The relationship between the L/T ratio and the O/E LHR has not been studied, despite their similarities. The purpose of this study was to clarify the relationship between the L/T ratio and the O/E LHR and to evaluate the compatibility of these parameters as prognostic predictors of fetal CDH based on the results of a nationwide Japanese survey.



**Materials and methods**

*Study population*

This retrospective cohort study was performed as part of a nationwide Japanese survey of neonatal CDH conducted in 2011. This study was conducted after being approved by the ethics committee of Osaka University Hospital (approval number 11017) and the independent ethics committees of five other participating institutions: Hyogo College of Medicine, National Center for Child Health and Development, Kyushu University, Nagoya University Hospital and Osaka Medical Center and Research Institute for Maternal and Child Health. The data obtained from 72 institutions that consented to participate in a questionnaire survey targeted to the departments of pediatric surgery and/or tertiary perinatal care centers of 159 educational hospitals were retrospectively evaluated. Data were collected as case report forms requesting further details about the patients by the data center located in Osaka University Graduate School of Medicine. The entered data were crosschecked twice by the data center and then were fixed after data cleansing. A total of 614 neonates with CDH were born between 2006 and 2010; the overall profiles of the patients are described elsewhere [24]. Among those subjects, the present study was conducted using the data of the 364 isolated CDH cases that were prenatally diagnosed.

Isolated CDH was defined as being present in CDH infants who did not have other serious congenital anomalies, such as major cardiac anomalies or unfavorable chromosomal abnormalities. Three cases of bilateral diaphragmatic hernia were excluded from the study. The contralateral lung area accompanied by the thorax area and/or the head circumference was measured at least one time in 242 out of the 364 cases. The initial and final measurements were reported in the case report form if those parameters were measured more than two times. A total of 242 study subjects (400 measurements), which accounted for 39.4% of all 614 CDH patients treated at 45 institutes, were ultimately included in the present analysis. Among those subjects, the thorax area measurement was reported 339 times for 210 patients and the head circumference measurement was reported 251 times for 154 patients. The contralateral lung area, the thorax area and the head circumference were simultaneously measured 191 times in 120 patients.

*Collected data*

The primary outcome measure was the survival to discharge, which was defined as surviving at the time of discharge from the hospital. The secondary outcome measure was the "intact discharge", which is a new concept for prognostic evaluation, defined as being discharged from the hospital without any major morbidity that requires home treatment, including ventilatory support, oxygen administration, tracheostomy, tube feeding, parenteral nutrition or vasodilator administration [4]. The patient demographics, including the gestational age, birth weight, Apgar score at 1 minute, presence of liver and stomach herniation, mode of delivery, gender and side of hernia, were reviewed. Whether a surgery could be performed, the size of the diaphragmatic defect, the surgical procedure performed, the use of high-frequency oscillatory ventilation (HFOV), nitric oxide inhalation (iNO), prostaglandin $E_1$ or extracorporeal membrane oxygenation (ECMO) were also reviewed. As the indication criteria for surgery were not defined prospectively, the operability of each case was determined according to the clinical decisions of each institution. The highest preductal $PaO_2$, best oxygenation index and the right to left shunting at the ductus which were determined within 24 hours after birth, were reviewed. The contralateral lung area (in square millimeters) and the thorax area (in square millimeters) were measured by manual tracing of the limit of the lung and thorax at the transverse section containing the four-chamber view of the heart in ultrasonography. The head circumference (in millimeters) was measured in the standard biparietal view of ultrasonography. The L/T ratio was defined as the area of the contralateral lung divided by the area of the thorax [19]. The observed LHR, which was the ratio of the contralateral lung to the head circumference, was divided by the appropriate normal mean for gestational age and multiplied by 100 to derive the O/E LHR and expressed as a percentage [21]. The expected LHRs were determined by the published formulas, which are freely available to all by the official calculator in the Tracheal Occlusion To Accelerate Lung Growth (TOTAL) trial website (access http://www.totaltrial.eu/) [12].

*Analysis of the relationship between the L/T ratio and the O/E LHR*

A simple regression analysis was conducted to investigate the relationship between the L/T ratio and the O/E LHR based on the simultaneous measurements in 120 cases. Although the initial and final simultaneous measurements were available in 71 cases, only a single simultaneous measurement was available in 49 cases. We decided to use all simultaneous measurements in order to obtain more accurate relationships between the two parameters. The linear regression equation between the L/T ratio and the O/E LHR was derived from the regression analysis. The L/T ratio values which corresponded to the cut-off values of the O/E LHR used in the TOTAL trial entry criteria were calculated according to the linear regression equation.

