

A new approach to risk stratification using fetal MRI to predict outcomes in congenital diaphragmatic hernia: the preliminary retrospective single institutional study

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Background: Congenital diaphragmatic hernia (CDH) is a condition with a wide range of severity. Prenatal diagnosis is essential to optimize postnatal management, especially for severe cases. The lung to head ratio (LHR) and liver herniation estimated by prenatal ultrasound has been used as prenatal predictors in CDH. However, reliability of these factors remains to be proven and prediction of outcome from prenatal imaging is still challenging. We propose our new stratification system using lung to liver signal intensity ratio (LLSIR) in fetal MRI, which has been shown to be related to pulmonary maturation.

Methods: Retrospective chart review was conducted on 25 infants with CDH treated from 2009 through 2016 in our hospital. We stratified patients according to fetal T2-weighted MRI as Grade I, detectable ipsilateral lung at the apex; Grade II, undetectable ipsilateral lung at the apex and contralateral LLSR ≥ 2.0 ; Grade III, undetectable ipsilateral lung at the apex and contralateral LLSR < 2.0 . To evaluate this stratification system, we analyzed survival, severity [inhaled nitric oxide (iNO) usage with or without extracorporeal membrane oxygenation (ECMO)], and requirement of patch closure.

Results: All 15 patients survived in Grade I, while 2 out of 6 died in Grade II, and 3 out of 4 died in Grade III ($P=0.003$). Four were severe in Grade I, and all in Grade II and III who survived ($P=0.007$). One needed patch in Grade I, and all in Grade II and III (OR: 414,238,332; 95% CI, 0– ∞). Liver herniation was noted in five patients, and significantly associated with survival ($P=0.04$), however, neither with severity ($P=1.00$) nor with the requirement of patch closure ($P=0.52$).

Conclusions: The risk stratification algorithm using contralateral LLSIR in fetal MRI could be useful and more reliable than liver herniation to predict survival, severity, and need of patch closure. Further investigation is warranted.

Keywords: Congenital diaphragmatic hernia (CDH); fetal magnetic resonance imaging (fetal MRI); prognostic factors; patch closure

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Introduction

Congenital diaphragmatic hernia (CDH) is associated with a wide range of morbidity and mortality. Patients with mild physiologic consequences of CDH almost always survive, while those with the severest consequences have significant mortality. Pre- and post-natal management of this latter group remains challenging and sometimes controversial. In these cases, mortality rate was reported as high as 70% to 80% (1,2).

There has been significant interest in identifying prognostic factors, pre- and postnatal, which could assist in optimizing treatment algorithms. Identification of prenatal prognostic factors is considered particularly important as a potential guide for both prenatal intervention and postnatal management (1-3).

Among proposed factors, the lung to head ratio (LHR) and liver herniation estimation by prenatal sonography have both been widely evaluated. However, the significance of these findings varies between examiners and centers, and even in experienced hands appears to be highly subjective (2).

Recently, prenatal magnetic resonance imaging (MRI), which can provide more objective cross-sectional quantification, has been evaluated as a potential method for identifying prognostic factors (4-6). Although total lung volume has been demonstrated to correlate with prognosis, adjustment of these calculations by gestational age or fetal body weight is not always feasible or available. Considering the difficulty of measurement of lung volumes with MRI, a morphologic study may be preferable (7). Liver herniation into the chest and the position of the stomach have been evaluated as alternative prognostic factors (8). However, the detection of these are not always possible, and it can be difficult to assign a degree of abnormality to these observations.

Lung to liver signal intensity ratio (LLSIR) has been found to be related to lung maturity in T2-weighted MRI, and appears to be associated with prognosis in CDH patients (9,10). Therefore, we propose consideration of a novel stratification system, using LLSIR in fetal MRI, to improve the simplicity and, preferably accuracy of prediction for postnatal prognosis in patients with CDH.

Methods

Patients

With IRB approval from our hospital (R29-11), a retrospective chart review was conducted. Between

September 2009 and February 2016, 31 patients underwent prenatal evaluation for CDH, with fetal MRI performed at our institution. Among these, six patients were excluded, due to other anomalies such as severe congenital heart disease, chromosomal aberrations, or poor image quality due to motion artifact precluding analysis. In total, 25 patients met study inclusion criteria.

