

# Quantitative Lung Index, Contralateral Lung Area, or Lung-to-Head Ratio to Predict the Neonatal Outcome in Isolated Congenital Diaphragmatic Hernia?

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**Objectives**—To estimate the accuracy of the quantitative lung index and contralateral lung area for prediction of the neonatal outcome in isolated congenital diaphragmatic hernia in comparison to other available prediction models.

**Methods**—Between January 2004 and December 2010, 108 fetuses with isolated (82 left-sided and 26 right-sided) congenital diaphragmatic hernia were prospectively evaluated. The quantitative lung index and observed-to-expected contralateral lung area were measured and compared to the neonatal survival rate and severe postnatal pulmonary arterial hypertension, along with the lung-to-head ratio, observed-to-expected lung-to-head ratio, and observed-to-expected total lung volume.

**Results**—Overall neonatal mortality was 64.8% (70 of 108). Severe pulmonary arterial hypertension was diagnosed in 68 (63.0%) of the cases, which was associated with neonatal death ( $P < .001$ ). Both the quantitative lung index and observed-to-expected contralateral lung area were significantly associated with neonatal survival and pulmonary arterial hypertension ( $P < .001$ ), with accuracy to predict survival of 70.9% and 70.0%, respectively, and accuracy to predict hypertension of 78.7% and 72.0%; however, they were both less accurate than the observed-to-expected total lung volume (83.3% and 86.1%;  $P < .01$ ). The lung-to-head ratio (73.1% and 78.7%) and observed-to-expected lung-to-head ratio (75.9% and 72.2%;  $P > .05$ ) had similar accuracy as the quantitative lung index and observed-to-expected contralateral lung area.

**Conclusions**—The observed-to-expected total lung volume is the most accurate predictor of the neonatal outcome in cases of isolated congenital diaphragmatic hernia. Both the quantitative lung index and observed-to-expected contralateral lung area, albeit reasonably accurate, do not produce the same level of accuracy and render similar results as the lung-to-head ratio and observed-to-expected lung-to-head ratio.

**Key Words**—congenital diaphragmatic hernia; neonatal outcome; pulmonary arterial hypertension; pulmonary hypoplasia

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The prognosis of fetuses with isolated congenital diaphragmatic hernia predominantly depends on the severity of pulmonary hypoplasia and pulmonary arterial hypertension.<sup>1,2</sup> Fetal tracheal occlusion has been shown to “revert” these complications by improving the fetal lung growth and, consequently, the survival rate.<sup>3–7</sup> The most widely used prenatal sonographic parameter for predicting the neonatal outcome is called lung-to-head ratio, which is an estimation of the fetal contralateral lung area by the fetal head circumference.<sup>8,9</sup> Some investigators have suggested that

this ratio varies throughout gestational age and have advocated the use of the observed-to-expected lung-to-head ratio.<sup>10,11</sup>

Recently, in a study of 108 fetuses with isolated congenital diaphragmatic hernia, our group showed that the lung-to-head ratio and observed-to-expected lung-to-head ratio have the same accuracy in predicting neonatal death, and the observed-to-expected total lung volume is the best predictor of the neonatal outcome because it considers both contralateral and ipsilateral lung volumes.<sup>12</sup> However, the discussion on the best prenatal sonographic predictors of the neonatal outcome in isolated congenital diaphragmatic hernia continues. In fact, citing the impact of gestational age, Quintero et al<sup>13</sup> recently suggested the use of the quantitative lung index, which is calculated as quantitative lung index = contralateral lung area / (head circumference / 10)<sup>2</sup>.

Consequently, our aim in this study was to estimate and compare the accuracies of the quantitative lung index, observed-to-expected contralateral lung area, lung-to-head ratio, observed-to-expected lung-to-head ratio, and observed-to-expected total lung volume in 108 cases of isolated congenital diaphragmatic hernia to determine the best predictive model.

## Materials and Methods

We conducted a secondary analysis of our previously published cohort of 108 fetuses with isolated (82 left-sided and 26 right-sided) congenital diaphragmatic hernia, who were prospectively evaluated between January 2004 and December 2010.<sup>12</sup> No fetal therapy was performed in this population. Approval from our Institutional Review Board was obtained before data collection.

As previously reported, we only enrolled and included patients with a sonographically verified gestational age, confirmed isolated congenital diaphragmatic hernia, normal fetal karyotype, absence of any other structural anomalies, and no fetal intervention or surgery. Of note, none of the included cases underwent termination of pregnancy because it is not permissible in our country.