*Patient outcome according to the prenatal prediction of the disease severity*

In the 226 cases of left isolated CDH whose liver herniation was evaluated, the survival to discharge rate was reviewed according to the classification of the disease severity used in the TOTAL trial, which were defined by the combination of the O/E LHR and the presence of liver herniation, as proposed by Deprest et al. [25]. In the cases whose O/E LHR was not measured, the O/E LHR was estimated from the L/T ratio using the linear regression equation. The patient demographics, prenatal and postnatal profiles, including parameters indicating the respiratory status, circulatory status, surgical findings and outcome, were compared among the prenatal risk-stratified classifications defined by the combination of the L/T ratio and the presence of liver herniation, as proposed by Usui et al. [16]. In the cases whose L/T ratio was not measured, the L/T ratio was estimated from the O/E LHR using the linear regression equation. The values of the O/E LHR and L/T ratio were represented by the initial values of two measurements in principle, and the final values were substituted for the patients whose initial value was not available in the case report form.

*Statistical analysis*

The statistical analyses were performed using the JMP software program (version 9.02; SAS Institute, Inc, Cary, NC, USA). The frequencies and percentages were used to describe categorical data. The means and standard deviation were used to describe continuous variables. The median and interquartile ranges were used to describe Apgar scores. The chi-square test and Fisher's exact test were used to analyze categorical data. The one-way analysis of variance with Tukey's post-hoc honestly significant difference test was used to compare continuous variables. The Kruskal-Wallis test was used for the comparison of the Apgar scores. The log-rank test and Kaplan-Meier method were used to compare the survival times. Values of $P < 0.05$ were considered to indicate statistical significance.

**Results**

An outline of the patient demographics is shown in Table 1. Of the 242 neonates with prenatally diagnosed isolated CDH, 177 (73.1%) were delivered by Caesarean section and 224 (92.6%) underwent surgical repair for diaphragmatic hernia at a median age of 56 hours after birth. Surgery could not be performed in 18 cases (7.4%) based on the clinical decisions of each institution. It was therefore assumed that these cases were extremely unstable and were considered to be in too serious of a condition to undergo a surgical repair. Two hundred patients (82.6%) survived until discharge, 177 (73.1%) of whom were discharged from the hospital without any major morbidity that required home treatment (**Table 1**).

Table 1

*Relationship between the L/T ratio and the O/E LHR*

Eighteen of the 120 infants whose L/T ratio and O/E LHR were simultaneously determined died, resulting in an 85.0 % survival rate. We found a strong positive correlation between the L/T ratio and the O/E LHR. The linear regression equation between the L/T ratio and the O/E LHR was: L/T ratio = 0.0233 + (0.00222 x O/E LHR), where the regression coefficient was 0.00222, correlation coefficient was 0.847 and coefficient of determination was 0.717 ($p<0.0001$) (**Figure 1**). According to this equation, 15%, 25%, 35% and 45% of the O/E LHRs, the cut-off values used in the TOTAL trial of left CDH patients, were found to be equivalent to 0.06, 0.08, 0.10 and 0.12 L/T ratios, respectively.

Figure 1

Figure 2, Table 2

*Patient outcome according to the prenatal prediction of the disease severity*

In the 226 cases of left isolated CDH, the survival to discharge rate was reviewed according to the four-step stratification proposed by Deprest et al. [25]. The survival rate exhibited a trend toward a decrease as the severity of the disease increased. However, the effect of the liver herniation seemed to be stronger in our series compared to those in the series described by Deprest et al. (**Figure 2**). In the prenatal risk-stratified classification [16], there were no significant differences in the patient demographics except for the side of hernia. There were unsurprisingly significant differences in the rate of liver-up and the L/T ratio based on how the each group was defined (**Table 2**). The highest preductal $PaO_2$ decreased, and the best oxygenation index increased, as the severity of the disease increased. The right to left shunting at ductus evaluated within 24 hours after birth, which suggest the severity of pulmonary hypertension, differed significantly among the three groups, which resulted in the differences in the numbers of patients who used iNO, prostaglandin $E_1$ and ECMO. Although surgical repair could not be performed in only two (1.3%) cases in group A, surgery was not possible in six out of 16 (35.3%) cases in group C due to their unstable conditions. There were also significant differences in the proportions of patients with diaphragmatic defects exceeding 75%, as rated by the surgical record, as well as the need for patch repair. There were significant differences in the morbidity and mortality among the three groups. The rate of survival to discharge was 93% and the intact discharge rate was 87% in group A, whereas the corresponding rates were 72% and 58% in group B and 35% and 18% in group C, respectively (**Table 3**). There were also statistically significant differences in the survival curves among the three groups (**Figure 3**).