The stratification algorithm

Stratification was performed utilizing coronal sections of T2-weighted MRI studies obtained after 29 weeks of gestation. LLSIR was calculated by the study radiologist (Y Sugioka) as reported by Oka *et al.* (11). We placed one region of interest (ROI) within the homogenous portion of the liver and the contralateral lung on the same section. LLSIR findings were graded as follows: Grade I, ipsilateral lung at the apex was detectable; Grade II, ipsilateral lung at the apex was undetectable and LLSIR was ≥ 2.0 ; Grade III, ipsilateral lung at the apex was undetectable and LLSIR was < 2.0 (Figures 1,2). The primary outcome was death, and the secondary outcomes included gestational age, birth weight, Apgar scores at 1 and 5 minutes, severity [usage of inhaled nitric oxide (iNO) alone or with extracorporeal membrane oxygenation (ECMO) defined as severe], and need of a synthetic patch for closure. In addition, we examined the association between liver herniation and survival, severity and need of patch closure in this cohort.

Statistical analysis was performed using chi square test (categorical variables) and Kruskal-Wallis test (continuous variables) to compare the distribution of variables among three grades. Continuous values were expressed as median (range). In addition, logistic regression models were conducted to calculate odds ratios (ORs) and 95% confidence intervals (CIs) of each grade for death and patch closure. Fisher's exact test was performed to analyze the association between the presence of liver herniation and survival, severity and the requirement of patch closure. All analyses were two-tailed and were conducted using JMP[®] 13.2

Results

Among 25 patients, 15 were Grade I, 6 were Grade II, and 4 were Grade III (Table 1). Median weeks of gestation at MRI were 33 weeks (range, 27–38 weeks) in Grade I, 33.5 weeks (range, 30–37 weeks) in Grade II and 31 weeks (range, 29–33 weeks) in Grade III (P=0.19). All Grade I patients survived, whereas 2 (33.3%) died in Grade II and

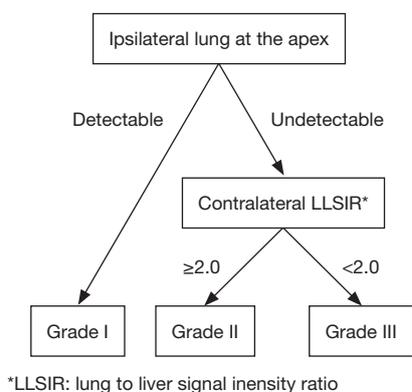


Figure 1 A new risk stratification algorithm. Grade I: ipsilateral lung at the apex is detectable; Grade II: ipsilateral lung at the apex is undetectable, and contralateral LLSIR is greater than or equal to 2.0; Grade III: ipsilateral lung at the apex is undetectable, and contralateral LLSIR is less than 2.0.

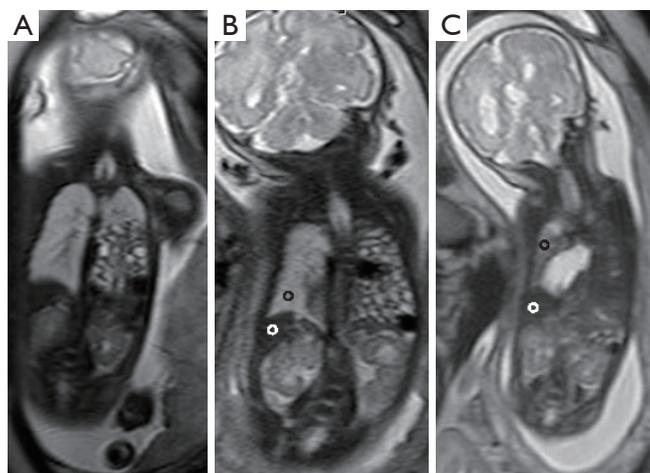


Figure 2 Fetal MRI findings. (A) Grade I; (B) Grade II; (C) Grade III. LLSIR is calculated with intensity of ROI from lung (black circles) and liver (white circles). MRI, magnetic resonance imaging; LLSIR, liver signal intensity ratio; ROI, region of interest.

