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Original Articles

The lung to thorax transverse area ratio has a linear correlation with the observed to expected lung area to head circumference ratio in fetuses with congenital diaphragmatic hernias

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ABSTRACT

Background/Purpose: The purpose of this study was to clarify the relationship between the lung to thorax transverse area ratio (L/T ratio) and the observed to expected lung area to head circumference ratio (O/E LHR), based on the results of a nationwide Japanese survey conducted in 2011, and to evaluate the compatibility of these prognostic predictors of fetal CDH.

Methods: Two hundred and forty-two prenatally diagnosed isolated CDH patients born between 2006 and 2010 were included in the present analysis. A regression analysis was conducted to investigate the relationship between the L/T ratio and the O/E LHR based on 191 simultaneous measurements of these parameters in 120 patients.

Results: The linear regression equation between the L/T ratio and the O/E LHR was: L/T ratio = 0.0233 + (0.00222 × O/E LHR), ($R = 0.847$, $p < 0.0001$). According to this equation, 25% of the O/E LHR, the cut-off value used in the fetal intervention for CDH, was equivalent to an L/T ratio of 0.08, a commonly accepted cut-off value for identifying the most severe cases of fetal CDH.

Conclusions: As there is a positive correlation between the L/T ratio and the O/E LHR, these two parameters proved to be used interchangeably according to the linear regression equation.

The mortality and morbidity of infants with congenital diaphragmatic hernia (CDH) mainly depend on the severity of pulmonary hypoplasia. Therefore, an accurate prenatal assessment of pulmonary hypoplasia is necessary to establish an optimal treatment strategy for individuals before birth. Although many prenatal prognostic parameters have previously been proposed by various investigators [1–4], measurement of the residual lung size seems to be one of the most reasonable and realistic methods [5–8].

The lung area to head circumference ratio (LHR) was the most commonly used predictor for CDH in the past [5,9,10]. The observed to expected (O/E) LHR has become a standard parameter used for determining the indications for fetal intervention to treat severe cases of CDH [11]. Of note, the O/E LHR was used in the Tracheal Occlusion To Accelerate Lung growth (TOTAL) trial of left CDH patients with severe pulmonary hypoplasia [12,13]. On the other hand, the lung to thorax transverse area ratio (L/T ratio), which was proposed before the publication of the LHR [5,6,9], has been widely used in Japan for the assessment of pulmonary hypoplasia in fetal CDH patients [6,14–16]. The LHR is no longer considered to be independently predictive of survival [17,18], as it was shown to increase according to the gestational age [11,19–21]. In contrast, the O/E LHR is not influenced by gestational age [22] as is the case with the L/T ratio [6,14,19], because it is standardized by the normal mean value of the LHR corresponding to the specific gestational age [11]. Both of the indicators are similarly based on the measurement of the contralateral lung area by using tracing methods [6,21,23] at the transverse section containing the four-chamber view of the heart.

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

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1. Materials and methods

1.1. Study population

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

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

1.2. Collected data

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

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

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

1.4. Patient outcome according to the prenatal prediction of the disease severity

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

1.5. Statistical analysis

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

2. Results

An outline of the patient demographics is shown in Table 1. Of the 242 neonates with prenatally diagnosed isolated CDH, 177 (73.1%)