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Prediction of functional pulmonary hypoplasia using MRI

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17 Abstract

18 Objective: The purpose of this study was to retrospectively examine the use
19 of lung-to-liver signal intensity ratio (LLSIR) on T2-weighted images to
20 predict functional pulmonary hypoplasia.

21 Method: The subjects of this study were pregnant women who underwent
22 magnetic resonance imaging (MRI).

23 Cases that required nitric oxide inhalation and those who died from
24 respiratory disorder were classified as functional pulmonary hypoplasia
25 (FPH). All other cases were presented as control group. We retrospectively
26 analyzed MRI and perinatal data. LLSIR was defined as the ratio of lung
27 signal intensity to liver signal intensity. We examined the relationship
28 between LLSIR and gestational age, compared the LLSIRs in the two groups,
29 and calculated the best cut-off value of the LLSIR to predict functional
30 pulmonary hypoplasia.

31 Results:

32 One hundred and ninety-one were eligible for this study and 12 cases were

classified as FPH. In the control group, LLSIR increased with age ($r = 0.383$, $p < 0.001$). We used the observed/expected LLSIR (o/e LLSIR), which was ratio of obtained LLSIR to expected LLSIR calculated by the regression line to correct the effect of gestational age. In the FHP group, o/e LLSIR was significantly lower than that in the control group ($p < 0.001$). A ROC curve analysis showed that cases with o/e LLSIR above 0.85 were less likely to cause functional pulmonary hypoplasia.

Conclusions: Low o/e LLSIR might reflect the histological characteristics of hypoplastic lung structures. O/e LLSIR promises to be a useful MRI parameter for screening functional pulmonary hypoplasia.

Key words: pregnancy, pulmonary hypoplasia, respiratory disorder, prenatal diagnosis, fetal MRI

Introduction

Respiratory disorder is a major cause of neonatal morbidity and mortality. The lung is one of the most essential organs surviving in the extra-uterine environment because of the dynamic changes it undergoes after childbirth. If respiratory disorders exist, the neonate would require intensive care immediately after birth. Therefore, it is important to predict neonatal pulmonary function in the prenatal period. Lung hypoplasia in the fetal life is an indispensable information to relay to parents in counselling sessions.

Fetal lung evaluation using two-dimensional ultrasound sonography has been practiced for many years. Lung-to-thorax transverse ratio (LTR) and observed/expected lung area to head circumference ratio (o/e LHR) evaluating fetal lung square measure are frequently used.[1,2] Magnetic resonance imaging (MRI) is not associated with any known adverse fetal effects during pregnancy, and is considered a non-invasive tool to provide additional information to that obtained in ultrasound examinations.[3] Previous studies have reported on the use of MRI to evaluate fetal lung volume in suspected

65 cases of pulmonary hypoplasia such as congenital diaphragmatic hernia
66 (CDH) .[4,5] However, these evaluations considered only the lung volume.
67 In previous studies, lung-to-liver signal intensity ratio (LLSIR) using
68 MRI on T2-weighted images was reported to predict normal lung
69 development.[6, 7] Lung signal intensity positively correlates with gestational
70 age reflecting the maturity of the pulmonary function in normal fetuses. Low
71 lung signal intensity is considered to reflect a low volume of lung fluid which
72 is associated with pulmonary hypoplasia.[6, 8, 9]. Although LLSIR positively
73 correlated with gestational age, normalization according to gestational age
74 was not performed in these studies. [6, 8, 9]
75 In this present study, we constructed the reference range of LLSIR
76 for normal fetuses and retrospectively assessed the use of LLSIR to predict
77 functional pulmonary hypoplasia with respect to gestational age.
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79
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Material and methods

The subjects of this study were pregnant women who underwent MRI examination in Toho university medical center Omori hospital, Tokyo, from April 2011 to December 2019. We retrospectively analyzed MRI data and examined the association of the data and fetal prognosis. This study was approved by the ethical committee of our institution (ID number M16248 and 19246), and the informed consent was disclosed on our institutional website. This study was registered with the Japanese Clinical Trial Registry "UMIN-CTR" (http://www.umin.ac.jp/ctr/index-j.htm) and given trial ID numbers UMIN000026945 and UMIN000040663.

The exclusion criteria included preterm birth cases before 28 gestational weeks, cases involving MRI before 25 gestational weeks, cases that could not be detected by MRI, cases with central nervous system and/or abdominal wall abnormalities that could cause respiratory disorders, cases that have undergone fetal therapy owing to pleural effusion, cases with liver abnormalities that could affect liver signal intensity, cases that resulted in

97 intrauterine fetal death, cases with chromosomal abnormalities, and women
98 whose perinatal data were not accessed.

99 Gestational age was calculated from the last menstrual period and
100 confirmed by crown rump length using ultrasonography at 7-11 weeks of
101 gestation.

