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Percent predicted lung volumes as measured on fetal magnetic resonance imaging: a useful biometric parameter for risk stratification in congenital diaphragmatic hernia

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Outcome

Abstract

Purpose: This study was aimed at determining whether a new method of analyzing lung volumes on fetal magnetic resonance (MR) imaging could be used to predict the degree of pulmonary compromise in congenital diaphragmatic hernia (CDH).

Methods: Seventeen fetuses with CDH were prospectively evaluated by MR. Lung volumes were measured using an established technique and expressed as a percentage of the predicted lung volume (PPLV). Predicted lung volume was determined by subtracting measured mediastinal volume from total measured thoracic volume. The PPLV was correlated with postnatal outcomes. Statistical analyses were performed using the Mann-Whitney, Spearman correlation, or Fisher exact tests ($P < .05$).

Results: Of the 14 liveborn patients, the PPLV was 20.3±10.4 (gestational age at MR, 22.3 ± 5.7 weeks). The PPLV was significantly associated with extracorporeal membrane oxygenation (ECMO) use, hospital length of stay, and survival. All patients with a PPLV of less than 15 required prolonged ECMO support and had a 40% survival rate. In contrast, only 11% of patients with a PPLV of greater than 15 required ECMO, and survival was 100%.

Conclusion: The PPLV as measured by fetal MR imaging can accurately predict disease severity in CDH. A value of less than 15 is associated with a significantly higher risk for prolonged support and/or death, despite aggressive postnatal management.

The lung-to-head ratio (LHR), as measured by prenatal ultrasound, is defined as the product of the orthogonal diameters of the right lung divided by the head circumference [1]. This biometric parameter is currently the only commonly used method for predicting outcomes in fetuses with congenital diaphragmatic hernia (CDH) [2,3]. Unfortunately, the LHR has only been well validated for left-sided defects during a very limited gestational window in the fetus, and the measurement itself is operator-dependent, thereby leading to poor reproducibility across different centers.

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In addition, recent evidence has suggested that the LHR may not be a reliable predictor of pulmonary hypoplasia and postnatal outcomes in this patient population [4-6]. For example, in a National Institutes of Health–sponsored trial, CDH neonates with liver herniation and an LHR of less than 1.4 had a 77% survival rate when treated with aggressive postnatal care [6]. In the setting of right-sided CDH and in left-sided CDH without liver herniation, the LHR has not been shown to be a reliable predictor of outcome [7,8]. Furthermore, a significant number of LHR measurements are in the intermediate range (ie, between 1.0 and 1.4), which precludes the ability of clinicians to make accurate and meaningful predictions regarding patient outcome [3].

Over the past decade, fetal magnetic resonance (MR) imaging has been proposed as a potentially more useful diagnostic modality for the assessment of pulmonary hypoplasia in CDH. Thus far, the predictive value of fetal MR in determining postnatal outcomes has been mixed [9-13]. However, most of the studies that have attempted to measure lung volumes using MR imaging have normalized these values based on gestational age [9,10,12,13]. Such methods for quantifying actual lung volumes may be inaccurate because expected fetal lung volumes in CDH are more likely to correlate with fetal size than with gestational age [14-16]. In the present study, we sought to determine whether a new method of analyzing lung volumes by MR, expressed as the percent of the predicted lung volume (PPLV), could be used to accurately predict the likelihood of significant pulmonary compromise in fetal CDH. This method of analysis is proposed in an effort to minimize the error introduced by the inherent variability in fetal size.

1. Materials and methods

This prospective study was conducted under an approved institutional review board protocol (M02-10-240). From December 2000 to January 2005, 74 fetuses with sonographically diagnosed CDH were referred to the Advanced Fetal Care Center at Children's Hospital Boston. Confirmatory prenatal sonograms (ATL 5000, Philips, Bothell, Wash, or Sequoia, Siemens, Mountain View, Calif) were performed. When gestational age was appropriate and fetal lie permitted, LHR was calculated during these examinations. Prenatal data obtained by the investigators included gestational age at diagnosis, side of hernia, and liver position.