Figure 3, Table 3

**Discussion**

Since the mortality and morbidity of neonates with CDH primarily depends on the severity of pulmonary hypoplasia, an accurate prenatal assessment of pulmonary hypoplasia is necessary for making a decision about the optimal treatment. Although many prenatal prognostic parameters have been reported previously [1-4], the assessment of the residual lung size seems to be one of the most reasonable and realistic methods. It has previously been reported that the LHR, which was first described in 1996 [5], was increased according to the gestational age in normal fetuses [21] and also in the fetuses with CDH [11, 19]. The reason for this increase in the LHR with the gestational age is due to the difference in the rate of the increase of the lung area and head circumference. Peralta et al. reported that there was a four-fold increase in the LHR between 12 and 32 weeks of gestation in normal fetuses because of these differences [21]. Approaches to standardize the LHR by using the normal mean value of the LHR have been proposed to provide a constant value throughout the gestational period [11]. The LHR was originally defined as the contralateral lung area determined using a two-dimensional perpendicular linear measurement, divided by the head circumference [5]. However, two other methods to determine the lung area were subsequently proposed [9, 21], and the tracing method was finally found to be the most reproducible method to measure the lung area [21, 23].

The L/T ratio has been widely used in Japan, because it was first described in 1990 for the assessment of pulmonary hypoplasia in CDH [6], and was has been applied for the assessment of pulmonary hypoplasia in CDH neonates since then [15, 16, 26]. The L/T ratio was originally reported to be constant throughout the gestational period in normal fetuses [6]. This parameter was redefined as the contralateral lung area, to make it more consistent with the LHR, divided by the area of the thorax as measured by the tracing method [19], although the original definition was determined by using the area of both lungs. Thus, there are several similarities between these two parameters. First, both parameters exhibit constant values throughout the gestational period, and the other is that only the contralateral lung area is measured by using the tracing method. However, the relationship between these two parameters has not been studied, despite their similarities.

A strong positive correlation between the L/T ratio and the O/E LHR was found, and a linear regression equation between the L/T ratio and the O/E LHR was obtained. According to this linear regression equation, several important cut-off values of both parameters can be interchanged. Interestingly, a 25% O/E LHR, the cut-off value for the most severe cases as used in the TOAL trial for fetal CDH, was found to be equivalent to a L/T ratio of 0.08, a commonly accepted cut-off value for identifying the most severe cases of fetal CDH in Japan. These results suggested that the patients considered to be the most severe cases in Japan also met the criteria for fetal intervention for left CDH patients with severe pulmonary hypoplasia in the TOTAL trial protocol, which was the first international prospective randomized controlled trial for fetoscopic tracheal occlusion [12, 13]. In the nationwide Japanese survey for fetal CDH, 57.7% of the patients were measured for the L/T ratio, and only 42.3% of the patients were measured for the O/E LHR. However, owing to this conversion equation, both of the parameters can be generated for the evaluation of the patient CDH severity if either of the parameters was measured.

To verify the accuracy and the universal applicability of the prenatal risk-stratified classification, which was proposed by Usui et al., and was defined as the combination of the L/T ratio and the presence of liver herniation [16], we applied the classification to this cohort as a different population from the original cohort using the conversion equation. Although the patient demographics except for the side of the hernia, were similar between the three groups classified using this system, the prenatal and postnatal profiles, including the stomach position, parameters indicating the respiratory status, circulatory status, surgical findings and outcome were significantly different between the three groups, suggesting that the prenatal risk-stratified classification is also valid in other cohorts, such as that in the nationwide Japanese questionnaire survey. The indication for a fetal intervention of the patients proposed by Deprest et al. [25] can be estimated by using the conversion equation in the patients whom the L/T ratio was solely measured without measurement of LHR. The rate of survival to discharge was 93% in the mild group, 80% in the moderate group, 52% in the severe group and 43% in the extreme group (**Figure 2**). Compared to this four-step stratification used in the TOTAL trial, our prenatal risk-stratified classification therefore seems to have better discrimination of disease severity. It is possible to describe the prenatal risk-stratified classification as shown in Table 4 using the O/E LHR instead of the L/T ratio according to the linear regression equation (**Table 4**).

