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Re-evaluation of stomach position as a simple prognostic factor in fetal left congenital diaphragmatic hernia: a multicenter survey in Japan

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KEYWORDS: congenital diaphragmatic hernia; fetus; gentle ventilation; liver; stomach

ABSTRACT

Objectives *To document outcome and to explore prognostic factors in fetal left congenital diaphragmatic hernia (CDH).*

Methods *This was a multicenter retrospective study of 109 patients with prenatally diagnosed isolated left CDH born between 2002 and 2007. The primary outcome was intact discharge, defined as discharge from hospital without major morbidities, such as a need for respiratory support including oxygen supplementation, tube feeding, parenteral nutrition or vasodilators. All patients were managed at perinatal centers with immediate resuscitation, gentle ventilation (mostly with high-frequency oscillatory ventilation) and surgery after stabilization. Prenatal data collected included liver and stomach position, lung-to-head ratio, gestational age at diagnosis and presence or absence of polyhydramnios. Stomach position was classified into four grades: Grade 0, abdominal; Grade 1, left thoracic; Grade 2, less than half of the stomach herniated into the right chest; and Grade 3, more than half of the stomach herniated into the right chest.*

Results *Overall intact discharge and 90-day survival rates were 65.1% and 79.8%, respectively. Stomach herniation was classified as Grade 0 in 19.3% of cases, Grade 1 in 45.9%, Grade 2 in 13.8% and Grade 3 in 21.1%. Multivariate analysis revealed that liver position was the strongest prognostic variable for intact discharge, followed by stomach position. Based on our results, we divided patients into three groups according to liver (up vs. down) and stomach (Grade 0–2 vs. Grade 3) position. Intact discharge rates declined significantly from liver-down (Group I), to liver-up with stomach Grade 0–2 (Group II), to liver-up with stomach Grade 3 (Group III) (87.0%, 47.4% and 9.5% of cases, respectively).*

Conclusion *Current status and outcomes of prenatally diagnosed left CDH in Japan were surveyed. Stomach herniation into the right chest was not uncommon and its grade correlated with outcome. The combination of liver and stomach positions was useful to stratify patients into three groups (Group I–III) with different prognoses.*

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is one of the most challenging anomalies for pediatric surgeons and neonatologists. The rate of prenatal detection has been increasing over time, and is now over 50%[1–3]. A recent survey by the Japanese Association of Pediatric Surgeons reported that 73.5% of neonatal CDH cases in Japan had been diagnosed prenatally[4]. Prenatal detection allows management at experienced centers and avoidance of inadvertent events such as pneumothorax, distention of

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the gastrointestinal tract or resuscitation failure. This has improved the outcome of patients diagnosed prenatally, but limitations have led to an ongoing debate regarding the role of fetal intervention.

The prognosis of a patient with prenatally diagnosed CDH is estimated from several factors, including liver position and measurement of contralateral lung size (i.e. lung-to-head ratio (LHR) or lung-to-thoracic ratio). Stomach position, whether herniated into the chest or not, was formerly used as a factor for prediction of prognosis[5–7]. We reported previously an observation that stomach herniation into the right chest is an ominous sign in fetal left CDH[8]. In this study, we investigated the prognostic value of stomach position using a new grading system.

METHODS

A retrospective chart review was conducted on all isolated prenatally diagnosed CDH patients born during the period 2002–2007 at the National Center for Child Health and Development, Kanagawa Children's Medical Center, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka University Hospital or Kyushu University Hospital. We included in the study cases with presence of a left-sided CDH without associated life-threatening or chromosomal anomalies. All patients delivered at our centers and neonates were managed by immediate resuscitation followed by neonatal intensive care, including gentle ventilation mostly with high-frequency oscillatory ventilation (HFO) and preoperative stabilization. All institutions had extracorporeal membrane oxygenation (ECMO) and nitric oxide (NO) inhalation capability, which were initiated according to the clinical decisions of each team; indication criteria were not defined prospectively. This study was approved by the institutional review boards of all participating centers.

Prenatal data

The following data were collected for each patient: gestational age at diagnosis, presence or absence of polyhydramnios (maximum vertical pocket ≥ 8 cm), position of fetal liver and stomach, and LHR measured on maternal admission. Only those cases with obvious liver herniation (more than one-third of the left thoracic space occupied by the liver) on prenatal imaging studies were grouped as 'liver-up', eliminating questionable cases. Position of the stomach was categorized as: Grade 0, abdominal; Grade 1, left thoracic; Grade 2, less than half of the stomach herniated into the right chest; and Grade 3, more than half of the stomach herniated into the right chest (Figure 1). The lung area was measured by multiplication of the longest diameter of the lung by its longest perpendicular diameter in the cross-sectional plane at the level of the four-chamber view of the heart.