3 (75.0%) died before 2 days of life in Grade III groups ($P=0.003$). Median gestational age and birth weight were 37 weeks (range, 37–39 weeks), 2,932 g (range, 2,378–3,502 g) in Grade I, 37 weeks (range, 37–38 weeks), 2,570 g (range, 2,466–3,018 g) in Grade II and 33 weeks (range, 32–37 weeks), 2,129 g (range, 1,652–2,510 g) in Grade III ($P=0.01, 0.007$, respectively). Median Apgar scores at 1 and 5 minutes were 3 (range, 2–8), 6 (range, 3–9) in Grade I, 2 (range, 1–3), 4.5 (range, 4–5) in Grade II, and 3 (range, 1–3),

3.5 (range, 1–4) in Grade III ($P=0.09, 0.03$, respectively). iNO was used for 4 (26.7%) patients in Grade I, all patients in Grade II and 1 in Grade III ($P=0.007$). ECMO was used in three patients in Grade II, 2 of whom survived and 1 who died. A synthetic patch closure was required for 1 (6.7%) patient in Grade I, for all 4 (100.0%) patients who survived in Grade II, and for 1 (100.0%) patient who survived in Grade III ($P<0.001$).

Compared to the Grade I and II patients, those in the Grade III group displayed significantly higher mortality (OR: 28.5; 95% CI, 1.9–420.5). Patients in Grade II and III (ipsilateral lung at the apex was undetectable) were more likely to require patch closure as compared to Grade I (OR: 414,238,332; 95% CI, 0– ∞) (Table 2).

Liver herniation was noted in five patients in this cohort. Although survival was significantly different between the presence (liver up) and absence (liver down) of liver herniation in fetal MRI ($P=0.04$), there was no significant difference between liver herniation and either severity ($P=1.00$) nor the need of patch closure ($P=0.52$) (Table 3)

Discussion

Our proposed stratification algorithm is based on the lung volume and maturity, as characterized by fetal MRI. Total lung volume has been previously demonstrated to contribute significant prognostic information (12,13). Recently, observed to expected (o/e) total lung volume in fetal MRI has been considered a factor which predicts postnatal survival (14). However, the measurement of total lung volume and correction with gestational age may not always be feasible or available. We found that patients with higher Grades tended to lower gestational age, birth weight, and Apgar score at 5 minutes. Ipsilateral lung detected at the apex (Grade I) resulted in sufficient total lung volume for not only survival, but also appears to predict relatively mild persistent pulmonary hypertension. In our series, ipsilateral lung was less definitively detected at mediastinum in one patient in Grade II (data not shown), which was thought to be more compressed than at the apex.

Although the prognostic factors in CDH were generally related to the hypoplastic lung and LLSIR has been shown to correlate with lung maturity (15,16), LLSIR was also shown to be the potential prognostic factor for CDH. We hypothesized that when ipsilateral lung was not detected at the apex, contralateral lung maturity provided important prognostic information. We selected LLSIR values greater than 2.0 as indicative of maturity (11) in this study, and

Table 1 Outcomes according to the grade system

Variables	Grade I (n=15)	Grade II (n=6)	Grade III (n=4)	P value
Gestation at fetal MRI, median [range] (weeks)	33 [27–38]	33.5 [30–37]	31 [29–33]	0.19
Right CDH, n (%)	0 (0)	1 (16.7)	0 (0)	–
Liver up, n (%)	2 (13.3)	1 (16.7)	2 (50.0)	–
Gestational age, median [range] (weeks)	37 [37–39]	37 [37–38]	33 [32–37]	0.01
Birth weight, median [range] (g)	2,932 [2,378–3,502]	2,570 [2,466–3,018]	2,129 [1,652–2,510]	0.007
Apgar score at 1 min, median [range]	3 [2–8]	2 [1–3]	3 [1–3]	0.09
Apgar score at 5 min, median [range]	6 [3–9]	4.5 [4–5]	3.5 [1–4]	0.03
Death, n (%)	0 (0)	2 (33.3)	3 (75.0)	0.003
Alive, n (%)	15 (100.0)	4 (66.7)	1 (25.0)	–
Severe ^a , n (%)	4 (26.7)	4 (100.0)	1 (100.0)	0.007
ECMO, n (%)	0 (0)	2 ^b (40.0)	0 (0)	–
Patch closure, n (%)	1 (6.7)	4 (100.0)	1 (100.0)	<0.001

^a, severe: requirement of iNO with or without ECMO; ^b, ECMO was used in 3 (60%) patients in Grade II, and 1 died. CDH, congenital diaphragmatic hernia; MRI, magnetic resonance imaging; ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide.

