors have been reported: pulmonary hypoplasia, intrathoracic liver position, need for ECMO, right-sided CDH, patch repair, prolonged oxygen supplementation and invasive ventilation, and others [21,24,27,28]. In this study, the more severely affected infants died before discharge and there were no survivors who received ECMO. These results may contribute in part to relatively favorable outcomes. In addition, genetic or environmental factors have been implicated in the pathogenesis of even isolated CDH [29,30]. Understanding the molecular mechanisms underlying the pathology of CDH and their impact on neurodevelopmental outcomes will be the subject of future research.

The extent of liver herniation would be associated with the size of the diaphragmatic defect and may decide the extent to which lung growth is restricted [11]. Therefore, as also shown in this study (Table 1), intrathoracic liver herniation is predictive of poor survival [28]. As the liver position is a predictor of severity, it is not surprising that liver herniation is not only predictive of survival but also predicts neurodevelopmental impairments in CDH patients [27,28]. Our findings suggested a possible association between the fetal liver herniation and language and/or social development, although this relationship did not reach statistical significance after adjustment for gestational age (Table 4, the rightmost panel of Fig. 1H). The direct mechanistic link between them is unclear; however, we speculate that no children with significant hearing loss could have contributed to the nonsignificant results in our cohort.

We acknowledge the limitations of our present study, namely its retrospective nature and small sample size. These preclude drawing definite conclusions or controlling for other potential covariates, including clinical and socioeconomic variables that may affect neurodevelopmental outcomes in multivariable regression analysis. In addition, there were patients lost to follow-up and no comparison with a control group of healthy infants. These may have introduced bias in the sense that an under-or overestimation of true problems may have occurred. Third, both of the two infants treated with ECMO died in this study. Given that ECMO is indicated for patients with severe CDH and survival is expected to be associated with poor neurodevelopmental outcomes, the present results may be partly underestimated. A final limitation was that the timing of LTR measurement varied in this study. Although LTR was reported not to be influenced by the gestational age [16], the prognostic value of LTR can differ based on the timing of measurement. Further studies are needed to determine the best timing of LTR measurement for predicting long-term outcomes.

## 5. Conclusion

A relationship between prenatal LTR and neurodevelopmental outcomes at 3 years of age could not be detected in our study cohort of fetuses with isolated left-sided CDH. Further studies with larger CDH cohorts are needed to determine whether prenatal parameters can predict long-term neurodevelopmental outcomes as well as to better understand the pathophysiology of neurodevelopmental impairments in this population.

## CRediT authorship contribution statement

T.S. and H.I. conceptualized and designed the study, contributed to the analysis and interpretation of the data, drafted the initial manuscript. T.K., G.E., and K.N. conceptualized and designed the study, contributed to the analysis and interpretation of the data, reviewed and revised the manuscript. J.F., M.O., S.K., and Y.F. made substantial contributions to the analysis and interpretation of the data, reviewed and revised the manuscript. Y. S, K·K, T.T., and S.O. supervised the study design, contributed to interpretation of the data, critically reviewed and revised the manuscript.

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## Declaration of competing interest

The authors have no conflicts of interest to declare.