Postnatal data

Data collected postnatally included sex, gestational age at birth, birth weight, mode of delivery, Apgar score at 1 min, need for HFO, NO inhalation, ECMO and patch repair. Major morbidities at discharge, such as a need for respiratory support including oxygen supplementation, tube feeding, parenteral nutritional support or vasodilators, were recorded.

Outcomes

The primary and secondary outcomes were intact discharge (defined as discharge from hospital without any need for respiratory support including oxygen supplementation, tube feeding, parenteral nutritional support or vasodilators to control pulmonary hypertension) and 90-day survival rate.

Statistical analysis

Data are reported as median (range) or frequency (percentage). Univariate analyses were performed using chi-square, Fisher's exact and Cochran–Armitage tests. Crude odds ratio (OR) and 95% CIs for intact discharge failure, including death, were calculated. Multiple logistic regression analysis was also performed to estimate the OR of the prenatal variables adjusting for correlation among them. We used a stepwise selection method (variable selection criteria, $P < 0.20$) to select the variables correlated with intact discharge failure. All reported P-values are two-sided and not adjusted for multiplicity. $P < 0.05$ was considered statistically significant. Data were analyzed with SAS version 9.1 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

The characteristics of the 109 patients with isolated left CDH managed by the five participating centers between January 2002 and December 2007 are summarized in Table 1. The distribution of liver and stomach positions is shown in Figure 2. Almost all (67/69) of the liver-down patients had stomach Grades 0–2, while more than half (21/40) of the liver-up patients had stomach Grade 3.

With respect to therapeutic interventions used after birth, all except one patient ($n = 108$, 99.1%) were ventilated with HFO. Inhaled NO was administered in 87 (79.8%) patients. ECMO was used in 16 (14.7%) patients, only four of whom survived to discharge, two with oxygen supplementation. Surgery to repair the diaphragm was performed in 98 (89.9%) patients, of whom 46 (46.9%) required patch repair.

At 90 days of postnatal life, 22 patients had died and 87 (79.8%) were alive. After 90 days, only four patients died (at 92, 136, 403 and 802 days) and only two patients were still in hospital at the time of the survey. Eighty-one patients survived to discharge, including 10 patients

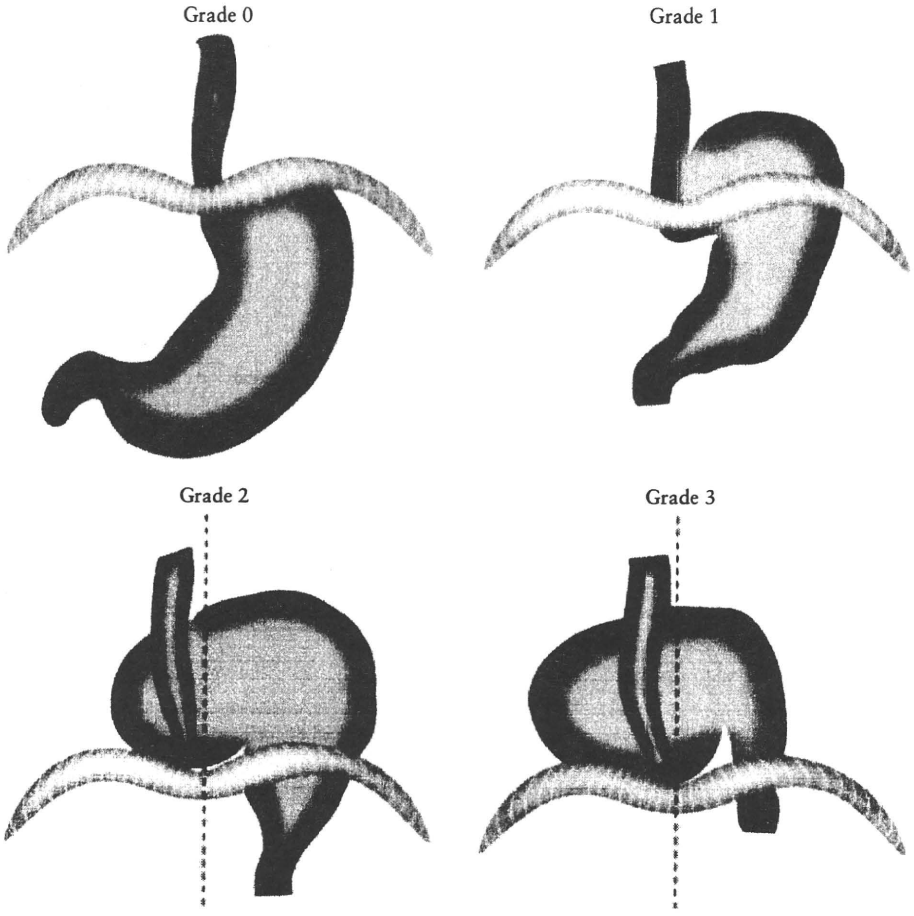

Figure 1 Schematic diagrams showing the four grades of stomach position in patients with left congenital diaphragmatic hernia. Stomach position was categorized as Grade 0, abdominal; Grade 1, left thoracic; Grade 2, less than half of the stomach herniated into the right chest; and Grade 3, more than half of the stomach herniated into the right chest.

with some major morbidities (seven patients required oxygen supplementation, four required tube feeding and two required vasodilators). Thus, the rate of intact discharge was 65.1% (71/109).