Fetal biometric and lung measurements were performed with a Voluson 730 ultrasound machine (GE Healthcare, Zipf, Austria) between 26 and 30 weeks' gestation. The observed-to-expected contralateral lung area was obtained by measuring the contralateral lung area at 26 to 30 weeks' gestation and using the nomogram reported by Peralta et al.<sup>11</sup> The quantitative lung index was calculated according to the formula of Quintero et al.<sup>13</sup> The lung-to-head ratio and observed-to-expected total lung volume were calculated using the formulas of Metkus et al<sup>8</sup> and Ruano et al.<sup>14,15</sup>

We have previously reported our perinatal management details.<sup>7,12</sup> Briefly, all cases were treated under the same protocol, which included intubation in the delivery room, transfer to the neonatal intensive care unit, immediate ventilator support, high-frequency oscillatory ventilation when necessary, and delayed congenital diaphragmatic hernia repair after preoperative respiratory and hemodynamic stabilization. The treatment protocol did not include extracorporeal membrane oxygenation, either preoperatively or postoperatively. Inhaled nitric oxide was administered in cases of persistent pulmonary arterial hypertension.

Our primary outcome was neonatal survival to the age of 28 days of life. The secondary outcome was the postnatal diagnosis of severe pulmonary arterial hypertension as defined by profound neonatal cyanosis associated with echocardiographic continuous right-to-left shunting through a persistent ductus arteriosus and a persistent difference in the preductal to postductal saturation gradient of greater than 20%, despite the use of nitric oxide.<sup>16,17</sup>

The data were analyzed using SPSS version 19.0 statistical software (SPSS Inc, Chicago, IL). The Student *t* and  $\chi^2$  tests were used to evaluate the association of the sonographic parameters with neonatal survival and postnatal diagnosis of severe pulmonary arterial hypertension. Correlations between variables were evaluated by the Pearson test. Receiver operating characteristic curves were calculated to evaluate the accuracy of each variable for the prediction of neonatal survival and postnatal diagnosis of severe pulmonary arterial hypertension. Best cutoffs (points with the highest sensitivity and lowest rate of false positivity) were then established. Statistical comparisons between the accuracies of the sonographic parameters were performed using the McNemar and Cochran *Q* tests. Statistical comparisons between the areas under the receiver operating characteristic curves of the different sonographic variables were also performed according to the tests of DeLong et al<sup>18</sup> and Hanley et al<sup>19,20</sup> (MedCalc software version 11.6; MedCalc, Mariakerke, Belgium).<sup>18–20</sup> Statistical differences were considered significant at  $P < .05$ .

## Results

The mean gestational age  $\pm$  SD at diagnosis of congenital diaphragmatic hernia was  $20.6 \pm 5.1$  weeks. Right-sided congenital diaphragmatic hernia was observed in 26 (24.1%) cases. Polyhydramnios was observed in 37 (34.3%) of 108 pregnancies. The mean gestational age at birth and newborn weight were  $37.3 \pm 1.9$  weeks' gestation and  $3016.2 \pm 469.7$  g, respectively. We did not find an association between the presence of a right-sided lesion, polyhy-

dramnios, neonatal weight, or gestational age at delivery and neonatal survival or postnatal diagnosis of severe pulmonary arterial hypertension. As reported previously, the neonatal mortality rate was 64.8% (70 of 108).<sup>12</sup> All neonatal survivors were doing well up to 6 months of age. Severe pulmonary arterial hypertension was diagnosed postnatally in 68 (63.0%) cases. Neonatal death occurred in 63 (92.6%) of 68 neonates with severe pulmonary arterial hypertension, versus 7 (15.0%) of 40 neonates without severe pulmonary arterial hypertension ( $P < .001$ ).

As presented in Table 1, both the observed-to-expected contralateral lung area and quantitative lung index were significantly reduced in neonates who died. The accuracies of these two models to predict neonatal survival were lower than those of the lung-to-head ratio and observed-to-expected lung-to-head ratio models. As presented in Figure 1, the observed-to-expected total lung volume had the highest accuracy for prediction of neonatal survival ( $P < .01$ ). Both observed-to-expected contralateral lung area and quantitative lung index were significantly associated with severe neonatal pulmonary arterial hypertension (Table 2) but had similar accuracy as the lung-to-head ratio and observed-to-expected lung-to-head ratio ( $P > .05$ ) and less accuracy than the observed-to-expected total lung volume ( $P < .01$ ; Figure 2).