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## References

[1] J.A. Tovar, Congenital diaphragmatic hernia, Orphanet J. Rare Dis. 7 (2012) 1.
[2] D. Ameis, N. Khoshgoo, R. Keijzer, Abnormal lung development in congenital diaphragmatic hernia, Semin. Pediatr. Surg. 26 (2017) 123–128.
[3] H. Okuyama, Y. Kitano, M. Saito, N. Usui, N. Morikawa, K. Masumoto, et al., The japanese experience with prenatally diagnosed congenital diaphragmatic hernia based on a multi-institutional review, Pediatr. Surg. Int. 27 (2011) 373–378.
[4] K.G. Snoek, I.K. Reiss, A. Greenough, I. Capolupo, B. Urlesberger, L. Wessel, Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH EURO consortium consensus - 2015 update, Neonatology 110 (2016) 66–74.
[5] L.E. Hollinger, T.L. Buchmiller, Long term follow-up in congenital diaphragmatic hernia, Semin. Perinatol. 44 (2020), 151171.
[6] R.M. Antiel, N. Lin, D.J. Licht, C. Hoffman, L. Waqar, R. Xiao, et al., Growth trajectory and neurodevelopmental outcome in infants with congenital diaphragmatic hernia, J. Pediatr. Surg. 52 (2017) 1944–1948.
[7] J. Jani, K.H. Nicolaides, R.L. Keller, A. Benachi, C.F. Peralta, R. Favre, et al., Observed to expected lung area to head circumference ratio in the prediction of survival in fetuses with isolated diaphragmatic hernia, Ultrasound Obstet. Gynecol. 30 (2007) 67–71.
[8] P. Dekoninck, E. Gratacos, T. Van Mieghem, J. Richter, P. Lewi, A.M. Ancel, et al., Results of fetal endoscopic tracheal occlusion for congenital diaphragmatic hernia and the set up of the randomized controlled TOTAL trial, Early Hum. Dev. 87 (2011) 619–624.
[9] Y. Kitano, H. Okuyama, M. Saito, N. Usui, N. Morikawa, K. Masumoto, et al., Re-evaluation of stomach position as a simple prognostic factor in fetal left congenital diaphragmatic hernia: a multicenter survey in Japan, Ultrasound Obstet. Gynecol. 37 (2011) 277–282.
[10] C.T. Albanese, J. Lopoo, R.B. Goldstein, R.A. Filly, V.A. Feldstein, P.W. Calen, et al., Fetal liver position and perinatal outcome for congenital diaphragmatic hernia, Prenat. Diagn. 18 (1998) 1138–1142.
[11] D. Mullassery, M.E. Ba'ath, E.C. Jesudason, P.D. Losty, Value of liver herniation in prediction of outcome in fetal congenital diaphragmatic hernia: a systematic review and meta-analysis, Ultrasound Obstet. Gynecol. 35 (2010) 609–614.
[12] T. Hasegawa, S. Kamata, K. Imura, S. Ishikawa, H. Okuyama, A. Okada, et al., Use of lung-thorax transverse area ratio in the antenatal evaluation of lung hypoplasia in congenital diaphragmatic hernia, J. Clin. Ultrasound 18 (1990) 705–709.
[13] S. Kamata, N. Usui, H. Okuyama, T. Sawai, S. Ishikawa, Y. Fukui, et al., Prenatal diagnosis of congenital diaphragmatic hernia and pulmonary hypoplasia and therapeutic strategy, Pediatr. Surg. Int. 11 (1996) 512–517.
[14] M. Nakata, M. Sase, K. Anno, M. Sumie, K. Hasegawa, Y. Nakamura, et al., Prenatal sonographic chest and lung measurements for predicting severe pulmonary hypoplasia in left-sided congenital diaphragmatic hernia, Early Hum. Dev. 72 (2003) 75–81.
[15] K. Tsukimori, K. Masumoto, S. Morokuma, T. Yoshimura, T. Taguchi, T. Hara, et al., The lung-to-thorax transverse area ratio at term and near term correlates with survival in isolated congenital diaphragmatic hernia, J. Ultrasound Med. 27 (2008) 707–713.
[16] N. Usui, Y. Kitano, H. Okuyama, M. Saito, N. Morikawa, H. Takayasu, et al., Reliability of the lung to thorax transverse area ratio as a predictive parameter in fetuses with congenital diaphragmatic hernia, Pediatr. Surg. Int. 27 (2011) 39–45.
