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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

Noriaki Usui · Yoshihiro Kitano · Hiroomi Okuyama · Mari Saito · Nobuyuki Morikawa · Hajime Takayasu · Tomoo Nakamura · Satoshi Hayashi · Motoyoshi Kawataki · Hiroshi Ishikawa · Keisuke Nose · Noboru Inamura · Kouji Masumoto · Haruhiko Sago

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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

N. Usui (✉)
Department of Pediatric Surgery,
Osaka University Graduate School of Medicine,
2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
e-mail: usui@pedsurg.med.osaka-u.ac.jp

Y. Kitano · N. Morikawa · H. Takayasu
Division of Surgery, National Center for Child Health and Development, Tokyo, Japan

M. Saito
Division of Clinical Research,
National Center for Child Health and Development,
Tokyo, Japan

T. Nakamura · S. Hayashi · H. Sago
Division of Maternal-Fetal and Neonatal Medicine,
National Center for Child Health and Development,
Tokyo, Japan

H. Okuyama
Department of Pediatric Surgery,
Hyogo College of Medicine, Hyogo, Japan

M. Kawataki · H. Ishikawa
Department of Perinatal Care, Kanagawa Children's Medical Center, Yokohama, Japan

K. Nose
Department of Pediatric Surgery,
Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan

N. Inamura
Department of Pediatric Cardiology,
Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan

K. Masumoto
Department of Pediatric Surgery,
Kyushu University, Fukuoka, Japan

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

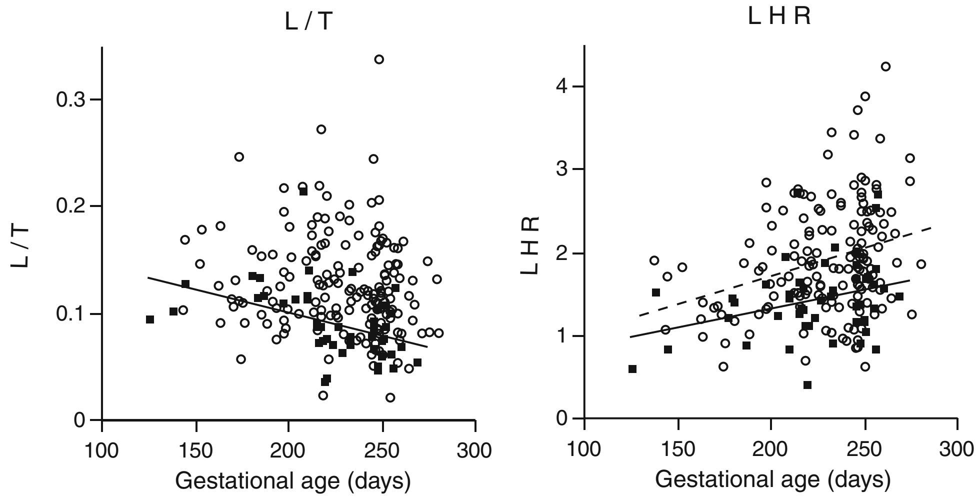

Fig. 1 Relationship between the gestational age with the L/T and the LHR in the fetuses with congenital diaphragmatic hernia by survival and non-survivors. The *open circles* and *dashed regression line* (LHR = 0.344 + 0.00677GA) represent the survivors and the *closed squares* and *solid regression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

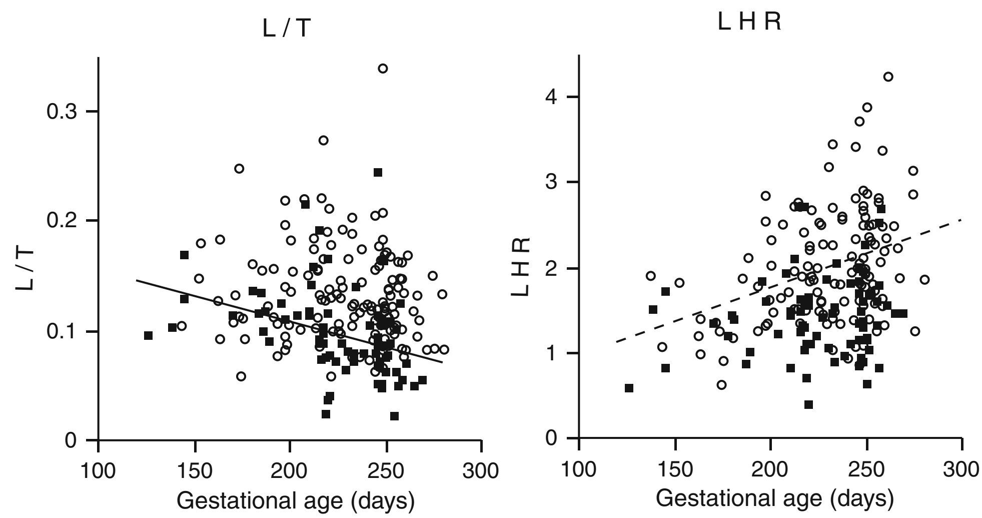

Fig. 2 Relationship between the gestational age with the L/T and the LHR in the fetuses with congenital diaphragmatic hernia according to intact discharge and non-intact discharge. The *open circles* and *dashed regression line* (LHR = 0.159 + 0.00796GA) represent the infants with intact discharge and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

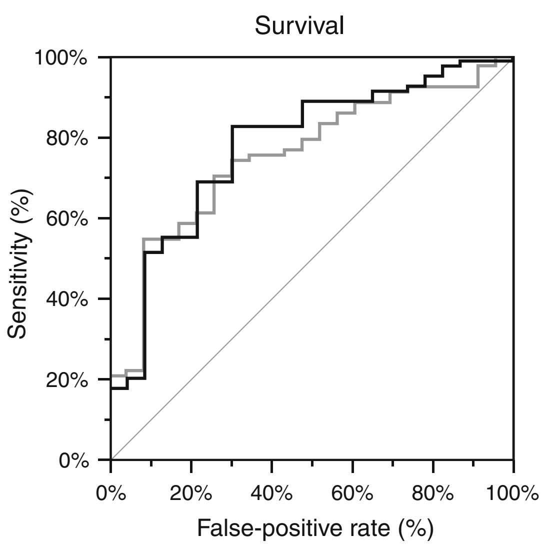

Fig. 3 The ROC curve for discriminating the outcome of survival based on the minimum L/T (*solid line*) and the maximum LHR (*light line*). The AUC for survival in L/T and LHR was 0.776 and 0.750, respectively

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

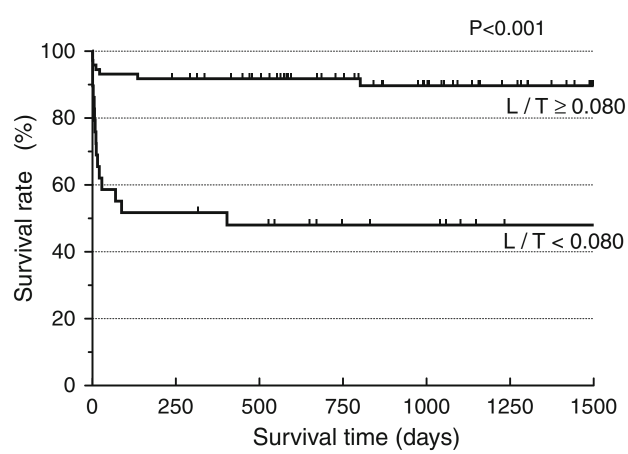

Fig. 4 Survival curves in the patients with isolated congenital diaphragmatic hernia divided by the minimum L/T at 0.080

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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