## Discussion

In this study, our aim was to estimate and compare the accuracies of the various available predictive models for neonatal morbidity and mortality in cases of isolated congenital diaphragmatic hernia. More specifically, we sought to estimate the accuracy of the quantitative lung index as proposed by Quintero et al<sup>13</sup> compared to the observed-to-expected contralateral lung area, lung-to-head ratio, observed-to-expected lung-to-head ratio, and observed-to-expected total lung volume. Although, as suggested by

Quintero et al,<sup>13</sup> there is a theoretical mathematical discussion to correct the ratio between the contralateral lung area and fetal head circumference for prediction of the neonatal outcome in isolated congenital diaphragmatic hernia, our results continue to support the concept that measuring the contralateral lung sizes is less effective than measuring the total lung volume.<sup>12</sup>

On the basis of the physiopathologic characteristics of congenital diaphragmatic hernia, it is well known that both lungs are hypoplastic.<sup>21–24</sup> However, one must keep in mind that there are differing degrees of pulmonary hypoplasia when considering each lung separately, and the lung ipsilateral to the diaphragmatic defect is usually more hypoplastic than the contralateral one. This fact may have important consequences for the physiopathologic characteristics of the malformation and may explain the better observed accuracy when using total fetal lung volume as a predictive model.

There are many methods to measure the contralateral lung size. In fact, the lung-to-head ratio and observed-to-expected lung-to-head ratio are widely used for clinical management and research by many investigators and physicians.<sup>3,25–27</sup> However, it is well accepted that neither model is 100% accurate in predicting the neonatal outcome, which has led to numerous attempts to develop a superior model. Although interesting,<sup>28</sup> this discussion will be fruitless as long as the focus remains on methods to measure the same fetal structure (contralateral lung size). Instead, attention should be focused on other parameters such as fetal pulmonary vascularity, which may indeed provide further information about the lung function in these cases.

Our study had limitations, which merit discussion. The study was conducted in one center without extracorporeal membrane oxygenation availability, which may have led to lower survival rates than centers in the United States. However, extracorporeal membrane oxygenation is not proven to improve the long-term survival rate in cases of

**Table 1.** Prediction of Neonatal Survival Using Different Sonographic Parameters in 108 Fetuses With Congenital Diaphragmatic Hernias

Parameter	Neonatal Death (n = 70)	Alive and Well (n = 38)	P	Cutoff	ROC Area	Sensitivity, %	Specificity, %	Accuracy, %	RR (95% CI)
Lung-to-head ratio	0.97 ± 0.31	2.19 ± 1.06	<.001	1.4	0.78	71.4	76.3	73.1	3.0 (1.7–5.4)
Observed-to-expected lung-to-head ratio	20.5 ± 6.5	31.3 ± 7.2	<.001	25.0	0.79	72.9	81.6	75.9	4.0 (2.0–7.8)
Observed-to-expected contralateral lung area	0.39 ± 0.13	0.79 ± 0.36	<.001	0.48	0.77	68.5	69.7	70.0	2.1 (1.2–3.4)
Quantitative lung index	0.36 ± 0.10	0.75 ± 0.37	<.001	0.49	0.79	71.4	70.0	70.9	2.4 (1.4–4.0)
Observed-to-expected total lung volume	0.26 ± 0.07	0.45 ± 0.12	<.001	0.35	0.82	82.9	84.2	83.3	5.2 (2.5–11.0)

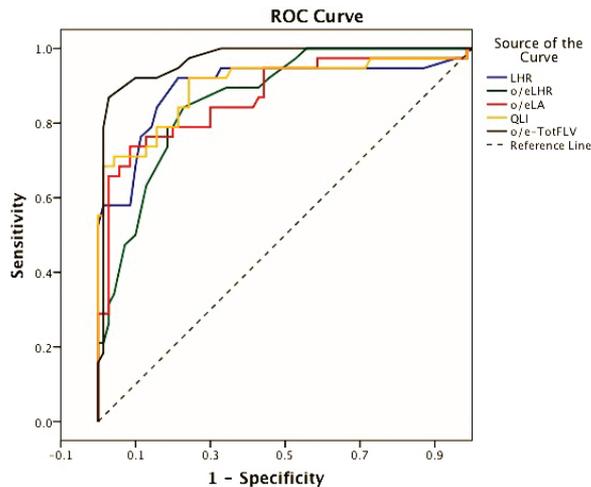
Values are mean ± SD where applicable. CI indicates confidence interval; ROC, receiver operating characteristic; and RR, relative risk.