Table 4

When the characteristics of both parameters were compared, the gestational variation and the procedure of the lung area measurements were similar. However, there were concerns that the individual fetal growth variation is not considered when determining the O/E LHR. There may be a possibility for an overestimation in a small-for-date fetus, as the O/E LHR of these fetuses, which should have a lower LHR compared to an appropriate-for-date fetus, would be evaluated based on the normal mean value. The L/T ratio includes, by nature, individual fetal growth variation, and it can be determined with standard values for gestational age or with for a relevant population. More importantly, calculating the L/T ratio is a simple task to perform.

A major limitation of this study is that it was conducted in a retrospective manner using a questionnaire. Many of the institutions had a small number of cases, and the treatment strategies, including the indication criteria for surgery, were determined by each institution. There may have been inaccurate measurement of both parameters due to the limited experience of the physicians with such infants. More accurate prospective studies and an analysis of the correlation based on the timing of the measurement are therefore needed to confirm the present findings. Despite these limitations, an excellent positive correlation was observed between the L/T ratio and O/E LHR in the present study, and these two parameters proved to be compatible according to a linear regression equation. These results suggested that the linear regression equation may become a useful tool for all populations.

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## Figure legends

**Figure 1:**

The relationship between the O/E LHR and the L/T ratio. There was a linear positive correlation between the L/T ratio and the O/E LHR. The linear regression line was: L/T ratio = 0.0223 + (0.00222 x O/E LHR), where the regression coefficient was 0.00222, the correlation coefficient was 0.847 and the coefficient of determination was 0.717 ($p<0.0001$). The open triangles represent the survivors and the closed triangles represent the non-survivors. The 25% O/E LHR was equivalent to a L/T ratio of 0.08 according to this equation, as indicated by broken lines.



**Figure 2:**

The survival rates depending on the O/E LHR measurements and presence of liver herniation.

*: Liver-up, liver occupying more than one-third of the thoracic space

**Figure 3:**

The survival curves for patients with isolated CDH, compared using the prenatal risk-stratified classification [16]. *, $P < .001$; **, $P < .001$; †, $P < .001$

**Table 1:**

The patient demographics

**Table 2:**

The patient demographics and prenatal findings according to the prenatal risk-stratified classification [16]

**Table 3:**

The respiratory status, circulatory status, intraoperative findings and outcomes according to the prenatal risk-stratified classification [16]

**Table 4:**

The prenatal risk-stratified classification described using the O/E LHR instead of the L/T ratio

**Table 1: The patient demographics**

| | |
|---|---|
| Number of patients | 242 |
| Gestational age (days) † | 264.3 ± 8.6 |
| Birth weight (g) † | 2746 ± 386 |
| Apgar score at 1min § | 4, (2 - 6) |
| Liver-up * | 68/239 (28.5%) |
| Contralateral stomach herniation ** | 35/236 (14.8%) |
| Caesarean section delivery | 177 (73.1%) |
| Gender (male) | 138 (57.0%) |
| Side of hernia (left) | 229 (94.6%) |
| Surgery performed for diaphragmatic hernia | 224 (92.6%) |
| Time of surgery after birth (hours) § | 56, (30 - 95) |
| Patch closure | 81/224 (36.2%) |
| Use of HFOV | 212/233 (91.0%) |
| Use of iNO | 166/241 (68.9%) |
| Use of ECMO | 19 (7.9%) |
| Survival to discharge | 200 (82.6%) |
| Intact discharge | 177 (73.1%) |

†: mean ± standard deviation, §: median, (interquartile range), *: Liver-up, liver occupying more than one-third of the thoracic space; **: Contralateral stomach herniation, more than half of the stomach was herniating into the contralateral thoracic cavity; HFOV: high-frequency oscillatory ventilation, iNO: inhaled nitric oxide, ECMO: extracorporeal membrane oxygenation

