Table 1 Characteristics of patients with left congenital diaphragmatic hernia

Characteristic	Median (range) or n (%)
Prenatal data	
Gestational age at diagnosis (weeks)	28 (17–40)
Liver position	
Up	40 (36.7)
Down	69 (63.3)
Stomach position	
Grade 0	21 (19.3)
Grade 1	50 (45.9)
Grade 2	15 (13.8)
Grade 3	23 (21.1)
Initial LHR	1.59 (0.37–4.23)
Gestational age at initial LHR (weeks)	31 (18–40)
Polyhydramnios	22 (20.2)
Postnatal data	
Gestational age at birth (weeks)	38.3 (28.4–41.0)
Birth weight (kg)	2.79 (1.04–4.03)
Sex	
Male	59 (54.1)
Female	50 (45.9)
Mode of delivery	
Vaginal	51 (46.8)
Cesarean section	58 (53.2)
Apgar score at 1 min	4 (1–9)

LHR, lung-to-head ratio.
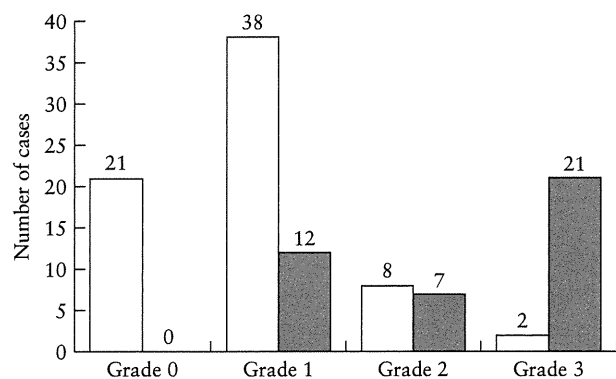
Figure 2 Frequency of each of the four grades of stomach position in liver-down (□) and liver-up (■) patients with left congenital diaphragmatic hernia. Stomach herniation into the right chest was not uncommon, especially in liver-up cases.

Table 2 Univariate analysis to determine factors significantly associated with intact discharge failure, including death, of patients with left congenital diaphragmatic hernia

Variable	Crude OR (95% CI)	P
Liver position (up)	17.58 (6.56–47.12)	< 0.001
Stomach position		
Grade 0	Reference	< 0.001*
Grade 1	6.3 (0.8–52.1)	—
Grade 2	13.3 (1.4–127.6)	—
Grade 3	95.0 (9.7–928.3)	—
LHR (per 0.5)	0.34 (0.20–0.60)	< 0.001
GA at diagnosis (< 30/≥ 30 weeks)	0.99 (0.96–1.02)	0.326
Polyhydramnios	1.43 (0.55–3.75)	0.463

*Cochran–Armitage test for trend. GA, gestational age; LHR, lung-to-head ratio; OR, odds ratio.

Table 3 Multiple logistic regression for intact discharge failure, including death, of patients with left congenital diaphragmatic hernia

Variable	Adjusted OR (95% CI)	P
Liver position (up)	6.52 (1.79–23.82)	0.005
Stomach position (per grade)	2.59 (1.21–5.53)	0.014
LHR (per 0.5)	0.58 (0.30–1.11)	0.100

A stepwise selection method (variable selection criteria, $P < 0.20$) was used to select the correlated variables from those in Table 2. LHR, lung-to-head ratio; OR, odds ratio.
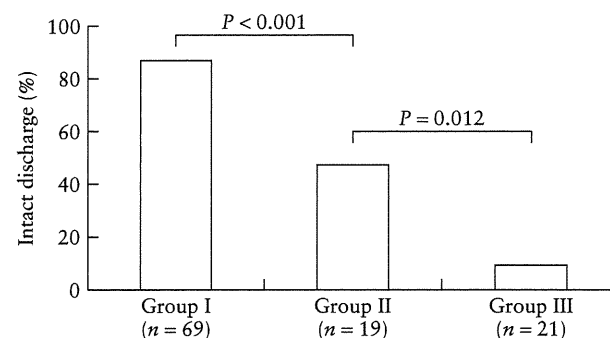
Figure 3 Our new grouping system of fetal patients with isolated left congenital diaphragmatic hernia using liver and stomach positions. Intact discharge rate was significantly different among the three groups (Group I, liver-down; Group II, liver-up and stomach position Grade 0–2; Group III, liver-up and stomach position Grade 3).

better long-term outcomes must be assessed in future studies.

Although LHR is the most commonly used prenatal predictor of survival[19,20], it is sometimes difficult to identify the margin of the hypoplastic lung in the severe form of CDH. Therefore, LHR is not free from interinstitution and interobserver variation. Additionally, unadjusted LHR has been shown to increase with gestational age[21–23]. The prognostic value of LHR has been questioned[24–26], and the observed to expected (o/e) LHR[22] has been developed to overcome this. O/e LHR measurement requires normal control values in each population.

Stomach position has been used previously as a prenatal prognostic factor for CDH[5–7]. However, its prognostic role was replaced by LHR, and little attention has been paid to stomach herniation into the right chest cavity. Previously, we observed in a small series that stomach herniation into the right chest is an ominous sign in fetal left CDH[8]. To test the hypothesis that herniation into the right chest is related to poor outcome, we developed a new grading system, categorizing the degree of stomach

herniation into four grades. We found that stomach herniation into the right chest is not uncommon, especially in liver-up cases (Figure 2). Multivariate analysis revealed the strongest prognostic variable for intact discharge to be liver position, followed by stomach position. The OR of LHR was not statistically significant, possibly because it was not adjusted for gestational age at measurement or because of the retrospective study design involving multiple centers.

Finally, we propose a simple classification for fetal left CDH involving liver and stomach position (Figure 3). This classification may be useful in estimating the patient's prognosis and in planning perinatal management, including maternal transport to high volume centers or those offering fetal intervention, especially in cases in which o/e LHR is difficult to obtain. The fact that Group III patients had only a 9.5% chance of intact discharge shows the limitations of a gentle ventilation strategy, and could be the starting point for future trials of fetal intervention in Japan.

A major limitation of this study was late diagnosis of CDH. The initial measurement of LHR was conducted at a median of 31 weeks of gestation. This fact should be considered when using the present data to identify candidates for fetal intervention now being performed at 26–28 weeks of gestation[13]. However, neither liver nor stomach position changes dramatically over time; none of the 23 liver-up patients before 30 weeks was judged as being liver-down after 30 weeks. Similarly, only two of the 10 patients with Grade 3 stomach herniation before 30 weeks were judged as being Grade 2 later in gestation. Another limitation was the retrospective study design using case report forms. Interobserver variation cannot be discounted since it was not possible to have all prenatal imaging reviewed by a single person. Because it was not possible in every center to collect o/e LHR[22], MRI lung volume[27] and MRI lung intensity[28], these measurements were not analyzed. Therefore, our findings need to be confirmed in future prospective studies.

ACKNOWLEDGMENTS

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ORIGINAL ARTICLE

Reliability of the lung to thorax transverse area ratio as a predictive parameter in fetuses with congenital diaphragmatic hernia

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Abstract

Purpose An accurate prenatal assessment of the patients' severity is essential for the optimal treatment of individuals with congenital diaphragmatic hernia (CDH). The purpose of this study was to clarify the reliability of the lung to thorax transverse area ratio (L/T) as a prenatal predictive parameter. *Methods* A multicenter retrospective cohort study was conducted on 114 isolated CDH fetuses with a prenatal diagnosis during the period between 2002 and 2007 at five participating centers in Japan. The relationship between the gestational age and the L/T was analyzed. The most powerful measurement point and accurate cutoff value of the L/T was determined by an analysis of a receiver operating characteristic curve, which was verified by comparing the patients' severity.