congenital diaphragmatic hernia; therefore, we do not suspect a substantial impact on our data.<sup>29,30</sup> Second, this study could have been biased by the fact that the present population represents fetuses who did not undergo fetal intervention, but, during this period, our center was investigating the effectiveness of fetal endoscopic tracheal occlusion for severe forms. Therefore, many fetuses with severe forms were referred to our center (referral bias). Besides, termination of pregnancy is not performed in our center. Nevertheless, we evaluated the accuracy of the various predictive models using the same set of variables; therefore, these limitations should have a minimal if any effect on the results. In addition, the reproducibility of all these prenatal pulmonary parameters needs further evaluation.

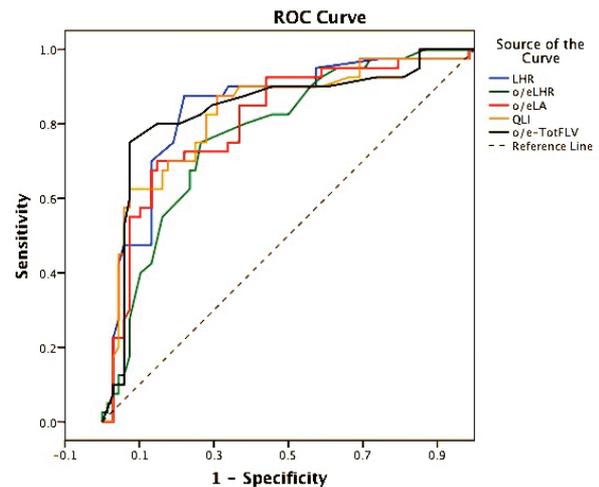
In this study, the laterality of the defect was not associated with the prognosis, which was reported in our previous study. The accuracy of the fetal lung parameters may not vary according to the side of the defect because all the parameters evaluated in this study represent measurements of lung sizes. In addition, the gestational age at the sonographic examination did not vary considerably (26–30 weeks), which precluded us from evaluating whether there is any influence of gestational age on the accuracy of these parameters.

In conclusion, we showed that the quantitative lung index has similar accuracy as the lung-to-head ratio and observed-to-expected lung-to-head ratio, all of which aim to measure the contralateral lung size. We propose that future efforts be directed at other fetal parameters such as total lung volume and lung function.

**Figure 1.** Receiver operating characteristic curve for prediction of neonatal death using the quantitative lung index (QLI), observed-to-expected contralateral lung area (o/e-LA), lung-to-head ratio (LHR), observed-to-expected lung-to-head ratio (o/e-LHR), and observed-to-expected total lung volume (o/e-TotFLV). Diagonal segments are produced by ties.



**Figure 2.** Receiver operating characteristic curve for prediction of post-natal severe pulmonary arterial hypertension using the quantitative lung index (QLI), observed-to-expected contralateral lung area (o/e-LA), lung-to-head ratio (LHR), observed-to-expected lung-to-head ratio (o/e-LHR), and observed-to-expected total lung volume (o/e-TotFLV). Diagonal segments are produced by ties.



**Table 2.** Prediction of Severe Pulmonary Arterial Hypertension Using Different Sonographic Parameters in 108 Fetuses With Congenital Diaphragmatic Hernias

Parameter	Hypertension (n = 70)	No Hypertension (n = 38)	P	Cutoff	ROC Area	Sensitivity %	Specificity %	Accuracy %	RR (95% CI)
Lung-to-head ratio Observed-to-expected	1.00 ± 0.70	1.90 ± 0.90	<.001	1.4	0.80	82.4	72.5	78.7	3.0 (1.8–5.0)
Observed-to-expected lung-to-head ratio	21.5 ± 8.0	28.9 ± 7.4	<.001	26.0	0.78	75.0	67.5	72.2	2.3 (1.4–3.7)
Observed-to-expected contralateral lung area	0.44 ± 0.26	0.70 ± 0.30	<.001	0.48	0.79	76.0	69.0	72.0	2.1 (1.2–3.4)
Quantitative lung index Observed-to-expected	0.41 ± 0.27	0.67 ± 0.30	<.001	0.49	0.81	82.4	72.5	78.7	3.0 (1.8–5.0)
Observed-to-expected total lung volume	0.28 ± 0.11	0.40 ± 0.12	<.001	0.35	0.85	92.6	75.0	86.1	3.7 (2.2–6.4)

Values are mean ± SD where applicable. Abbreviations are as in Table 1.

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