The results of univariate analysis are shown in Table 2 and those of multivariate analysis are in Table 3. Adjusted ORs of liver position and stomach position for intact discharge failure were statistically significant. While the OR of LHR was not statistically significant, the magnitude of this risk was not negligible. Adjusted ORs of these three variables became less significant than the crude ORs because they confounded each other.

Stomach position grade was also correlated with the need for patch repair, the need for patch repair being 0% (0/20) for Grade 0, 46% (22/48) for Grade 1, 62% (8/13) for Grade 2 and 94% (16/17) for Grade 3 ($P < 0.001$).

Based on these results, we divided patients into three groups according to liver (up vs. down) and stomach (Grade 0–2 vs. Grade 3) position (Figure 3). Intact discharge rates declined significantly from Group I (liver-down), to Group II (liver-up with stomach Grade 0–2), to Group III (liver-up with stomach Grade 3) (87.0%, 47.4% and 9.5% of cases, respectively).

DISCUSSION

This multicenter study has revealed the outcomes of prenatally diagnosed left CDH managed at perinatal centers with immediate resuscitation and gentle ventilation: a 90-day survival rate of 79.8% and an intact discharge rate of 65.1%. The results compare favorably with reports from leading centers of the world[9,10], considering that patients were all diagnosed prenatally and had relatively low birth weight. Our results reflect the current status in Japan as a whole, compared with previous reports that reflected smaller, single centers[11,12].

A new concept for prognostic evaluation of CDH, intact discharge, was introduced in this study. Intact discharge was defined as discharge from hospital without any respiratory, nutritional or circulatory support. Previously, studies had been focused mainly on therapies that reduce perinatal and neonatal mortality of CDH[13–15]. However, it is well known that to save the lives of the more severely affected patients results in a significant increase in survivor morbidity[16–18]. Intact discharge may serve in counseling the parents and could be an important goal of prenatal intervention. Whether patients with intact discharge have

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.

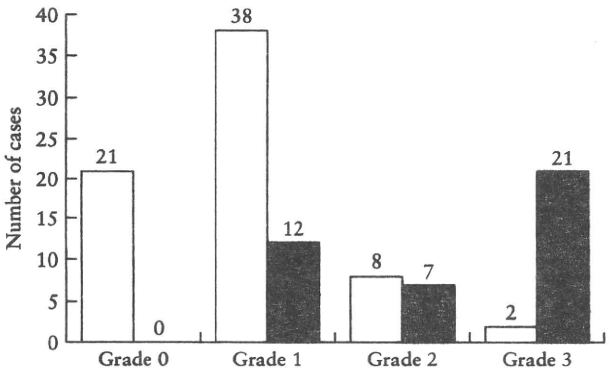

Figure 2 Frequency of each of the four grades of stomach position in liver-down (□) and liver-up (■) patients with left congenital diaphragmatic hernia. Stomach herniation into the right chest was not uncommon, especially in liver-up cases.

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.

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.

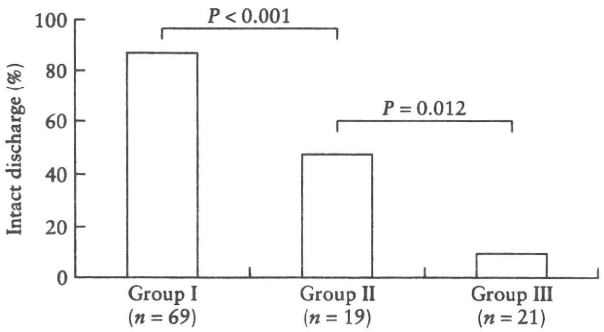

Figure 3 Our new grouping system of fetal patients with isolated left congenital diaphragmatic hernia using liver and stomach positions. Intact discharge rate was significantly different among the three groups (Group I, liver-down; Group II, liver-up and stomach position Grade 0–2; Group III, liver-up and stomach position Grade 3).

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.