Results There was a negative correlation between the gestational age and the L/T in the non-survivors, and no correlation in the survivors. There were significant differences in the parameters which represented the patients' severity including the respiratory and circulatory status, the surgical findings, and the final outcomes between the groups divided at 0.080 in the minimum value of the L/T during gestation.
Conclusion The L/T was not strongly influenced by the gestational age, and it was found to be a reliable prenatal predictive parameter in fetuses with isolated CDH.

Keywords Congenital diaphragmatic hernia · Prenatal diagnosis · Predictive parameter · Prognostic factor · Pulmonary hypertension · Severity

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Introduction

Postnatal mortality and morbidity of fetuses with congenital diaphragmatic hernia (CDH) mainly depends on the severity of the pulmonary hypoplasia. An accurate prenatal assessment of pulmonary hypoplasia is essential to plan an optimal treatment strategy for individual cases before birth. Many prenatal prognostic parameters, which are estimated by ultrasonography or MRI, such as fetal lung size [1–4], liver or stomach position [5–7], signal intensity of the fetal lungs [8], and pulmonary artery blood flow [9] have been previously proposed by various investigators. The lung area to head circumference ratio (LHR) [1, 10] and the lung to thorax transverse area ratio (L/T) [2, 11] are the predictive parameters in which the fetal lung size is measured by ultrasonography. However, several investigators have been skeptical about the reliability and usefulness of LHR in predicting the outcome of the fetuses with CDH [12–14]. It is necessary for the LHR to be standardized by the normal values obtained from normal fetuses, because the LHR increases significantly with gestational age in fetuses with CDH [11, 15] as well as in normal fetuses [15, 16]. Therefore, the LHR value is no longer considered independently predictive of survival [6]. In contrast, L/T was originally reported to be a constant parameter throughout the gestational period in the normal fetuses [2]. However, it is unclear whether the L/T changes significantly with gestational age in fetuses with CDH [15]. The purpose of this study was to clarify the reliability of the L/T by an analysis of the change in the L/T with gestational age and to identify the most accurate cutoff value of the L/T for a prediction of patients' postnatal severity in isolated CDH.

Materials and methods

Study population

This multicenter retrospective cohort study included the prenatally diagnosed, isolated CDH fetuses that were born at five participating centers during the period between January 2002 and December 2007. The National Center for Child Health and Development, Kanagawa Children's Medical Center, Osaka Medical Center and Research Institute for Maternal and Child Health, Kyushu University Hospital, and Osaka University Hospital participated in this study. Patients with serious associated anomalies such as major cardiac anomaly and unfavorable chromosomal abnormalities were not included in this study. Cases with bilateral diaphragmatic hernia and cases where neither the LHR nor L/T was measured were also excluded from this study. All patients were inborn and managed by immediate resuscitation followed by neonatal intensive care including gentle ventilation with high-frequency oscillatory ventilation. To successfully carry out the gentle ventilation strategy, the goals of the arterial blood gas data were set at $PaCO_2 < 70$ mmHg and preductal $SpO_2 \geq 90\%$/preductal $PaO_2 \geq 70$ mmHg. Once these gas data were obtained, the ventilator settings including FiO_2 and the mean airway pressure decreased immediately. Inhaled nitric oxide (NO) was used in the patients with persistent pulmonary hypertension of the newborn. This study was approved by the institutional review board of each participating center.

Collected data

The primary outcome measures were the overall survival, which was defined as surviving until the end of the observation period, and intact discharge, which was defined as being discharged from the hospital without any need for home treatment such as ventilatory support, oxygen administration, tube feeding, and parenteral nutrition. The postnatal factors including the Apgar scores at 1 and 5 min, highest PaO_2 and lowest $PaCO_2$ in the pre-ductal artery within 24 h after birth, duration of NO inhalation, duration of ventilatory support, duration of oxygen inhalation, need for extra corporeal membrane oxygenation (ECMO), need for prostaglandin E_1 administration [17], surgical findings and survival time were also collected. The L/T and the LHR were measured at the transverse section containing the four-chamber view of the heart by ultrasonography. The L/T was defined as the area of contralateral lung divided by the area of the thorax [11]. 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 [1, 18]. The L/T and the LHR values were collected up to three measurement times according to the gestational age at diagnosis; the earliest measurement before 30 weeks of gestation, the earliest measurement between 30 and 35 weeks of gestation, and the earliest measurement after 35 weeks of gestation.

Analysis of relationship and determination of cutoff value in L/T and LHR

The relationship between the gestational age with the L/T and the LHR was analyzed by subgroups divided according to the outcomes. Logistic regression models were used with the survival and intact discharge as response variables to explore the most powerful measurement point of the L/T and LHR for a prediction of outcomes. The explanatory variables were the earliest value, the latest value, the minimum value, and the maximum value during the gestation. Then the receiver operating characteristic (ROC) curves was calculated to examine the performance of each

value. The area under the ROC curve (AUC) was used as an index of global performance, with an AUC of 0.5 indicating no discrimination ability. The efficacy of a screening test is dependent not only on its overall accuracy assessed by the AUC, but also on the consequences of misclassification associated with sensitivity and specificity. The point maximizing the difference between the sensitivity and the false-positive rate was evaluated as the most accurate cut off point of L/T and LHR for discriminating the survival and intact discharge. The patients' postnatal profiles, including the parameters which represented the severity concerning respiratory status, circulatory support, surgical findings, and prognosis, were compared between the groups divided at the accurate cutoff value to assess the usefulness of the adequate cutoff value of appropriate L/T.

Statistical analysis

The median and interquartile range or the mean and standard deviation were used to describe continuous variables; frequency and percentages were used to describe the categorical data. Either the Wilcoxon rank sum test or Student's t test was used for comparison of continuous variables. Fisher's exact test was used for analysis of categorical data. The log-rank test and Kaplan–Meier method were used to compare the duration of respiratory managements and survival time. p values of less than 0.05 were considered to indicate statistical significance.

Results

The L/T or LHR were measured at least one time in 114 patients with isolated unilateral fetal CDH who were managed in the participating centers in the study period. Eighty-seven infants (73.3%) were alive until the end of the observation period and 74 infants (64.9%) were discharged from the hospital without any home treatment. The median survival time of the survivors was 1,052 (595–1,496) days, and the median survival time of the non-survivors was 12 (2–57) days. Among them, the L/T was measured 211 times in 103 patients, the LHR was measured 200 times in 100 patients and both of them were measured simultaneously 168 times in 89 patients.

Relationship between L/T and LHR with gestational age

No correlation was observed between the gestational age and the L/T in survivors, although there was a negative correlation between those variables in non-survivors. On the other hand, there were positive correlations between the gestational age and the LHR both in survivors and

non-survivors (Fig. 1; Table 1). A negative correlation was observed only between the gestational age and the L/T in infants who died or needed home treatment. On the contrary, a positive correlation was recognized only between the gestational age and the LHR in patients with intact discharge (Fig. 2; Table 1).

Determination of most appropriate cutoff value in L/T for discriminating the outcome

The AUC for discriminating the survivors demonstrated the maximum when the minimum value of the L/T was applied (Table 2). In contrast, the AUC for discriminating the survivors demonstrated the maximum when the maximum value of LHR was applied (Table 2). The difference between the sensitivity and the false-positive rate was maximized with the cutoff value of 0.080 for the minimum L/T and with the cutoff value of 2.04 for the maximum LHR (Table 2). The best AUC in the L/T was greater than the best AUC in the LHR (Table 2; Fig. 3). The AUC for discriminating the intact discharge also demonstrated a maximum when either the minimum value of the L/T was applied or the maximum value of LHR was applied (Table 3). The difference between the sensitivity and the false-positive rate of the minimum L/T was also maximized with the cutoff value of 0.080 (Table 3).