**Table 2. The patient demographics and prenatal findings according to the prenatal risk-stratified classification [16]**

| | Group A | Group B | Group C | *P* |
|---|---|---|---|---|
| Definition of the group [16] | L/T ratio ≥ 0.08 with liver-down | L/T ratio ≥ 0.08 with liver-up * or L/T ratio < 0.08 with liver-down | L/T ratio < 0.08 with liver-up * | |
| Number of patients | 151 | 71 | 17 | |
| Gender (male) | 89 (58.9%) | 36 (50.7%) | 12 (70.6%) | 0.265 |
| Side of hernia (left) | 149 (98.7%) | 64 (90.1%) | 13 (76.5%) | < 0.001 |
| Gestational age at birth (days) | 265 ± 7.7 | 263± 10.6 | 264 ± 6.9 | 0.313 |
| Birth weight (kg) | 2.76 ± 0.37 | 2.68 ± 0.45 | 2.87 ± 0.26 | 0.141 |
| Caesarian section delivery | 109 (72.2%) | 53 (74.7%) | 12 (70.6%) | 0.908 |
| Liver-up * | 0 (0.0%) | 51 (71.8%) | 17 (100%) | < 0.001 |
| Contralateral stomach herniation | 5/148 (3.4%) | 20/71 (28.2%) | 10/17 (58.8%) | < 0.001 |
| L/T ratio | 0.148 ± 0.053** | 0.106 ± 0.039† | 0. 059 ± 0.020‡ | < 0.001 |

*: Liver-up, liver occupying more than one-third of the thoracic space; Contralateral stomach herniation, more than half of the stomach was herniating into the contralateral thoracic cavity; L/T ratio, contralateral lung to thorax transverse area ratio; **, *P* < .05 A vs B; †, *P* < .05 B vs C; ‡, *P* < .05 C vs A;

**Table 3. The respiratory status, circulatory status, intraoperative findings and outcomes according to the prenatal risk-stratified classification [16]**

| | Group A | Group B | Group C | *P* |
|---|---|---|---|---|
| Definition of the group [16] | L/T ratio ≥ 0.08 with liver-down | L/T ratio ≥ 0.08 with liver-up * or L/T ratio < 0.08 with liver-down | L/T ratio < 0.08 with liver-up * | |
| Number of patients | 151 | 71 | 17 | |
| Apgar score at 1 min | 5 (3-7) (n=143) | 4 (2-5) (n=66) | 2.5 (1.25-4) (n=16) | < 0.001 |
| Highest preductal $PaO_2$ (Torr) § | 257 ± 134** (n=145) | 199 ± 135† (n= 69) | 75 ± 70‡ (n=17) | < 0.001 |
| Best oxygenation index § | 5.7 ± 5.9** (n=143) | 14.3 ± 17.5† (n=68) | 32.0 ± 24.5‡ (n=17) | < 0.001 |
| Right to left shunting at ductus § | 55/143 (38.5%) | 40/68 (58.8%) | 13/17 (76.5%) | 0.001 |
| Use of HFOV | 130/145 (89.7%) | 64/69 (92.8%) | 16/17 (94.1%) | 0.680 |
| Use of iNO | 85/151 (56.3%) | 63/71 (88.7%) | 15/16 (93.8%) | < 0.001 |
| Use of prostaglandin $E_1$ | 45/149 (30.2%) | 35/71 (49.3%) | 14/17 (82.4%) | < 0.001 |
| Use of ECMO | 4 (2.7%) | 9 (12.7) | 5 (29.4%) | < 0.001 |
| Inoperable cases | 2 (1.3%) | 10 (14.1%) | 6 (35.3%) | < 0.001 |
| Diaphragmatic defects ≥ 75% †† | 27/149 (18.1%) | 38/61 (62.3%) | 8/11(72.7%) | < 0.001 |
| Patch closure | 31/149 (20.8%) | 40/61 (65.6%) | 8/11 (72.7%) | < 0.001 |
| Survival to discharge | 141 (93.4%) | 51 (71.8%) | 6 (35.3%) | < 0.001 |
| Intact discharge | 131 (86.8%) | 41 (57.8%) | 3 (17.7%) | < 0.001 |

*, Liver-up, liver occupying more than one-third of the thoracic space; §, The highest pre $PaO_2$, best oxygenation index and the right to left shunting at ductus were determined within 24 hours after birth; ††, The size of the diaphragmatic defect was rated by a surgeon according to the surgical record. **, $P < .05$ A vs B; †, $P < .05$ B vs C; ‡, $P < .05$ C vs A HFOV, high-frequency oscillatory ventilation, iNO, nitric oxide inhalation; ECMO, extracorporeal membrane oxygenation