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ORIGINAL ARTICLE

The Japanese experience with prenatally diagnosed congenital diaphragmatic hernia based on a multi-institutional review

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Abstract
Purpose To review the recent Japanese experience with prenatally diagnosed congenital diaphragmatic hernia (CDH) based on a multi-institutional survey.
Methods A multicenter, retrospective cohort study was conducted on 117 patients born between 2002 and 2007 with isolated prenatally diagnosed CDH. All patients were managed by maternal transport, planned delivery, immediate resuscitation and gentle ventilation. The primary outcome measurements were the 90-day survival and intact discharge. The examined prenatal factors included gestational age (GA) at diagnosis, lung-to-head ratio (LHR), lung-to-thorax transverse area ratio (L/T) and liver position. Physical growth and motor/speech development were evaluated at 1.5 and 3 years of age. Data were expressed as the median (range).
Results The mean GA at diagnosis was 29 (17–40) weeks. The LHR and L/T were 1.56 (0.37–4.23) and 0.11 (0.04–0.25), respectively. There were 48 patients with liver up. The mean GA at birth was 38 (28–42) weeks. The 90-day survival rate and intact discharge rate were 79 and 63%, respectively. Twelve patients had major morbidity at discharge, and 71% of these patients had physical growth or developmental retardation at 3 years of age.
Conclusion This multicenter study demonstrated that the 90-day survival rate of isolated prenatally diagnosed CDH was 79%, and that subsequent morbidity remained high.

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A new treatment strategy is needed to reduce the mortality and morbidity of severe CDH.

Keywords Congenital diaphragmatic hernia · Gentle ventilation · Prenatal diagnosis · Fetus · Multicenter study

Introduction

Congenital diaphragmatic hernia (CDH) is one of the most challenging anomalies faced by pediatric surgeons and neonatologists. During the past few decades, many innovative techniques, including high-frequency oscillation (HFO), inhaled nitric oxide (NO), extracorporeal membrane oxygenation (ECMO) and gentle ventilation (GV), have been introduced for the treatment of CDH [1, 2]. Additionally, prenatal diagnosis has also made a contribution to the improvement of the outcome of CDH [3, 4]. In many high-volume centers, immediate start of gentle ventilation following planned delivery has become the standard strategy for the treatment of prenatally diagnosed CDH. Despite these advances in fetal and neonatal care, mortality and morbidity remain high in a subset of severe CDH. To offer appropriate information to the family before birth, and to develop a multi-institutional consensus on selection criteria for fetal intervention, it is necessary to analyze the most recent outcomes of prenatally diagnosed CDH. This study was conducted to review the modern experience of prenatally diagnosed CDH treated in five Japanese centers dedicated to this condition.

Materials and methods

A multicenter retrospective study was conducted on 117 patients born between 2002 and 2007 with isolated prenatally diagnosed CDH. Patients with associated life-threatening or chromosomal anomalies were excluded. The participating centers included three children's medical centers and two university hospitals. All patients were managed by maternal transport, planned delivery, immediate resuscitation and gentle ventilation. To achieve GV, the goals of the blood gas parameters were set at $PaCO_2$ < 60–70 mmHg and pre-ductal SpO_2 > 90%. Once these gas data were obtained, ventilator settings, including FiO_2 and mean airway pressure (MAP), were decreased promptly. The upper limit of MAP was set at 18–20 cmH_2O. In each center, HFO, NO and ECMO were available from the entry criteria of each patient. Diaphragmatic repair was performed when respiratory and circulatory stabilization was achieved. The goal of the preoperative stabilization was appropriate blood pressure to keep diuresis and appropriate blood gas data (PaCO2 < 60–70 mmHg, pre-ductal SpO2 > 90%).

This study was approved by the institutional review board of the participating centers (the approved number of subjects was 314).

We reviewed the charts of all patients and their mothers to collect the following data.

Prenatal data

The prenatal data examined included gestational age (GA) at diagnosis, the presence of polyhydramnios, initial lung-to-head ratio (LHR), initial lung-to-thorax transverse area ratio (L/T) and liver position (liver up/liver down). When LHR or L/T was measured several times, the earliest data were analyzed as the initial data.

Postnatal data

Data abstracted postnatally included: GA at birth; birth weight; sex; side of defect; mode of delivery; Apgar score at 1 min; use of NO, HFO and ECMO; highest MAP; duration of mechanical ventilation; duration of oxygen supplementation; date of surgery; need for patching; date of discharge; and significant morbidity at discharge. Significant morbidity included the need for respiratory support (supplemental oxygen, mechanical ventilation), nutritional support (tube feeding, parenteral nutrition) or circulatory support (use of vasodilators).

Physical growth (height and body weight) and motor/speech development were evaluated at 1.5 and 3 years of age. Height or body weight less than −2SD was defined as physical growth retardation. The inability to walk alone was defined as motor developmental retardation. The inability to speak more than 3 words at 1.5 years or to talk normally at 3 years was defined as speech developmental retardation.

Outcome measures

The primary outcomes of the study were 90-day survival and intact discharge. Intact discharge was defined as discharge from the hospital without any of the significant morbidities mentioned above.

Comparisons

To investigate the prognostic factors, comparisons of the prenatal and postnatal data were made between the 90-day survivors and 90-day non-survivors.