Comparison of the patients' severity in each predictive group divided by the cutoff value of the L/T

The patients were divided into two predictive groups according to the cutoff value of 0.080 in the minimum value of the L/T. Although there was no significant difference in the patients' demographic profiles between the two groups, there were statistically significant differences in the respiratory status such as Apgar scores, arterial blood gas data, and the duration of respiratory support, in the necessity of circulatory support such as ECMO and prostaglandin E_1 administration, in the surgical findings such as operability, diaphragmatic defect size and the need for patch closure and in the final outcomes (Table 4). There was also a significant difference in the survival curve between the two groups (Fig. 4).

Discussion

Although the original definition of the L/T was calculated from both areas of the contralateral lung and ipsilateral lung [2], the L/T was calculated as the ratio of the contralateral lung area to the thorax area in this study, as it has been used in the measurement of the LHR and has also been reported previously in the measurement of the L/T [11]. It seems to

Fig. 1 Relationship between the gestational age with the L/T and the LHR in the fetuses with congenital diaphragmatic hernia by survival and non-survivors. The *open circles* and *dashed regression line* (LHR = 0.344 + 0.00677GA) represent the survivors and the *closed squares* and *solid regression lines* (L/T = 0.187 − 0.000434GA, LHR = 0.386 + 0.00455GA) represent the non-survivors. *GA* gestational age
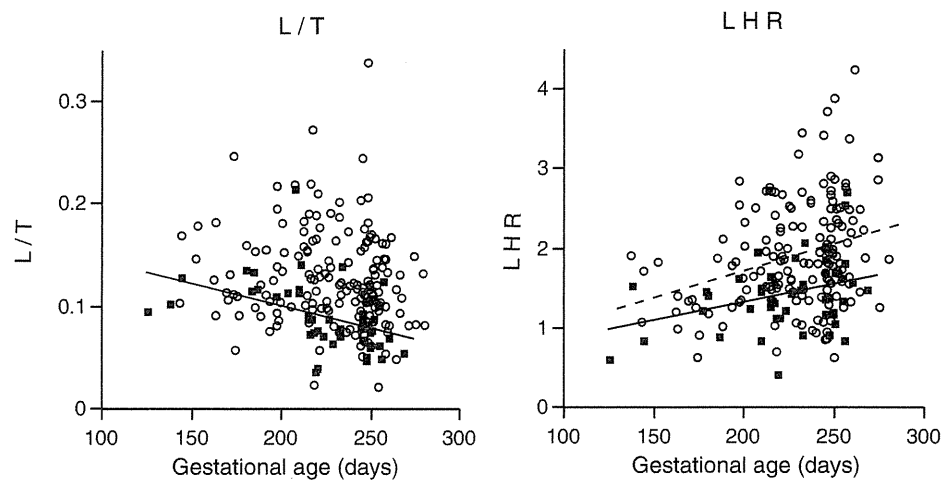

Table 1 Relationship between the gestational age, the lung to thorax transverse area ratio (L/T), and the lung area to head circumference ratio (LHR) in the fetuses with congenital diaphragmatic hernia according to survival and intact discharge

Outcome	Gestational age with L/T			Gestational age with LHR		
	n	CC	p	n	CC	p
Survival	166	−0.141	0.056	151	0.296	<0.001
Non-survival	45	−0.411	0.001	49	0.301	0.022
Intact discharge	139	−0.113	0.163	126	0.356	<0.001
Died or needed home treatments	72	−0.343	0.001	74	0.172	0.109

CC correlation coefficient

Fig. 2 Relationship between the gestational age with the L/T and the LHR in the fetuses with congenital diaphragmatic hernia according to intact discharge and non-intact discharge. The *open circles* and *dashed regression line* (LHR = 0.159 + 0.00796GA) represent the infants with intact discharge and the *closed squares* and *solid regression line* (L/T = 0.201 − 0.000469GA) represent the infants without intact discharge. *GA* gestational age
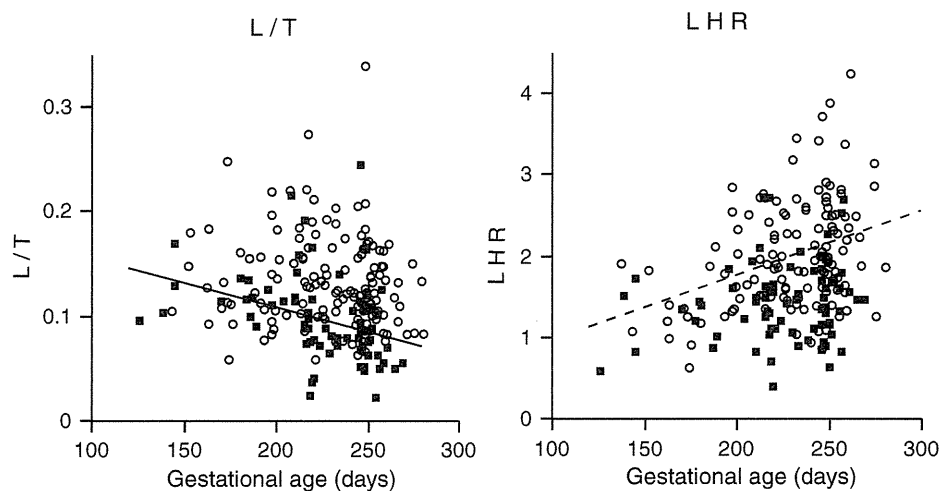
be reasonable to use only the contralateral lung area for determination of the L/T, because the ipsilateral lung is invisible in many cases at the transverse section containing the four-chamber view of the heart because of cranial dislocation of the ipsilateral lung [11]. There is also a possibility of over-estimation in measuring the ipsilateral lung area because of the close similarity of ultrasonographic appearance of the ipsilateral lung and the intestine or

spleen. A manual tracing of the limit of the lungs, which is conducted in the measurement of the L/T, has been reported to be the most reproducible measurement rather than a multiplication of lung diameters for the assessment of lung area [16, 18].

The present study found that the LHR were increased according to the gestational age both in the subgroups of survivors and non-survivors, as it has been previously

Table 2 The AUC and the best cutoff value for survival which maximize the difference between the sensitivity and false-positive rate in various representative values of L/T and LHR during gestation

AUC area under the ROC curve

[a] Maximum area under the receiver-operating characteristic (ROC) curve

| Representative value of L/T and LHR	AUC	Difference between sensitivity and false-positive rate	The best cutoff value
L/T			
The earliest value	0.721	0.347	0.077
The latest value	0.761	0.457	0.107
The minimum value	0.776[a]	0.521	0.080
The maximum value	0.739	0.444	0.142
LHR			
The earliest value	0.735	0.498	1.59
The latest value	0.729	0.441	1.85
The minimum value	0.746	0.476	1.59
The maximum value	0.750[a]	0.459	2.04
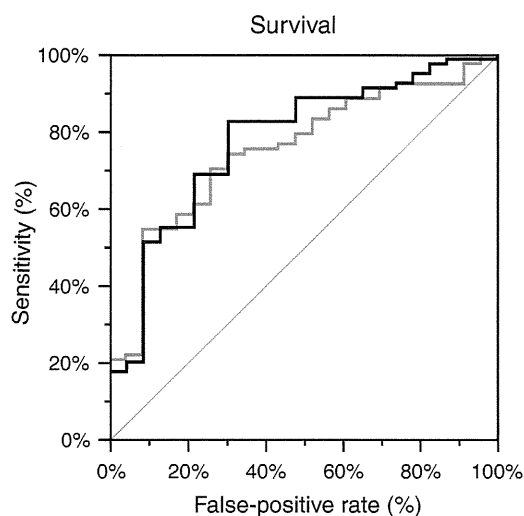
Fig. 3 The ROC curve for discriminating the outcome of survival based on the minimum L/T (*solid line*) and the maximum LHR (*light line*). The AUC for survival in L/T and LHR was 0.776 and 0.750, respectively

reported in normal fetuses [16] and in the fetuses with CDH [11, 15]. The reason for the increase of LHR with the gestational age is due to the difference in the rate of the

increase of the lung area and head circumference. Peralta reported that there was a fourfold increase in the LHR between 12 and 32 weeks of gestation in normal fetuses because of these differences [16]. This explains the difficulty in identifying a common cutoff value in LHR which is able to predict the survival, independently of the timing of prenatal assessment. Standardizing the LHR by using the expected LHR has been proposed to provide a constant value throughout period of gestational and thus excellent performance of the ROC curve [15]. However, determining the observed to expected LHR requires the expected LHR in normal fetuses for a standardizing in each population, and thus it has less availability in each population.