Forty-four patients underwent further evaluation with ultrafast MR imaging at our institution. Ten of these fetuses were excluded from further analysis because of a known structural cardiac anomaly (n = 5), chromosomal abnormalities (n = 3), or multiple gestation pregnancy (n = 1). Fetal lung volumes were prospectively measured in 17 (48.6%) of the remaining fetuses using a 1.5-T system (TwinSpeed; GE, Waukesha, Wis) equipped with various coils as appropriate for patient size. Multiple single shot, fast spin-echo

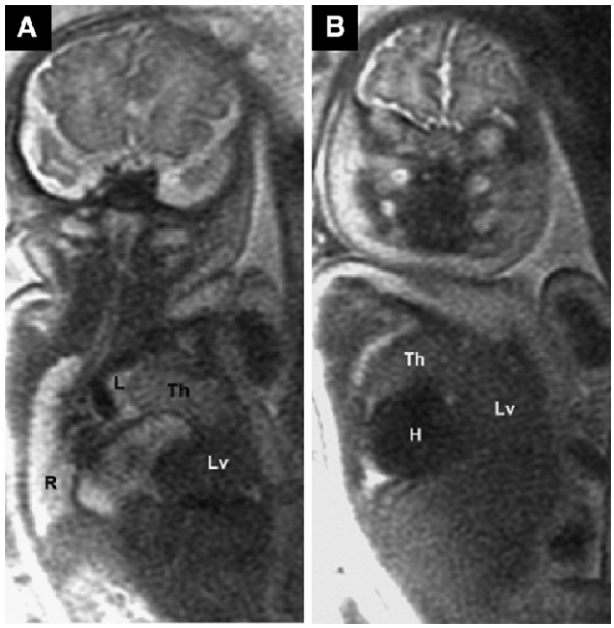

Fig. 1 Coronal fast spin-echo T2-weighted fetal MR images (A, posterior and B, anterior) in a 35-week-gestation fetus with a liver-up, left sided CDH. Anatomical structures were easily defined and include right lung (R), left lung (L), liver (Lv), heart (H), and thymus (Th). The predicted lung volume for each patient was determined by subtracting mediastinal volume from total thoracic volume.

T2-weighted and fast technique T1-weighted images were obtained in the sagittal, axial, and coronal planes (Fig. 1). All MR images were analyzed and reviewed by a staff radiologist (CEB). The volume of each lung (when visible), thorax, and mediastinum were determined for each patient using a 3-dimensional (3-D) rendering of the region of interest as outlined on consecutive T2-weighted coronal images, archived on a Vitrea workstation (Vital Images, Minnetonka, Minn). The thorax was defined by the thoracic cage, intact diaphragm, and extrapolation of the intact diaphragm across to the contralateral side, excluding the structures of the chest wall. The mediastinum was defined as including the central airway, thymus, heart, great vessels, and visible vessels of the hila. The predicted lung volume for each patient was determined by subtracting mediastinal volume from total thoracic volume. Lung volumes were expressed as a percentage of the predicted lung volume (PPLV), defined as the sum of the volumes of the right and left lungs divided by the predicted lung volume, multiplied by 100.

Expectant mothers were counseled by a multidisciplinary care team. No patient was treated by prenatal tracheal occlusion. All patients were delivered at neighboring tertiary care centers. Controlled intubation during ex utero intrapartum treatment (EXIT procedure) was performed in selected cases based on liver herniation and relative lung size. One fetus was immediately placed on extracorporeal membrane oxygenation (ECMO) during the EXIT procedure without a ventilatory trial. Regardless of delivery mode, all neonates were treated under a management

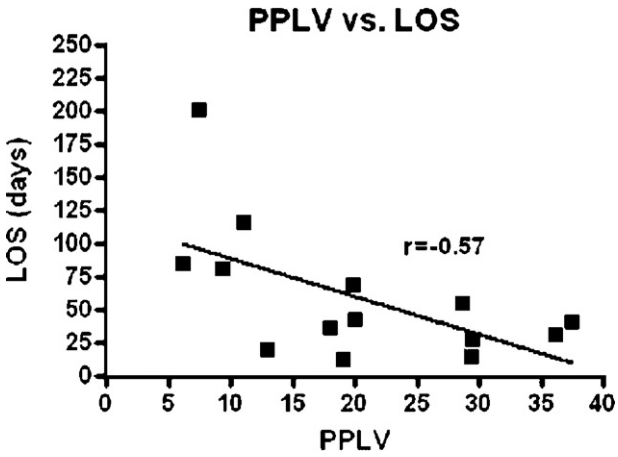

Fig. 2 Scatterplot of the correlation between the PPLV and hospital LOS. A low PPLV was significantly associated with a prolonged hospital stay.

strategy emphasizing minimal barotrauma, as previously reported from our institution [17].

The principle outcome variables were need for ECMO support, hospital length of stay (LOS), and survival to hospital discharge. Outcomes were also assessed categorically after stratification of patients into 2 groups based on a PPLV cutoff value of 15. Statistical analyses were performed using the Mann-Whitney *U*, Spearman nonparametric correlation, and Fisher exact tests, as appropriate, using commercially available software (Instat, San Diego, Calif). *P* values of less then .05 were considered significant. All values are reported as the mean ± SD, unless otherwise indicated.