Statistical analyses

Data were expressed as the median with the range. The statistical significance of differences was determined by Fisher's exact probability test or the chi-square test for categorical data and the Wilcoxon-test for continuous data. Differences with a P value of <0.05 were considered as significant.

Results

Prenatal data

The GA at diagnosis was 29 (17–40) weeks, and 24 patients had polyhydramnios. The initial LHR was 1.55 (0.37–4.23) and the initial L/T was 0.11 (0.04–0.25), measured at 31 (18–40) weeks. There were 48 patients with liver up and 69 patients with liver down.

Table 1 Postnatal data

Postnatal data	Median (range), *n* (%)
Gestational age at birth (weeks)	38 (28–42)
Birth weight (kg)	2.78 (1.04–4.04)
Sex	
Male	63 (53.9)
Female	54 (46.2)
Mode of delivery	
Vaginal	55 (47.0)
C-section	62 (53.0)
Apgar score at 1 min	4 (1–9)
HFO	
Yes	116 (99.1)
No	1 (0.9)
NO	
Yes	94 (80.3)
No	23 (19.7)
ECMO	
Yes	19 (16.2)
No	98 (83.8)
Highest MAP (cmH_2O)	14 (12–15)[a]
Side of the defect	
Left	109 (93.2)
Right	6 (5.1)
Bilateral	2 (1.7)
Diaphragmatic repair	
Yes	104 (88.9)
No	13 (11.1)
Age at repair (hours)	69 (26–101)[a]
Diaphragmatic closure	
Direct	54 (51.9)
Patch	50 (48.1)
Survivors	
Duration of mechanical ventilation (days)	20 (11–101)[a]
Duration of O_2 supplementation (days)	32 (17–54)[a]

[a] Median (interquartile range)

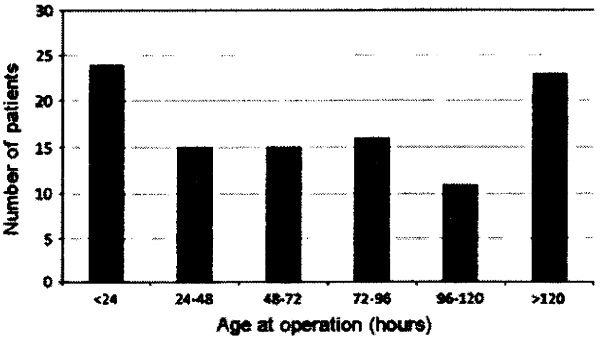

Fig. 1 Age distribution at surgery (hours). Each *bar* indicates the number of patients every 24 h after birth

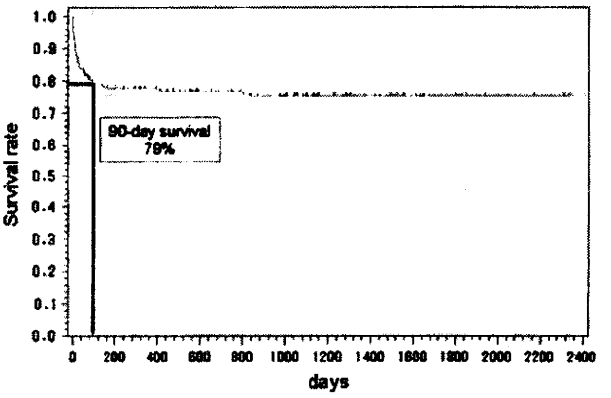

Fig. 2 The survival curve reached a plateau at 90 days. The 90-day survival rate was 79%

Postnatal data

The patients' postnatal characteristics are shown in Table 1. The GA at birth was 38 (28–42) weeks, and the birth weight was 2.78 (1.04–4.04) kg. The mode of delivery was vaginal in 55 patients and cesarean section in 62 patients. HFO was used in 116 patients (99%) and NO in 94 patients (80%). ECMO was used in 19 patients (16%); 7 of these patients survived for 90 days and 2 patients had an intact discharge. The highest MAP was 14 (12–15) cmH_2O. The side of the diaphragmatic defect was left in 109 patients, right in 6 patients, and bilateral in 2 patients. Diaphragmatic repair was performed in 104 patients (direct closure: 54 patients; patch closure: 50 patients); closure was conducted at a median of 69 h after birth. Figure 1 shows the number of patients who underwent diaphragmatic repair every 24 h after birth. The timing of surgery was almost equally distributed up to more than 120 h.