On the other hand, the L/T has been reported to be a constant parameter in normal fetuses, [2] and in fact, it had no correlation with gestational age in the survivors or in the patients with intact discharge. The L/T in non-survivors or patients who needed home treatment decreased according to the gestational age, but it may imply that there is a possibility to determine the most powerful measurement point of the L/T to predict poor outcomes. The latest L/T should be theoretically more reliable than the earliest L/T for the prediction of outcome because the L/T had a downward trend in those patients with poor prognosis. In

Table 3 The AUC and the best cutoff value for intact discharge which maximize the difference between the sensitivity and false-positive rate in various representative values of L/T and LHR during gestation

AUC area under the ROC curve

[a] Maximum area under the receiver-operating characteristic (ROC) curve

Representative value of L/T and LHR	AUC	Difference between sensitivity and false positive rate	The best cutoff value
L/T			
The earliest value	0.740	0.367	0.080
The latest value	0.784	0.465	0.092
The minimum value	0.798[a]	0.511	0.080
The maximum value	0.729	0.372	0.142
LHR			
The earliest value	0.790	0.474	1.59
The latest value	0.819	0.556	1.72
The minimum value	0.804	0.559	1.59
The maximum value	0.835[a]	0.372	1.79

Table 4 Patient demographics and the postnatal severity of the fetuses with isolated congenital diaphragmatic hernia in the groups divided by the L/T at 0.080

	n	L/T < 0.080 (n = 30)	L/T ≥ 0.080 (n = 73)	p
Gender (M/F)	103	19/11	39/34	0.390
Side of hernia (left/right)	103	28/2	71/2	0.578
Gestational age at diagnosis (weeks)[a]	103	27.8 ± 5.0	29.0 ± 5.9	0.305
Gestational age at birth (weeks)[a]	103	38.0 ± 1.2	38.0 ± 2.0	0.952
Body weight at birth (kg)[a]	103	2.60 ± 0.50	2.81 ± 0.52	0.063
Polyhydramnios (%)	103	36.7	27.4	0.356
Apgar score at 1 min[a]	101	3.28 ± 1.67	4.88 ± 2.18	<0.001
Apgar score at 5 min[a]	99	4.64 ± 2.04	5.76 ± 2.24	0.024
Highest pre PaO_2 (mmHg)[b]	90	116 (45–237)	266 (177–374)	<0.001
Lowest pre $PaCO_2$ (mmHg)[b]	103	36.7 (29.2–51.4)	31.2 (26.0–43.7)	0.041
Duration of NO inhalation (days)[b]	95	19 (14–40)	8 (5–13)	<0.001
Duration of ventilatory support (days)[b]	103	35 (28–545)	19 (11–31)	<0.001
Duration of O_2 inhalation (days)[b]	103	251 (42–555)	30 (16–53)	<0.001
Need for ECMO (%)	103	33.3	5.5	<0.001
Need for PGE_1 administration (%)	103	60.0	23.3	<0.001
Inoperable cases (%)	103	23.3	5.5	0.013
Over 75% defect of diaphragm (%)	83	89.5	37.5	<0.001
Need for patch closure (%)	92	82.6	36.2	<0.001
Intact discharge rate (%)	103	26.7	82.2	<0.001
Overall survival rate (%)	103	46.7	90.4	<0.001

NO nitric oxide, *ECMO* extra corporeal membrane oxygenation, *PGE₁* prostaglandin E_1

[a] Mean ± standard deviation

[b] Median with interquartile range

fact, the AUC of the latest L/T was greater in comparison to the AUC of the earliest L/T (Table 2). However, the AUC indicated a maximum sensitivity when the L/T was represented by the minimum value during gestation. This may be related to a measurement deviation of L/T and there may be a limit of reliability of this methodology. An earlier assessment of the infants is more desirable to determine the indications for fetal intervention [19, 20]. Neither the LHR nor the L/T may independently be sufficient to determine the indications for fetal intervention; thus, a combination of these and other prenatal factors such as liver position may be necessary, because the liver position has been reported to be one of the most predictive factors [1, 5, 21–23].

Although the LHR increased according to the gestational age in the patients with intact discharge, there is no increase of the LHR in infants without intact discharge. The LHR may be a beneficial indicator for discriminating the favorable patients who can be discharged from hospital without any home treatment. In fact, the best AUC for intact discharge in the LHR was greater than the best AUC for intact discharge in the L/T (Table 3). Interestingly, the most powerful measurement point and accurate cutoff value of L/T for discriminating the outcome of intact

discharge was the same value in the same explanatory variable as that used to discriminate the survivors, namely 0.080 in the minimum L/T (Table 3).

The groups divided by a cutoff value of a minimum L/T of 0.080 demonstrated a significant difference in the postnatal severity including respiratory status, need for
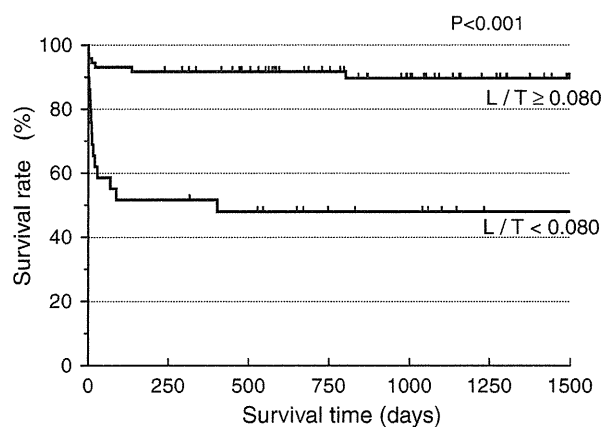

Fig. 4 Survival curves in the patients with isolated congenital diaphragmatic hernia divided by the minimum L/T at 0.080

respiratory support, need for circulatory support, surgical findings, and prognosis, which seems to be reflected in pulmonary hypoplasia. Therefore, the L/T was able to accurately estimate the severity of the infants in the perinatal and perioperative period, and we may be able to develop several different treatment programs in terms of perinatal and perioperative management to adjust for the predicted severity as estimated by the L/T.

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Original articles

Prenatal risk stratification for isolated congenital diaphragmatic hernia: results of a Japanese multicenter study

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Abstract
Background/Purpose: The aim of this study was to establish a prenatal prognostic classification system for risk-stratified management in fetuses with isolated congenital diaphragmatic hernia (CDH).
Methods: A multi-institutional retrospective cohort study of isolated CDH, diagnosed prenatally in fetuses delivered during the 2002 to 2007 period at 5 participating institutions in Japan, was conducted. The risk stratification system was formulated based on the odds ratios of prenatal parameters for mortality at 90 days. The clinical severity in CDH infants were compared among the stratified risk groups.
Results: Patients were classified into the 3 risk groups: group A (n = 48) consisted of infants showing liver-down with contralateral lung–to–thorax transverse area ratio (L/T) ratio $\geq$0.08; group B of infants showing liver-down with L/T ratio <0.08 or liver-up with L/T ratio $\geq$0.08 (n = 35), and group C of infants showing liver-up with L/T ratio <0.08 (n = 20). The mortality at 90 days in groups A, B, and C were 0.0%, 20.0%, and 65.0%, respectively. The intact discharge rates were 95.8%, 60.0%, and 5.0%, respectively. This system also accurately reflected the clinical severity in CDH infants.
Conclusions: Our prenatal risk stratification system, which demonstrated a significant difference in postnatal status and final outcome, would allow for accurate estimation of the severity of disease in fetuses with isolated CDH, although it needs prospective validation in a different population.
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Congenital diaphragmatic hernia (CDH) remains one of the most challenging anomalies facing pediatric surgeons and neonatologists, as it has a broad spectrum of severities dependent on components of pulmonary hypertension and hypoplasia of the lungs. An accurate prenatal severity assessment is essential for standardization of prenatal and postnatal care for individual cases because severity directly affects mortality and morbidity. Prenatal prognostic classification of CDH would provide the family with more precise information about the course of treatment and allow a management protocol based on risk to be established. This may minimize excessive treatment and medical expenses for low-risk patients while maximizing effective management in high-risk patients.