2. Results

There were 12 left-sided and 5 right-sided hernias. Seventy-one percent had prenatal evidence of liver herniation. Three pregnancies were electively terminated, resulting in 14 patients with postnatal outcomes data. The gestational age at MR imaging and gestational age at birth were 22.3 ± 5.7 weeks and 37.3 ± 1.1 weeks, respectively. The birth weight was 2949 ± 414 g. Six patients underwent controlled intubation as part of an EXIT procedure. Forty-seven percent required substantial ECMO support for a mean time of 313.3 ± 126.5 hours. The median LOS among survivors was 41 days. There were 3 deaths secondary to pulmonary hypoplasia and/or sepsis, yielding an overall survival rate of 78.6%.

Table 1 Relationship between prenatal variables and survival

	Survivors (n = 11)	Nonsurvivors (n = 3)
PPLV	23.2 ± 9.9*	9.9 ± 2.8
Liver herniation	6 (55%)	3 (100%)
Right-sided hernia	2 (18%)	1 (33%)
GA at diagnosis (wk)	22.6 ± 6.3	21.2 ± 2.4
GA at birth (wk)	37.4 ± 0.9	37.0 ± 1.7
Birth weight (kg)	3.03 ± 0.4	2.67 ± 0.6

GA, gestational age.
* $P < .05$ compared with nonsurvivors.

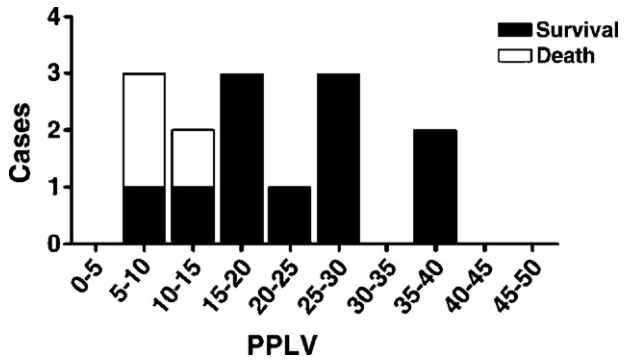

Fig. 3 Bar graph of survival in patients according to the PPLV. A PPLV of less than 15 was associated with lower survival.

Fetal lung volumes were successfully measured in all cases. The contralateral and ipsilateral lung volumes measured 6.0 ± 3.6 and 0.9 ± 1.3 mL, respectively. The ipsilateral lung was not visualized in 8 (57.1%) cases. The total thoracic volume was 39.2 ± 19.1 mL, and the mediastinal volume was 11.4 ± 9.9 mL. The calculated PPLV was 20.3±10.4.

The PPLV was significantly higher in those who did not require ECMO when compared to those who had ECMO (27.3 ± 7.6 and 11.1 ± 4.9, respectively; $P = .003$). Based on a PPLV cutoff value of 15, all patients with a low PPLV required significantly more ECMO support (5 of 5) when compared to those with a high PPLV (1 of 9; $P = .003$). The PPLV was significantly correlated with hospital LOS ($r = -0.57$, $P = .034$) (Fig. 2). Surviving infants with a PPLV of less than 15 were discharged from the hospital at median of 101.5 days of life. In contrast, patients with a PPLV of more than 15 were discharged from the hospital at a median of 37.0 days of life ($P = .036$).

Survivors had a significantly increased PPLV when compared to nonsurvivors (23.2 ± 9.9 and 9.9 ± 2.8, respectively; $P = .048$) (Table 1). No other prenatal variable was a significant predictor of survival. Fetuses with a PPLV of greater than 15 had a significantly increased survival rate (100%) when compared to survival rates in fetuses with a PPLV of less than 15 (40%, $P = .028$) (Fig. 3).

3. Discussion

Over the past 2 decades, there have been numerous attempts to use prenatal ultrasound as an imaging tool to accurately predict the degree of pulmonary hypoplasia in CDH [1,18-23]. Ultrasound markers that have been associated with a higher mortality include a diagnosis before 25 weeks gestation, an intrathoracic stomach, right-sided defect, polyhydraminos, and liver herniation [3,18].

Additionally, various sonographic biometric parameters, including the LHR, have been purported to be a useful predictor of poor outcomes [1,24]. Unfortunately, the validity of the LHR is not universally accepted, and the more recent studies have not found the LHR to be reliable for predicting lung hypoplasia [5]. Therefore, aside from the detection of additional anomalies that would otherwise portend a worse outcome, the usefulness of ultrasound as a prognostic tool in the evaluation of CDH remains controversial.