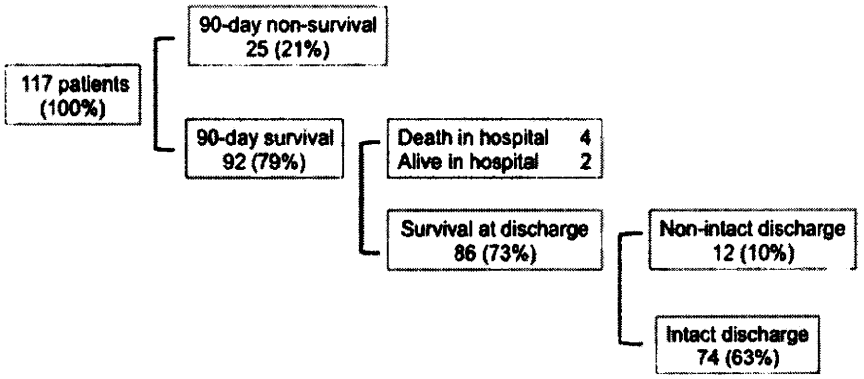

Fig. 3 Summary of the outcomes

Table 2 Comparisons of the incidence of physical growth and motor/speech retardation (intact discharge vs. non-intact discharge)

	Intact discharge ($n = 74$)	Non-intact discharge ($n = 12$)	p
1 year and 6 months			
Any retardation	44% (26/59)	80% (8/10)	0.045
Physical growth	24% (14/59)	60% (6/10)	0.029
Motor/speech	30% (18/59)	70% (7/10)	0.029
3 years			
Any retardation	27% (10/37)	71% (5/7)	0.036
Physical growth	16% (6/37)	57% (4/7)	0.037
Motor/speech	19% (7/37)	43% (3/7)	0.323

Table 3 Comparisons of prenatal data, birth weight and gestational age at birth between 90-day survivors and non-survivors

	90-day survivors ($n = 92$)	90-day non-survivors ($n = 25$)	p
GW at diagnosis (weeks)	29.0 ± 5.8	27.3 ± 5.4	0.249
Polyhydramnios	23% (17/91)	41% (7/24)	0.261
LHR	1.772 ± 0.703	1.273 ± 0.435	0.004
L/T	0.126 ± 0.043	0.096 ± 0.040	0.006
Liver up	28% (26/92)	88% (22/25)	<0.001
Birth weight	2.743 ± 0.526	2.700 ± 0.488	0.404
GA at birth (weeks)	38.0 ± 2.1	37.6 ± 1.7	0.127

Data are expressed as the mean ± SD

Among the survivors, the median duration of mechanical ventilation and O_2 supplementation were 20 and 32 days, respectively.

Outcome measures

Figure 2 shows the overall survival curve, which reached a plateau at 90 days. The 90-day survival was 79% (92/117). Among the survivors, six patients did not qualify for hospital discharge: four patients died in the hospital after 90 days of age, and two patients were still alive in the hospital at the age of 18 and 24 months. Therefore, 86 patients (73%) survived to discharge, including 12 with some major morbidities. Finally, the rate of intact discharge was 63% (74/117). These results are summarized in Fig. 3.

The details of the major morbidities at discharge in 12 patients are as follows:

supplemental O_2: 5;
supplemental O_2 + vasodilator: 2;
supplemental O_2 + tube feeding: 1;
supplemental O_2 + mechanical ventilation + tracheostomy: 1;
tube feeding: 3.

In the 12 non-intact discharge patients, the rate of physical or developmental retardation was 80% at 1.5 years and 71% at 3 years of age. In contrast, in the intact discharge patients, the rate of physical or developmental retardation was significantly lower (Table 2).

With regard to the relations of liver position and outcomes, the 90-day survival rate was 54% (26/48) in liver up and 96% (66/69) in liver down. The intact discharge rate was 29% (14/48) in liver up and 87% (60/69) in liver down. There were significant differences ($p < 0.05$) in the rate of 90-day survival and intact discharge between liver up and liver down patients.

Comparisons

There were no differences in GA at diagnosis, the incidence of polyhydramnios, birth weight and GA at birth between the 90-day survivors and 90-day non-survivors. The initial LHR and L/T were significantly higher in 90-day survivors compared to non-survivors. The incidence of liver up was significantly higher in 90-day non-survivors (Table 3).

Discussion

This is the first Japanese multicenter study of prenatally diagnosed CDH managed by planned delivery and followed by GV. Because five high-volume centers participated in this study, the data from a large series of prenatally diagnosed CDH could be collected in a comparatively short period. As most of the new strategies for CDH treatment, including HFO, NO, ECMO and GV, were introduced in the 1990s, all patients in this study were treated based on these established modern treatments throughout the study period. Therefore, this study should have revealed the most current outcomes for prenatally diagnosed CDH with minimal historical bias.

Our outcomes were somewhat better than the data from the large CDH study group registry in the USA, which noted a 70.5% "survival to discharge" of 1,222 infants born between 1995 and 2006 with prenatal diagnosis [5]. In most of the previous reports, including the CDH study group, "survival to discharge" was taken as the primary outcome. However, the rescue of more severely affected patients resulted in more patients with severe morbidities, including long-term respiratory support, nutritional support and circulatory support. In this study, a total of 12 patients were discharged with major morbidities (9 on respiratory support, 4 with tube feeding and 2 receiving vasodilators). Our results indicate that significant numbers of CDH patients are alive with major morbidities, resulting in poor quality of life. Thus, survival to discharge does not accurately reflect the treatment results if quality of life is taken into account. Because the overall survival curve reached a plateau at 90 days, 90-day survival does seem to be a good index to evaluate the short-term outcomes of CDH.