Several prenatal prognostic parameters for fetal CDH have previously been proposed by other investigators [1-14]. It has been validated by multiple centers that the presence of liver herniation is among the most reliable predictors of severity and mortality in CDH [1-6]. Stomach position was also studied as a prognostic indicator along with liver herniation [8-10]. Moreover, estimation of fetal lung size or evaluation of fetal lung characteristics has reportedly been used for severity prediction [11-18]. Among these fetal lung assessments, the lung area–to–head circumference ratio (LHR) is the most commonly used as a prenatal prognostic factor [8,11,18]. However, LHR is no longer considered to be independently predictive of survival by several investigators [2,19-21] because it has been shown to increase according to gestational age [15,16,22,23]. The observed to expected LHR has been proposed to provide a constant value throughout the gestational period [22], but in that study, this value was standardized by the normal lung size value of each population corresponding to gestational age without taking individual fetal growth into consideration.

In contrast, the contralateral lung–to–thorax transverse area ratio (L/T ratio) appears to be a reliable predictive parameter in fetal CDH, as it was originally reported to be constant throughout the gestational period in normal fetuses [12], and is reportedly not strongly influenced by gestational age even in fetuses with CDH [15,16]. Although combining several reliable prognostic parameters including the L/T ratio may contribute to the establishment of a prenatal risk stratification system for fetal CDH, such approaches have not been successful to date. The aim of this study was to establish a prenatal prognostic classification system for risk-stratified management of fetuses with isolated CDH based on a combination of fetal ultrasonographic findings including liver position and L/T ratio.

1. Materials and methods

1.1. Patient selection and data collection

We conducted a multicenter retrospective review of the medical records of 117 fetuses with isolated CDH,

diagnosed prenatally, born at 5 participating centers during the period between January 2002 and December 2007 [10,24]. Patients with serious associated anomalies such as major cardiac malformations and chromosomal abnormalities were excluded. Two cases with bilateral diaphragmatic hernia and 12 without L/T ratio measurements were excluded from the analysis. All 103 eligible patients were managed by maternal transport, with immediate resuscitation followed by neonatal intensive care mostly with high-frequency oscillatory ventilation. In all institutions, the blood gas parameter goals were $PaCO_2 < 60$ to 70 mm Hg and preductal $SpO_2 > 90\%$, under the concept of permissive hypercapnia [25] and permissive hypoxia. All institutions had extracorporeal membrane oxygenation (ECMO) and nitric oxide inhalation (iNO) capability, which were initiated according to the clinical decisions of each institution; indication criteria were not defined prospectively. Diaphragmatic repair was performed when respiratory and circulatory functions had stabilized. As the criteria of preoperative stabilization were not defined prospectively, operability of each patient was determined according to the clinical decisions of each institution. This study was approved by the institutional review boards of all 5 participating centers.

The primary outcome measure was mortality at 90 days. Prenatal ultrasonographic findings including polyhydramnios, fetal liver position, fetal stomach position, and the L/T ratio were collected at 3 times, according to gestational age at diagnosis: the earliest determination before 30 weeks of gestation, between 30 and 35 weeks of gestation, and after 35 weeks of gestation. Polyhydramnios was regarded as positive if the maximal vertical pocket was more than 8 cm. Only those patients with obvious liver herniation (ie, whose liver occupied more than one third of the thoracic space) were regarded as liver-up. Those with slight liver herniation or with liver herniation first recognized during surgery were regarded as liver-down. Fetal stomach position was categorized as contralateral stomach herniation, defined as more than half of the stomach having herniated into the contralateral thoracic cavity (equivalent to grade 3 in our previous report [10]) or others. The L/T ratio was measured at the transverse section containing the 4-chamber view of the heart by ultrasonography [12]. Briefly, the L/T ratio was defined as the area of the contralateral lung, which was determined by tracing around the contralateral lung, divided by the area of the thorax surrounded by the inner border of the bilateral ribs, the sternum, and the vertebra [15]. The cutoff value of the L/T ratio was set at 0.08 based on our previous studies [15,16,26]. Polyhydramnios, liver-up, and contralateral stomach herniation were categorized as positive if 1 of the 3 determinations was positive. The L/T ratio value was represented by the minimal value of 3 determinations, as in our previous report [16].

Postnatal factors, including sex, gestational age at birth, birth weight, mode of delivery, hernia side, Apgar scores at 1 and 5 minutes, preductal arterial blood gas data within

24 hours after birth, use of circulatory support (ECMO, prostaglandin I_2 administration, prostaglandin E_1 administration, iNO), ductus arteriosus (DA) shunt direction within 24 hours after birth, size of diaphragmatic defect judged intraoperatively, need for patch closure, duration of respiratory support (iNO, mechanical ventilation, oxygen administration), duration of hospitalization, 90-day survival, survival to discharge, intact discharge, and survival time, were collected as secondary measures. Intact discharge was defined as being discharged from the hospital with no need for home treatments such as ventilatory support, oxygen administration, tube feeding, and/or parenteral nutrition.

1.2. Analysis of prenatal factors and formulation of the prenatal risk stratification system

Odds ratios (OR) of prenatal parameters for mortality at 90 days were compared by univariate and multivariate analyses. According to the magnitude of the OR, patients were first stratified by the most powerful factor, and then each stratified group was subsequently divided into 2 subgroups by the second most powerful factor. The risk stratification system was formulated based on the results of the mortality at 90 days in each subgroup. Patient demographics and prenatal and postnatal profiles including parameters indicating the respiratory status, circulatory status, surgical findings, and outcome were compared among the groups classified using this approach.

1.3. Statistical analysis

Univariate analyses were performed to assess the magnitude of risks associated with prenatal variables for mortality at 90 days using the χ^2 test and Fisher exact test. Multiple logistic regression analysis was also performed to estimate the ORs for prenatal variables adjusted for confounding. The stepwise selection method (P value criteria <.20) was used to select variables correlating with the mortality at 90 days. Crude ORs and adjusted ORs with 95% confidence intervals (CI) were calculated. The mean and SD

were used to describe continuous variables. The median and interquartile range were used to describe ordinal scales or durations of treatment in the cases with censoring. The frequency and percentages were used to describe categorical data. One-way ANOVA with Tukey post hoc honestly significant difference test was used for comparison of continuous variables. The Kruskal-Wallis test was used for comparison of Apgar scores. The χ^2 test and Fisher exact test were used for analysis of categorical data. The log-rank test and Kaplan-Meier method were used to compare the treatment durations and survival times. P values lower than .05 were considered statistically significant. Statistical analyses were performed with JMP (version 8.02; SAS Institute, Cary, NC).