102 Functional pulmonary hypoplasia (FPH) was defined as cases that
103 required nitric oxide inhalation and those who died from respiratory disorder.
104 Other cases were defined as control group.

105 MRI was performed in all cases by using a 1.5T imager (Siemens)
106 with a phased-array surface coil. Half-Fourier single-shot turbo spin-echo
107 sequences (repetition time (TR) 1000 ms, echo time (TE) 85 ms, field of view
108 (FOV) 256 mm, slice thickness 6 mm, matrix 256 × 230, and flip angle 150°)
109 were performed. No sedation agent was administered to prevent fetal
110 movement during MRI.

111 In previous studies and this study, the liver was used as the reference
112 structure because it is homogeneous during gestation, sufficiently sized, and

close to the lung. We calculated both the lung and liver signal intensities using region of interest (ROI) analysis. LLSIR was defined as the ratio of lung signal intensity to liver signal intensity. All ROIs were over 100 mm^2 and placed in homogeneous areas to avoid being affected by other structures such as the vascular system and bronchus, and kept away from the heart to avoid heart movement (Figure 1).

We calculated the average of the LLSIRs that were computed twice in each case to correct measurement errors. All LLSIR calculations were performed by one author (J.S). Further examination was performed in cases where the subjects underwent MRI twice or more.

Statistical analysis

Mann-Whitney U test was performed to compare independent data between the two groups. The receiver operating characteristic (ROC) curve analysis was performed to assess the cut-off value of o/e LLSIR to detect functional pulmonary hypoplasia. To validate the ROC analysis, the area under the curve (AUC) was also assessed. Using the threshold values, sensitivity, specificity, positive predictive value, and negative predictive values were calculated. Two-sided p values < 0.05 were considered statistically significant in all tests. All statistical analyses were performed using SPSS software version 20.0 (IBM Corp., Armonk, NY, USA).

Result

In the study period, 273 pregnant women were examined using MRI. One hundred and ninety-one were eligible for this study according to our exclusion criteria. Twelve cases (6.3%) were classified as the FPH group.

The gestational age at MRI examination were 25.3th to 39.3th (median: 33.3th and average: 32.7th) in the control group, and 27.1th to 37.1th (median: 31.8th and average: 32.3th) in the FPH group. There was no significant difference between the control and FPH group in terms of maternal age, gestational age at MRI, gestational age at birth, and birth weight (Table 1). LLSIR ranged from 1.25 to 4.83 (median: 2.50 and average: 2.55) in all cases, 1.57 to 4.83 (median: 2.50 and average: 2.59) in the control group, and 1.25 to 2.84 (median: 1.80 and average: 1.85) in the FPH. In the FHP group, LLSIR was significantly lower than that in the control ($p < 0.001$).

The main indications for MRI of these 191 cases were as follows: malposition of the placenta (n = 77), fetal anomalies (n = 37), pregnancy-complicated uterine fibroma (n = 35), and twin-to-twin transfusion syndrome

(TTTS) (n = 25) (Table 2).

In the control group, the LLSIR positively correlated with gestational age by the regression line ($Y = 0.128 + 0.0.075X$ ($r = 0.383$, $p < 0.001$, Y is LLSIR, and X is gestational age.)) (Figure 2). To correct the effect of gestational age, observed/expected LLSIR (o/e LLSIR) was adopted, which was a ratio of obtained LLSIR to expected LLSIR that was calculated by the regression line. o/e LLSIR was 0.42 to 1.68 (median: 1.00 and average: 0.99) in all cases, 0.55 to 1.68 (median: 1.00 and average: 1.00) in the control group, and 0.43 to 1.28 (median: 0.70 and average: 0.74) in the FPH. In the FHP group, o/e LLSIR was significantly lower than that in the control ($p = 0.001$). (Figure 3).

The ROC curve analysis is shown in Figure 4. The area under curve was 0.86. Using this ROC curve analysis, the optimal cut-off value for o/e LLSIR was 0.85 (sensitivity of 83.3%, specificity of 78.2%, positive predictive value of 20.4%, and negative predictive value of 98.6%). The high negative predictive value indicated that o/e LLSIR was excellent for examining

functional pulmonary hypoplasia.

In 12 FPH cases, 10 required nitric oxide inhalation, and two died from respiratory disorder. Indications for MRI were CDH (n = 3), Potter syndrome (n = 2), selective intrauterine growth restriction (n = 2), TTTS (n = 1), posterior urethral valve (n = 1), autosomal recessive polycystic kidney disease (n = 1), multicystic dysplastic kidney (n = 1), and thanatophoric dysplasia (n = 1). Of the FPH group, 58% related to oligohydramnios (Table 3).

Discussion

In this study, o/e LLSIR was proven to predict FPH. Using the cut-off value of 0.85 for o/e LLSIR, the negative predictive value was 98.6%. This indicates that o/e LLSIR is a useful MRI parameter for the screening of functional pulmonary hypoplasia.