Our data have also shown that the rate of physical or developmental retardation at 1.5 and 3 years of age in the intact discharge patients was lower compared to the non-intact discharge patients. This suggests that intact discharge is a useful index to predict the long-term outcome of CDH.

This study has also clarified the latest treatment policy. With regard to the timing of delivery, the median gestational weeks at planned delivery was 38 weeks (range 28–42). According to the CDH study group, infants born at 37–38 weeks, compared with those born at 39–41 weeks, had less use of ECMO and a trend toward a higher survival rate was found among infants born through elective cesarean delivery [5]. Because the degree of pulmonary hypoplasia and vascular abnormalities become relatively more severe as gestation progresses [6, 7], there may be a potential benefit from delivering infants with CDH early. Although the best timing of delivery is unclear, 38 weeks is the most common and may be an appropriate timing for delivery of fetuses with CDH.

With regard to the mode of delivery, our data showed that cesarean section was likely to be selected in severe cases. Although the best mode of delivery remains unclear in prenatally diagnosed CDH, recent data have suggested that elective cesarean delivery may be associated with greater rates of survival without ECMO [8]. A prospective randomized trial is needed to determine the best mode of delivery for fetuses with CDH.

The timing of surgery also remains controversial. Some centers delay surgery until physiologic stabilization has occurred, while others prefer early surgery immediately after birth [3]. As a result, the timing of surgery was almost equally distributed to up to 120 h after birth in this study. Our data showed that the timing of surgery was not related to the survival rate. This lack of importance may be due to the progress made in the postoperative medical management of the patients.

With regard to the mode of ventilation, HFO was used immediately after birth in almost all cases. HFO has become the first-line ventilator mode for CDH in Japan. While ECMO was used in 19 patients, only 2 patients who were on ECMO had an intact discharge. Because of the advances in neonatal respiratory care, the role of ECMO has become limited in the treatment of prenatally diagnosed CDH in comparison to the past. A prospective randomized study may be necessary to determine if ECMO can improve the outcome of prenatally diagnosed CDH.

Our data have revealed that the initial LHR and L/T were significantly higher in 90-day survivors compared to 90-day non-survivors. Because of the wide distribution of LHR and L/T in each group, it is difficult to determine a cutoff to distinguish fetuses with expected poor outcome from fetuses with good outcome. Although LHR has been the most common method for lung assessment, there are several reports that have described that LHR is not a reliable predictor of outcome in fetuses with CDH [9–11]. According to our data, liver position was strongly correlated with 90-day survival as well as LHR and L/T. It is important to consider these factors together to predict outcomes of prenatally diagnosed CDH more precisely. In addition to LHR, L/T and liver position, measurement of other prognostic factors, such as total fetal lung volume [12], herniated liver volume [13, 14] and the observed to expected normal mean for gestation (o/e) LHR [15], are also required to establish an entry criteria for fetal intervention.

A major limitation of this study is the late diagnosis. The initial measurement of LHR and L/T were conducted at 31 weeks of gestation. Although L/T is consistent during gestation [16], LHR increases with gestation. It is therefore preferable to use o/e LHR to obtain a gestation-independent prediction of survival [15]. This fact should be considered when using our data as a selection criterion for fetal

intervention, which is currently being performed at 26–28 weeks' gestation.

The present study has demonstrated that a significant number of CDH patients are alive with major morbidities, despite good survival rate. A new treatment strategy, including fetal intervention, is therefore needed to reduce the mortality and morbidity of severe CDH.

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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 $SpO_2 \geqq 90\%$/preductal $PaO_2 \geqq 70$ 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