[17] N. Usui, H. Okuyama, Y. Kanamori, K. Nagata, M. Hayakawa, N. Inamura, et al., The lung to thorax transverse area ratio has a linear correlation with the observed to expected lung area to head circumference ratio in fetuses with congenital diaphragmatic hernias, J. Pediatr. Surg. 49 (2014) 1191–1196.
[18] S. Kido, N. Hidaka, Y. Sato, Y. Fujita, K. Miyoshi, K. Nagata, et al., Re-evaluation of lung to thorax transverse area ratio immediately before birth in predicting postnatal short-term outcomes of fetuses with isolated left-sided congenital diaphragmatic hernia: a single center analysis, Congenit. Anom. 58 (2018) 87–92.
[19] K. Masumoto, R. Teshiba, G. Esumi, K. Nagata, Y. Takahata, S. Hikino, et al., Improvement in the outcome of patients with antenatally diagnosed congenital diaphragmatic hernia using gentle ventilation and circulatory stabilization, Pediatr. Surg. Int. 25 (2009) 487–492.
[20] Y. Kono, N. Yonemoto, S. Kusuda, S. Hirano, O. Iwata, K. Tanaka, et al., Developmental assessment of VLBW infants at 18 months of age: a comparison study between KSPD and Bayley III, Brain Dev. 38 (2016) 377–385.
[21] R.A. Cortes, R.L. Keller, T. Townsend, M.R. Harrison, D.L. Farmer, H. Lee, Survival of severe congenital diaphragmatic hernia has morbid consequences, J. Pediatr. Surg. 40 (2005) 36–45, discussion -6.
[22] E. Danzer, M. Gerdes, J.A. D'Agostino, E.A. Partridge, C.H. Hoffman-Craven, J. Bernbaum, et al., Preschool neurological assessment in congenital diaphragmatic hernia survivors: outcome and perinatal factors associated with neurodevelopmental impairment, Early Hum. Dev. 89 (2013) 393–400.
[23] J.T. Church, R. Mon, T. Wright, M.A. Coughlin, M. Ladino-Torres, C. Tapley, et al., Neurodevelopmental outcomes in CDH survivors: a single institution's experience, J. Pediatr. Surg. 53 (2018) 1087–1091.
[24] E. Danzer, M. Gerdes, J. Bernbaum, J. D'Agostino, M.W. Bebbington, J. Siegle, et al., Neurodevelopmental outcome of infants with congenital diaphragmatic hernia prospectively enrolled in an interdisciplinary follow-up program, J. Pediatr. Surg. 45 (2010) 1759–1766.
[25] E. Danzer, M. Gerdes, J.A. D'Agostino, C. Hoffman, J. Bernbaum, M.W. Bebbington, et al., Longitudinal neurodevelopmental and neuromotor outcome in congenital diaphragmatic hernia patients in the first 3 years of life, J. Perinatol. 33 (2013) 893–898.
[26] S.K. King, M. Alfaraj, R. Gaiteiro, K. O'Brien, T. Moraes, T. Humpl, et al., Congenital diaphragmatic hernia: Observed/expected lung-to-head ratio as a predictor of long-term morbidity, J. Pediatr. Surg. 51 (2016) 699–702.
[27] L. Montalva, G. Raffler, A. Riccio, G. Lauriti, A. Zani, Neurodevelopmental impairment in children with congenital diaphragmatic hernia: not an uncommon complication for survivors, J. Pediatr. Surg. 55 (2020) 625–634.
[28] E. Danzer, H.L. Hedrick, Neurodevelopmental and neurofunctional outcomes in children with congenital diaphragmatic hernia, Early Hum. Dev. 87 (2011) 625–632.
[29] L. Yu, R.R. Hernan, J. Wynn, W.K. Chung, The influence of genetics in congenital diaphragmatic hernia, Semin. Perinatol. 44 (2020), 151169.
[30] F. Schulz, E. Jenetzky, N. Zwink, C. Bendixen, F. Kipfmueller, N. Rafat, et al., Parental risk factors for congenital diaphragmatic hernia - a large german case-control study, BMC Pediatr. 21 (2021) 278.