Since the inception of our fetal care program in 2000, we have measured the LHR as part of the prenatal sonographic evaluation of CDH but have not found it to be a reliable parameter. Instead, fetal MR imaging has been our preferred imaging modality for the assessment of lung hypoplasia in all CDH cases, regardless of gestational age [25]. Magnetic resonance volumetry has the ability to quantify an actual total lung volume rather than a cross-sectional area. When expressed as a PPLV, this parameter is a much more intuitive measurement that may enhance communication between clinicians of various specialties and with families. A high-quality MR study with minimal fetal motion artifact can be obtained in most patients without regard to fetal positioning. In contrast to both two-dimensional and 3-D ultrasound, MR imaging provides much better soft-tissue contrast of the fetal lung in relationship to adjacent structures [26,27]. Furthermore, MR imaging has also been shown to be more reliable than ultrasound in detecting the presence or absence of liver herniation [28]. These features, combined with newer, commercially available imaging software systems that allow one to accurately obtain lung volume measurements, give MR imaging a clear advantage over other ultrasound-based technologies in the assessment of risk in CDH.

The purpose of this prospective study was to determine whether a new method of analyzing fetal lung volumes by MR imaging could be used to predict outcomes in CDH. The PPLV proved to be a significant predictor of ECMO use. All patients with a PPLV of less than 15 required prolonged ECMO support. In contrast, only 1 patient with a PPLV of more than 15 required ECMO. Moreover, the PPLV was significantly associated with hospital LOS, with higher PPLV patients typically discharged from the hospital at 4 to 5 weeks of age if ECMO was not used. To our knowledge, this is the first study to demonstrate the association between MR-based fetal lung volumes and outcome variables related to hospital resource use. Given the relatively high survival rates for prenatally diagnosed CDH managed at our institution, these data should be helpful in providing expectant mothers with more accurate prognostic information regarding the anticipated hospital course for their baby. Whether the PPLV may also be a predictor of short-term as well as long-term pulmonary morbidity remains an avenue for further exploration.

The other major finding from this study was the significance of the PPLV in predicting survival. The association between MR-based fetal lung volumes and overall survival is in accordance with some of the more recent prospective studies from Europe [12,13]. Unfortunately, both of these studies have relied on gestational age-based normograms and, therefore, do not take into account the known variability in relative fetal somatic growth among CDH patients during the late second and entire third trimester. Therefore, the true denominator in these studies is likely to be inaccurate. Furthermore, it may be difficult for many North American pediatric surgeons to fully embrace the conclusions from these studies, given the lack of ECMO support and the much lower survival rates reported in these series. Even when the ipsilateral lung could not be visualized on MR imaging, our data suggest that the survival rate at our institution is still above 60%. In the largest European study to date, the reported survival rate in this setting was only 17.9% [12].

Based on a threshold PPLV value of 15, survival rates were markedly decreased in patients with a low PPLV, when compared to those with a high PPLV. Interestingly, no other prenatal variables, including the presence of liver herniation, proved to be a predictor of eventual outcome in our series, perhaps because most of our patients with liver herniation still survived. We have yet to quantitatively measure the volume of fetal liver within the thorax. It is conceivable that a large amount of fetal liver volume within the thoracic cavity may be an important predictor of outcome, as has been suggested in a retrospective study by Walsh et al [9]. Whether fetal liver volume is an independent predictor of outcome, regardless of the measured fetal lung volume, remains to be determined.

A single radiologist performed all MR volumetric calculations to minimize any learning curve that may be present. Nevertheless, we feel that our unique approach to measuring fetal lung volumes can be easily learned without extensive training. The total thoracic volume is not difficult to obtain, and mediastinal structures can usually be delineated from the adjacent lung parenchyma by MR imaging based on signal intensity. Indeed, preliminary studies in CDH fetuses from one group have shown that the interobserver agreement in MR total lung volume measurements is 0.95, a value that compares quite favorably to 0.82, which is the reported intraclass correlation coefficient value for the LHR [11].

In conclusion, the results from this prospective study suggest that the PPLV, as measured by MR imaging, can predict severity of disease in CDH. A value of less than 15 is associated with a need for prolonged respiratory support and/or death, despite aggressive postnatal management. A value of greater than 15 is associated with good outcomes. However, despite the encouraging data presented here, it is important to realize that this study is somewhat limited by the relatively small number of cases that have been analyzed to date. In addition, the actual PPLV that one might consider as commensurate with survival may vary, depending on the expertise of the institution managing neonates with CDH. We therefore cannot fully endorse the clinical utility

and prognostic importance of our approach at this time. Larger studies should be performed to fully validate these results and to compare MR volumetry with the LHR as a prognosticator of outcome. However, at least for now, we believe that our MR-based approach for assessing risk of pulmonary compromise in CDH has a high level of accuracy and may ultimately play a role in the identification of fetuses that would most benefit from prenatal interventions and/or planned delivery with aggressive, state-of-the-art postnatal care.

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