2. Results

2.1. Analysis of prenatal factors and formulation of the prenatal risk stratification system

Crude ORs for the factors significantly associated with mortality at 90 days were 18.6 for liver-up, 13.6 for L/T ratio <0.08, and 11.0 for contralateral stomach herniation. Adjusted ORs for liver-up and L/T ratio <0.08 were statistically significant, whereas that for contralateral stomach herniation did not reach statistical significance (Table 1). The mortality at 90 days of 4 subgroups, first stratified by the most powerful factor (liver herniation) and subsequently by the second most powerful factor (L/T ratio), are shown in Figure 1 (Fig. 1). The mortality at 90 days of all cases was 19.4%, whereas that of fetuses with liver-down and L/T ratio ≥0.08 was 0.0%. We thus defined the latter as group A (low-risk group). Fetuses with liver-down and L/T ratio <0.08 and those with liver-up and L/T ratio ≥0.08 were combined into group B (intermediate-risk group), since they had the same mortality at 90 days of 20.0%. The mortality at 90 days of fetuses with liver-up and L/T ratio <0.08 was 65.0%, and these constituted group C (high-risk group). The numbers of patients in groups A, B, and C were 48, 35, and 20, respectively (Fig. 1).

| Table 1	Univariate and multivariate analyses for mortality at 90 days		
Variable	n (%)	OR for mortality at 90 d (95% CI)	P
Univariate analysis		Crude OR	
Liver-up (ref: liver-down)	45 (43.7)	18.6 (4.04-86.3)	<.001
L/T ratio <0.08 (ref: ≥0.08)	30 (29.1)	13.6 (4.28-43.2)	<.001
Contralateral stomach herniation (ref: others)	25 (24.3)	11.0 (3.64-33.1)	<.001
Polyhydramnios (ref: no polyhydramnios)	31 (30.1)	2.27 (0.83-6.21)	.114
Multiple logistic regression analysis		Adjusted OR	
Liver-up (ref: liver-down)	45 (43.7)	9.34 (1.92-70.2)	.011
L/T ratio <0.08 (ref: ≥0.08)	30 (29.1)	8.28 (2.33-33.3)	.002
Contralateral stomach herniation (ref: others)	25 (24.3)	2.61 (0.64-10.5)	.173

mortality at 90 days
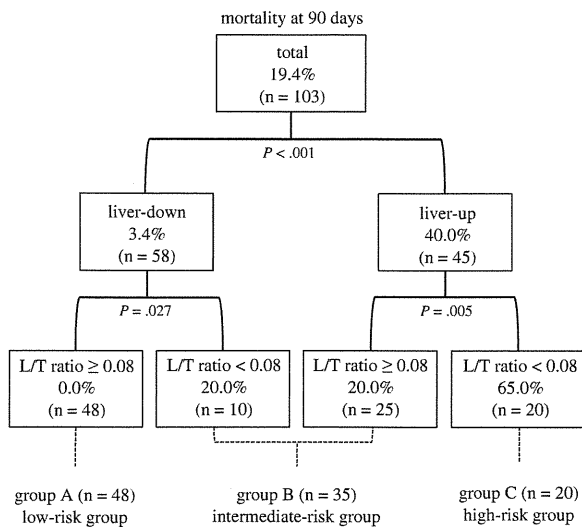
Fig. 1 Mortality at 90 days of subgroups stratified by liver position and L/T ratio. Group A includes patients with liver-down and L/T ratio ≥0.08; group B patients with liver-down and L/T ratio <0.08 or liver-up and L/T ratio ≥0.08; group C patients with liver-up and L/T ratio <0.08.

2.2. Comparison of CDH severity in each prenatal risk group

There were no significant differences in patient demographics, including sex, gestational age at diagnosis, gestational age at birth, and birth weight, among the 3 groups. The only exception was mode of delivery. Groups B and C had higher rate of cesarian sections, which were performed according to the clinical decisions of each institution, as the criteria of cesarian sections were not defined prospectively. Although the incidences of polyhydramnios did not differ significantly, not surprisingly, there were significant differences in liver-up and the L/T ratio as well as stomach herniation based on how the stratification system was formulated (Table 2). Apgar scores and preductal arterial blood gas data were significantly worse in group C.

There were also significant differences in the duration of respiratory support such as iNO, artificial ventilation, and O_2 administration. Consequently, there were significant differences in the duration of hospitalization among the 3 groups (Table 3). DA shunt directions evaluated within 24 hours after birth, which suggest the severity of pulmonary hypertension, differed significantly among the 3 groups. The number of the patients who used circulatory support such as ECMO, prostaglandin I_2 administration, prostaglandin E_1 administration, and iNO were 14, 23, 35, and 86, respectively. There were significant differences in the use of such circulatory support to manage pulmonary hypertension among the 3 groups (Table 4). Although diaphragmatic repair could be performed in all group A patients, surgery was not possible in 4 group B patients (11.4%) and in 7 group C patients (35%) due to their unstable conditions. There were also significant differences in the proportions of patients with diaphragmatic defects exceeding 75%, as judged intraoperatively. Among the 13 group C patients undergoing surgery, 12 (92.3%) required patch closure, whereas only 10 (20.8%) required patch closure in group A (Table 5). There were significant differences in morbidity and mortality among the 3 groups. The rate of survival to discharge was 100.0% and the intact discharge rate was 95.8% in group A, whereas the corresponding rates were 74.3% and 60.0% in group B, and 20.0% and 5.0% in group C (Table 5). There were also statistically significant differences in survival curves among the 3 groups (Fig. 2).

3. Discussion

An accurate prenatal severity assessment for individual fetuses with CDH is essential for standardization of prenatal and postnatal treatments, since CDH has a broad spectrum of severities that directly affects the mortality and morbidity for the patients. We endeavored to establish such a risk stratification system by applying a combination of several reliable prognostic parameters previously proposed for use in fetuses with CDH [1-18]. These prognostic parameters are

Table 2 Demographics and prenatal findings of fetuses with CDH

	Group A (n = 48)	Group B (n = 35)	Group C (n = 20)	P
Sex (male/female)	23/25	23/12	12/8	.254
Side of hernia (right/left)	0/48	2/33	2/18	.119
Gestational age at diagnosis (wk), mean ± SD	29.6 ± 5.9	27.5 ± 5.2	28.3 ± 5.5	.231
Gestational age at birth (d), mean ± SD	266 ± 14.3	266 ± 12.4	266 ± 10.2	.995
Birth weight (kg), mean ± SD	2.82 ± 0.50	2.74 ± 0.51	2.61 ± 0.59	.302
Caesarian section (%)	23.8	60.0	75.0	.001
Polyhydramnios (%)	20.8	40.0	35.0	.148
Liver-up (%)	0.0	71.4	100.0	<.001
Stomach herniation (%)	4.2	25.7	70.0	<.001
L/T ratio, mean ± SD	0.121 ± 0.032*	0.099 ± 0.028†	0. 058 ± 0.016‡	<.001

*$P < .05$, A versus B; †$P < .05$ B, versus C; ‡$P < .05$, C versus A.

Table 3   Respiratory status and respiratory support in CDH patients

	Group A (n = 48)	Group B (n = 35)	Group C (n = 20)	P
Apgar 1 min, median (interquartile range)	5 (3-7) (n = 48)	3.5 (2-6) (n = 34)	3 (2-4) (n = 19)	.002
Apgar 5 min, median (interquartile range)	6 (4.25-7.75) (n = 48)	5 (3.5-8) (n = 33)	3.5 (2-5.25) (n = 18)	.006
Highest pre-PaO$_2$ (mm Hg), mean ± SD**	284 ± 122* (n = 44)	211 ± 132 (n = 25)	129 ± 117‡ (n = 18)	<.001
Lowest pre-PaCO$_2$ (mm Hg), mean ± SD**	33.4 ± 11.2 (n = 42)	36.8 ± 16.3† (n = 29)	49.8 ± 26.0‡ (n = 19)	.002
Duration of iNO (d), median (interquartile range)	8 (5-12)	11 (7-19)†	34 (22-40)‡	<.001
Duration of ventilation (d), median (interquartile range)	14 (9-28)*	30 (21-48)†	545 (30-747)‡	<.001
Duration of O$_2$ administration (d), median (interquartile range)	23 (15-38)*	43 (37-73)†	555 (529-748)‡	<.001
Duration of hospitalization (d), median (interquartile range)	48 (39-69)*	73 (56-108)	162 (95-545)‡	<.001

    * $P < .05$, A versus B; †$P < .05$, B versus C; ‡$P < .05$, C versus A.
    ** Highest pre-PaO$_2$ and lowest pre-PaCO$_2$ were measured within 24 hours after birth.

divided broadly into 2 categories. One is the indirect factor of pulmonary hypoplasia, which is an estimation of how much viscera (ie, liver herniation and stomach position) compresses the fetal lungs. The other is the direct parameter of fetal lung development itself. The magnitudes of ORs in univariate and multivariate analyses for mortality at 90 days were compared, and 2 powerful prenatal factors were eventually identified in each category.