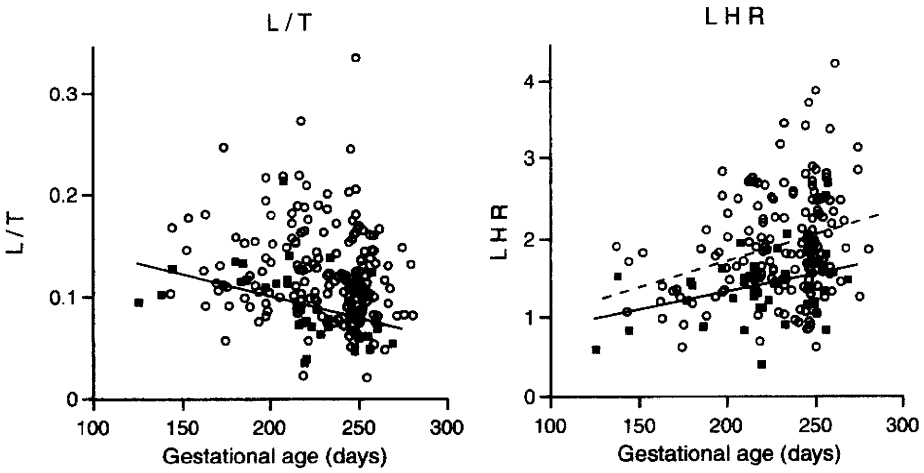

Fig. 1 Relationship between the gestational age with the L/T and the LHR in the fetuses with congenital diaphragmatic hernia by survival and non-survivors. The *open circles* and *dashed regression line* (LHR = 0.344 + 0.00677GA) represent the survivors and the *closed squares* and *solid regression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

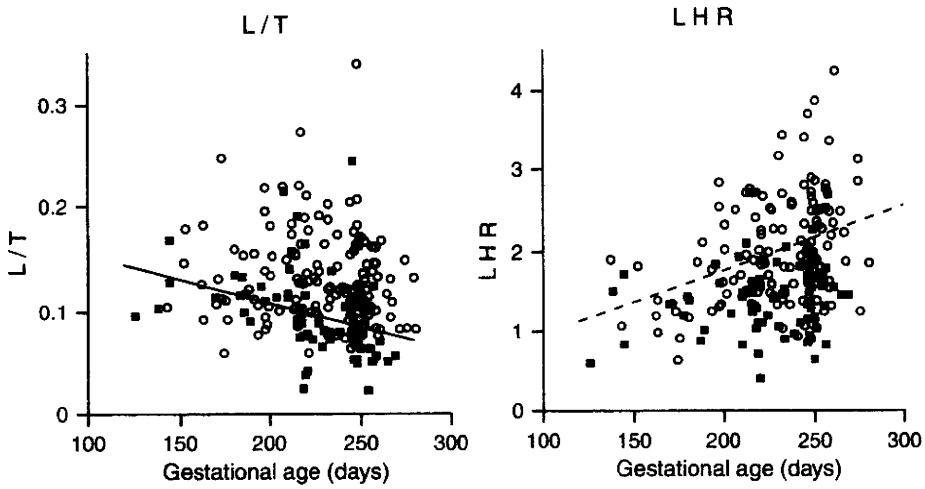

Fig. 2 Relationship between the gestational age with the L/T and the LHR in the fetuses with congenital diaphragmatic hernia according to intact discharge and non-intact discharge. The *open circles* and *dashed regression line* (LHR = 0.159 + 0.00796GA) represent the infants with intact discharge and 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

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

AUC area under the ROC curve

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

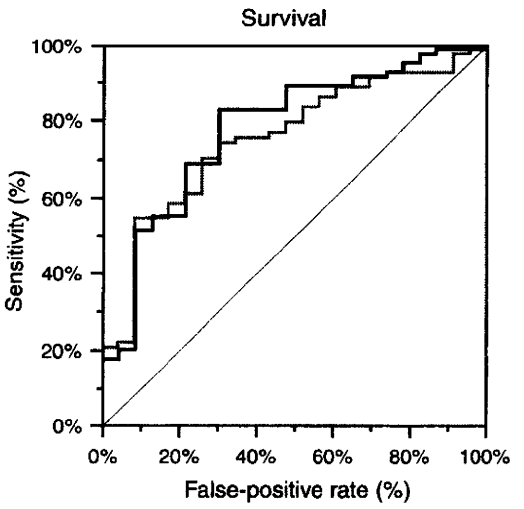

Fig. 3 The ROC curve for discriminating the outcome of survival based on the minimum L/T (*solid line*) and the maximum LHR (*light line*). The AUC for survival in L/T and LHR was 0.776 and 0.750, respectively

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

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

AUC area under the ROC curve

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

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, *PGE_1* 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

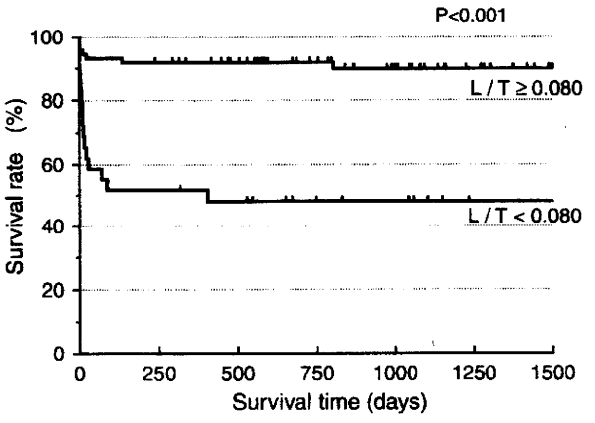

Fig. 4 Survival curves in the patients with isolated congenital diaphragmatic hernia divided by the minimum L/T at 0.080

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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