Table 2 Logistic regression for survival and requirement of patch closure

Grade	Death		Patch closure	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Grade I	0 (0)	1.0 (ref.)	1 (6.7)	1.0 (ref.)
Grade II	2 (33.3)	1.0 (ref.)	4 (100.0)	414,238,332 (0–∞)
Grade III	3 (75.0)	28.5 (1.9–420.5)	1 (100.0)	414,238,332 (0–∞)

Comparison between Grade I and II vs. Grade III for death, Grade I vs. Grade II and III for patch closure. OR, odds ratio.

Table 3 Outcomes according to presence of liver up

Outcomes	Liver down	Liver up	P value
Survival			0.04
Alive	18	2	
Dead	2	3	
Severity			1.00
Moderate ^a	8	3	
Severe ^b	7	2	
Closure			0.52
Direct closure	13	1	
Patch closure	5	1	

^a, moderate: no need of iNO; ^b, severe: requirement of iNO with or without ECMO. iNO, inhaled nitric oxide; ECMO, extracorporeal membrane oxygenation.

validated this as predictive of outcome, suggesting that this value reflects contralateral lung maturation. When values were less than 2.0, contralateral lung maturation was insufficient to support survival (Grade III), whereas contralateral lung maturation was more likely to allow survival (Grade II), although with a requirement for intensive management using iNO or ECMO.

Furthermore, it was revealed that all cases graded I and II with undetectable ipsilateral lung at the apex required a synthetic patch for closure. To our knowledge, there has been no previous identification of anatomic features on prenatal imaging which have been reported to be associated with patch closure in the English literature.

o/e-LHR and liver herniation estimated by prenatal ultrasound sonography have been widely accepted as prognostic factors for survival of patients with CDH. As o/e LHR measured by ultrasonography was highly subjective

and competency and reliability were achieved only by experienced operators (17), the data were available in only ten cases of this cohort. Although, some reports showed o/e-LHR was correlated with not only survival but also disease severity (18,19). o/e-LHR was deemed not to be a good predictor for ECMO utilization and other factors related to severity (14,20,21). In our series, o/e-LHR in two patients with severe CDH who required ECMO were both more than 50% (data not shown).

Whether liver herniation is a prognostic factor for survival and severity is also controversial. Ruano *et al.* reported that liver herniation was not correlated to the mortality or the need for ECMO (22). Although a meta-analysis revealed that liver herniation was associated with poorer prognosis, the definition of liver herniation varied (23), which is difficult to use in clinical practice. In our series, although liver herniation regardless of proportion was significantly associated with mortality, there were no significant differences between liver herniation and either severity nor need of patch closure. This data could provide information optimizing operative planning for such infants.

The most advantageous feature in this stratification system compared to other prenatal prognostic factors is that image-defined stratification with the calculation of LLSIR is relatively easy on MRI images without any specific techniques nor the need of experienced examiners.

There are several limitations in our study. First, this was a retrospective single institution study, with small number of patients. Second, LLSIR was calculated by a single radiologist who was blinded to clinical outcomes, limiting the ability to demonstrate reproducibility of this metric. Third, we used MRI studies obtained after 29 weeks of gestation. However, it is possible that LLSIR changes dynamically during fetal development as lung maturity progresses, and thus the optimal timing of MRI for the grading system needs to be clarified.

Conclusions

Despite the above limitations, our pilot data suggests that this image-based stratification system, based on anatomic features and tissue characteristics detected by MRI, may provide additional useful information for patients with CDH. We propose that further investigation with a prospective multi-institutional study is warranted to validate this stratification system. The use of LLSIR in fetal MRI may add prognostic information regarding postnatal

survival, disease severity, and the requirement for patch closure in CDH.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the institutional review board (IRB) of our hospital (R29-11).

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