The fetal liver position was the most powerful prognostic factor judging from OR magnitude. It has already been reported by many investigators that fetal liver herniation is the most reliable predictor of the severity and mortality in fetuses with CDH [1-6]. Although stomach position was also a good prognostic indicator, along with liver herniation [8-10], we selected fetal liver herniation based on the OR being larger than that for stomach herniation. Furthermore, these 2 predictors seemed to be mutually confounding factors. There is marked variation in the definition of liver herniation, and the "liver-up" concept differs markedly among authors [5,7]. In the present study, we defined liver-up as liver herniation in which the liver occupied more than one third of the thoracic cavity [10] based on previous studies [4,6], because there is a possibility of overestimating the affect of lung compression if situations such as slight liver herniation and liver herniation first recognized during surgery are included among the "liver-up" cases. Liver herniation occupying one third of the thoracic cavity turns out to be a good cutoff value for prediction, as liver-up defined by this means demonstrated a satisfactory OR.

The L/T ratio was the second most powerful prognostic parameter in our analysis. Many factors, such as lung area [11,12,16,18], volume [4,13,14], and signal intensity on magnetic resonance imaging [17], as well as pulmonary artery blood flow [27], have previously been proposed as means of estimating fetal lung development. Among these parameters, the simplest approach is to determine the fetal lung area using 2-dimensional ultrasonography, as is now widely done in multiple centers. LHR [8,11,18] has long been the most commonly used parameter for evaluating the fetal lung area. However, LHR was shown to increase according to gestational age [15,16,22,23]. Therefore, LHR is no longer considered to be independently predictive of survival by several investigators [2,19-21]. In contrast, we have previously demonstrated that the L/T ratio, which is not markedly influenced by gestational age even in fetuses with CDH [15,26]. We studied in detail to compare the reliability of L/T ratio and LHR in the same database and found that the L/T ratio is more reliable than the LHR [16]. Moreover, a manual tracing of the lung borders, which is conducted to obtain the L/T ratio, is reportedly a more reproducible measurement than the multiplication of the lung diameters, which is used for LHR determination [23,28]. The observed to expected LHR was proposed to provide a constant value throughout the gestational period, and it showed excellent receiver operating characteristic curve performance [22]. However, determining the observed to expected LHR requires the expected LHR in normal fetuses to be used for standardization of each relevant patient population, and the

Table 4   Circulatory status and circulatory support in CDH patients

	Group A (n = 48)	Group B (n = 35)	Group C (n = 20)	P
Left to right dominant shunt at DA (%)*	39.1 (n = 46)	36.4 (n = 33)	0.0 (n = 18)	.007
Right to left dominant shunt at DA (%)*	37.0 (n = 46)	51.5 (n = 33)	72.2 (n = 18)	.036
Use of ECMO (%)	2.1	14.3	40.0	<.001
Use of prostaglandin I$_2$ (%)	8.3	28.6	45.0	.002
Use of prostaglandin E$_1$ (%)	14.6	40.0	70.0	<.001
Use of iNO (%)	70.8	94.3	95.0	.005

    * Shunt direction at the DA was evaluated within 24 hours after birth.

Table 5 Operative findings, morbidity, and mortality

	Group A (n = 48)	Group B (n = 35)	Group C (n = 20)	P
Inoperable cases (%)	0.0	11.4	35.0	<.001
Diaphragmatic defects exceeding 75% (%)	17.8 (n = 45) *	81.5 (n = 27) *	100.0 (n = 11) *	<.001
Need for patch closure (%)	20.8 (n = 48)	71.0 (n = 31)	92.3 (n = 13)	<.001
90-d Survival (%)	100.0	80.0	35.0	<.001
Survival to discharge (%)	100.0	74.3	20.0	<.001
Intact discharge (%)	95.8	60.0	5.0	<.001

* The size of diaphragmatic defect was not determined in several cases due to lack of intraoperative information.

availability is relatively low for some populations. Furthermore, there appears to be a problem in that individual fetal growth variation is not considered when determining the observed to expected LHR, relying instead on a standardized mean value from fetuses showing normal growth [22].

In the present study, ECMO and iNO were performed in 14 (13.6%) and 86 (83.5%) patients, respectively. As compared with previous reports [3,13,29-31], our results demonstrated less frequent use of ECMO and high use of iNO. In recent years, there has been an obvious trend in institutions in Japan to use ECMO less frequently with an associate increase in the use of iNO and prostaglandin E_1 administration for pulmonary hypertension [32-34], as was described by the CDH study group [35]. We usually use iNO without hesitation, if there is only a slight difference between the preductal and postductal oxygen saturation or blood gas data to reduce pulmonary artery resistance, with the ultimate goal of preventing right ventricular failure by removing the afterload on the right ventricle [32,33]. At present, in the 5 participating institutions, ECMO is being applied only for the most severe respiratory insufficiency cases. However, some infants with extremely severe pulmonary hypoplasia have been considered not to be indicated even for ECMO. This may account for the high mortality rate (64.3%) of our ECMO cases and the high inoperable rate (9.0%) of our non-ECMO cases.

One major limitation of this study is that the liver positions and L/T ratios were determined by various

Fig. 2 Survival curves for patients with isolated CDH, compared using the prenatal risk stratification system. * $P < .001$; †$P < .001$; ‡$P < .001$.

investigators at each participating institution, rather than by a small number of sonologists or other experienced judges, as would have been ideal to assure consistency. There may be some variation in the accuracy of the measurements in the present study and a prospective study in which the parameters determined by limited number of investigators may be needed to verify the accuracy of this risk stratification system. The other limitation of this study is that the risk group could not be confirmed until the end of gestation. In the present study, the presence of liver-up and an L/T ratio <0.08 were judged based on the worst value among the 3 representative measurements conducted before 30 weeks of gestation, between 30 and 35 weeks of gestation, and after 35 weeks of gestation. Because this process was applied for all of our determinations, the cases finally classified into the high-risk group were not always graded as being in this group from the beginning. Therefore, this system may not be useful for determining the need for maternal transport to a center offering fetal intervention [36]. Severity must be evaluated as early as possible, ideally before 28 weeks of gestation, to optimize the effects of early fetal intervention.

We have previously endeavored to devise a simple classification system based only on indirect factors reflecting how much the viscera compress the fetal lungs (ie, liver and stomach position) by applying a uniform multicenter survey [10]. This simple classification system has a clear advantage for screening candidates for fetal intervention, since the risk group can be determined by the findings of the earliest fetal evaluation. Compared with the previous simple classification system, the new risk stratification system was found to be more reliable in terms of accuracy and the ability to clearly separate the mortality and morbidity of the CDH patients, which suggests that it has an advantage for risk-stratified management after birth.

The incidence of right-sided CDH was relatively low in our cohort [24] compared with the previous reports [35,37]. The reason for this shift was unclear. However, the incidence did not seem to be markedly influenced by selective termination of pregnancy for fetuses with right-sided CDH, as only 13 (12.6%) cases had been diagnosed before 22 weeks of gestation, when the termination of pregnancy is legally accepted in our country [38]. We sought to treat right-sided CDH together with left-sided CDH in this study. Even though the incidence of liver-up and the original contralateral
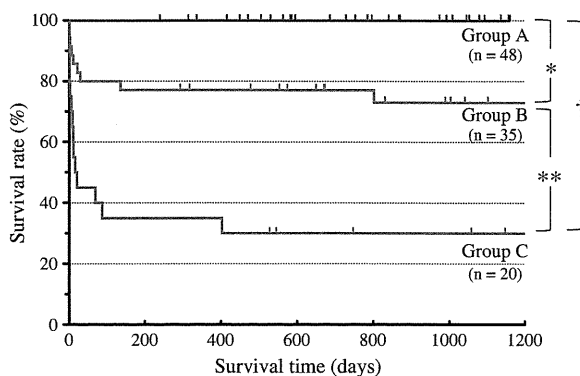
lung area may differ between right- and left-sided CDH due to anatomical reasons, we considered it to be more practical to apply the same stratification to both sides in fetuses with CDH. All 4 cases with right-sided CDH were classified into the intermediate- or high-risk group according to their L/T ratios. Consequently, the results are therefore considered to be consistent with those of previous studies [8,39].

Our prenatal risk stratification system, which demonstrated a significant difference in postnatal status and final outcome, may allow for accurate estimation of the severity of disease in fetuses with isolated CDH such that management protocols could be established according to risk. This would minimize excessive treatment and medical expenses for low-risk patients and maximize effective management in high-risk patients. As the present study was a retrospective analysis, a prospective study in a different population will therefore be needed to verify the accuracy and the universal applicability of this risk stratification system.

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ELSEVIER

Original contribution

Squamous metaplasia in the cyst epithelium of type 1 congenital pulmonary airway malformation after thoracoamniotic shunt placement

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Summary Thoracoamniotic shunting is the treatment of choice for management of the fetus with type 1 congenital pulmonary airway malformation. Thoracoamniotic shunting has been performed to reduce life-threatening risks such as fetal hydrops. However, caution is needed because of possible complications. Here, we report that thoracoamniotic shunting can cause histologic changes in the cyst epithelia. In 5 of 8 patients treated prenatally with thoracoamniotic shunting, squamous metaplasia in the cyst epithelia was seen; whereas squamous metaplasia was not found in 6 patients who were not treated with this procedure. Our results reveal that long-term exposure to the intrauterine environment could possibly lead to the change in the nature of cyst epithelium and consequent squamous metaplasia.
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1. Introduction

Congenital pulmonary airway malformation (CPAM), formerly known as *cystic adenomatoid malformation*, of the lung is a rare lung disorder characterized by an increased proliferation and cystic dilation of terminal respiratory bronchioles [1-3]. Although the etiology of CPAM is not clear, it has been suggested that it may be caused by a maturation defect in bronchopulmonary development [4,5].

It has been also shown that the presence of bronchial atresia is strongly associated with CPAM, which supports this concept [6].

Congenital pulmonary airway malformation (ie, cystic adenomatoid malformation) was originally classified into 3 groups based on the relative size of the cysts [3]. Currently, CPAM is classified into 5 types based on the presumed site of development of the malformation. Among these 5 types, type 1 CPAM is the most prevalent one, accounting for approximately 60% to 70% of all CPAM lesions [2,3]. Type 1 CPAM consists of 1 or more air- or air/fluid-filled large cysts. The cyst sizes range from 1 to 10 cm. These cysts are often surrounded by underdeveloped alveolar parenchyma and varying number of smaller cysts. Microscopically, the

cysts are lined by epithelium that varies from a low cuboidal epithelium to a ciliated pseudostratified columnar epithelium [2,7]. The cyst walls also consist of connective tissue similar to those of bronchi of the patient's uninvolved lung. Cartilage islands may be seen in some cases. It has been reported that tufts of mucigenic cells exist on the surface on large cysts or within the smaller bronchiolar-like structures adjacent to the larger cysts in about 35% of type 1 CPAM cases [2]. Past reports indicate that these cells are involved with the occurrence of bronchioloalveolar carcinoma in both older patients with type 1 CPAM and patients who have had a type 1 CPAM removed in infancy [8-13].

Type 1 CPAM usually causes respiratory distress in the newborn period. Thus, surgical removal of the involved lobe is often required to prevent respiratory distress and allow the other lobes to expand normally. Recent advances in antenatal diagnosis and prenatal ultrasound have allowed us to correctly diagnose and monitor fetuses with type 1 CPAM [14,15]. Fetal interventions are applied to fetuses with life-threatening conditions such as hydrops fetalis or polyhydramnios. Thoracoamniotic (TA) shunting is the treatment of choice for management of the fetus with type 1 CPAM and involves shunt insertion under ultrasound guidance [16-18]. Thoracoamniotic shunting has been performed to reduce life-threatening risks such as poly-hydramnios, mediastinal shift, and fetal hydrops [17-19]. However, caution is needed because of possible complications. It has been reported that displacement of the catheter into the amniotic or thoracic cavity, catheter occlusion, premature delivery, and fetal demise can occur [19]. Here, we report that TA shunting can cause histologic changes in the cyst epithelia. In 5 of 8 patients treated prenatally with TA shunting, squamous metaplasia in the cyst epithelia was seen; whereas squamous metaplasia was not found in 6

patients who were not treated with TA shunting. These findings suggest that TA shunting could change the nature of the cyst epithelium as a consequence of long-term exposure to the intrauterine environment.

2. Materials and methods

2.1. Indications for TA shunting in fetal CPAM type 1

In the Department of Maternal-Fetal and Neonatal Medicine at the National Center for Child Health and Development, Tokyo, Japan, the indications for TA shunting in fetal CPAM type 1 include the following:

1. Macrocystic CPAM with large cysts
2. CPAM volume ratio greater than 1.6 [20] or hydrops fetalis
3. Before 34 weeks of gestation

We did not perform TA shunting on patient 1 with hydrop fetalis (Table 1). Instead, we performed thoracocentesis because the cysts were separated by the septum, which implied ineffectiveness of TA shunting.

2.2. Case selection

Between 2004 and 2011, TA shunts were used on 8 of 14 fetuses diagnosed as having type 1 CPAM in the Center for Maternal-Fetal and Neonatal Medicine at the National Center for Child Health and Development, Tokyo, Japan. Shunts were offered in pregnancies complicated by hydrops fetalis, polyhydramnios, or at a significant risk for pulmonary

Table 1   Clinical and microscopic data for type 1 CPAM

	TA shunt	Sex	Age (wk)	Weight (g)	Apgar score	Surgical removal (d)	Follow-up	Additional features
1	(−)	M	35	2800	2.2	0	Death at 2 mo, 17 d	Hydrops fetalis
2	(−)	F	37	2410	8.9	24	Free of disease at 1 y, 3 mo	
3	(−)	M	38	2800	8.9	23	Free of disease at 1 y, 1 mo	
4	(−)	F	39	3250	7.7	0	Free of disease at 7 y and 1 mo; rib deformity	
5	(−)	M	40	3400	7.8	12	Free of disease at 6 y, 8 mo	
6	(−)	M	39	3368	8.9	14	Free of disease at 2 mo	
7	(+)	F	28	1490	ND	0	Death at 1 d	Hydrops fetalis
8	(+)	F	33	3544	1.5	0	Free of disease at 7 mo, 25 d	Hydrops fetalis
9	(+)	F	37	3282	7.9	0	Free of disease at 1 y, 9 mo	Polyhydramnios
10	(+)	F	38	2858	8.9	0	Free of disease at 2 mo, 15 d	Hydrops fetalis
11	(+)	M	38	2722	8.8	0	Free of disease at 1 y, 5 mo; rib deformity	
12	(+)	F	38	2790	8.9	0	Free of disease at 4 y, 9 mo; rib deformity	Hydrops fetalis
13	(+)	F	37	2775	8.8	0	Free of disease at 1 mo	Hydrops fetalis
14	(+)	M	38	3032	8.9	0	Free of disease at 1 mo	Hydrops fetalis

Abbreviations: M, male; F, female; ND, no data.