In this study and previous ones, LLSIR in the control group positively correlated with gestational age.[6, 8-12]. This result may indicate that LLSIR reflects normal fetal lung maturation. On the T2-weighted images, higher intensities were indicative of more tissue fluid. In the late canalicular stage, the epithelial cells of the fetal lungs started producing lung fluid. As the number of epithelial cells increased, the volume of fetal lung fluid increased. Consequently, airways and alveoli spaces were filled with adequate fluid at the neonatal period.[13] The normal fetal lung exhibited high signal intensity on the T2-weighted images which suggested adequate lung fluid in the airways and alveoli.

In early gestation, the fetal lung showed low signal intensity, which

209 indicated less lung fluid because it was premature; however, it increased
210 throughout gestation. Therefore, we adopted o/e LLSIR. Previously, Oka *et al.*
211 *had* reported a positive correlation of LLSIR with gestational age, but did not
212 correct the values with gestational age[8]. Another study by Yamato *et al* also
213 reported a positive correlation with gestational age in normal cases, but not
214 in CDH. These two studies ignored the gestational change[9,] and adopting o/e
215 LLSIR in our study was meaningful.

216 O/e LLSIR was a useful parameter to predict FPH during the
217 prenatal period. Previous studies reported that the absolute value of LLSIR
218 was lower in the FPH group compared to that in the normal fetus.[8, 10, 12, 14, 15]
219 As described above, high intensity may indicate increased fluid levels in the
220 airways and alveoli with normal lung maturation. Meanwhile, in FPH cases,
221 low intensity on the fetal lung reflecting low lung fluid may suggest
222 pulmonary immaturity. Using the cut-off value of 0.85 for o/e LLSIR which
223 was calculated by the ROC analysis, the negative predictive value was 98.6%.
224 This indicates that o/e LLSIR is a useful MRI parameter for the screening of

functional pulmonary hypoplasia because of its high negative predictive value.

In this study, 53.3% cases in the FPH group related to oligohydramnios. The previous studies mainly focused on pulmonary hypoplasia in cases with congenital diaphragmatic hernia[8, 9, 12, 14]. Pulmonary hypoplasia can be classified into two groups in terms of its etiology. The first is pulmonary hypoplasia caused by mechanical pressure to lungs which may result from CDH, congenital pulmonary airway malformation (CPAM), and skeletal dysplasia syndrome. In these conditions pulmonary hypoplasia is mainly due to the maldevelopment of lung tissues. The second results from oligohydramnios. Inadequate fluid exchange between the alveoli space and amnion cavity due to oligohydramnios leads to a defect of the epithelial cells of the lung resulting in functional hypoplasia. [16,17] Moessinger *et al.* reported that drainage of lung fluid in sheep led to pulmonary hypoplasia.[18] Oligohydramnios was also reported to compromise lung cells and airway space sizes, and interfere with epithelial development in mice.[19] Physical forces are required for regulating fetal lung growth and maturation. [20] The

241 fetus exhibits breathing movements and this is considered normal in human
242 fetal growth and development..[21] Distended pressure formed by lung fluid
243 within the airways is a primary physical force that stimulates lung
244 development.[22] Various degrees of lung stretches promoted the functional
245 maturation of the pulmonary alveolar epithelial cells which produced
246 surfactants, in a study involving rats.[23] In long term oligohydramnios cases,
247 the combined effects of less fetal lung fluid and fetal breathing movement
248 inhibition caused by mechanical pressure to thorax may lead to hypoplasitic
249 lungs. In this study, pulmonary hypoplasia caused by oligohydramnios and
250 CDH showed lower o/e LLSIRs. This result indicated that o/e LLSIR is a
251 useful predictor for pulmonary hypoplasia regardless of etiology.

252 Pulmonary hypoplasia may lead to severe neonatal conditions.
253 Prenatal examination to predict pulmonary function is important for
254 perinatal care because intensive care is required immediately after birth.
255 Many biometric parameters have been used to assess the risks of pulmonary
256 hypoplasia. LTR and o/e LHR by 2D-ultrasound have been performed widely

257 because of their simplicity.[1,2] Fetal lung volume examination using 3D-
258 ultrasound is as effective as total fetal lung volume examination using MRI
259 in assessing the severity of pulmonary hypoplasia for CDH cases;[4,5,24]
260 however assessment is done based on the volume of fetal lungs only. LLSIR
261 assesses pulmonary function by the amount of lung fluid which may reflect
262 histological lung maturation. LLSIR could be the alternative to assess
263 pulmonary function that is not related to lung volume.

264 In contrast to computed tomography in which tissue density can be
265 expressed as an absolute value, signal intensity assessments on MRI require
266 a reference structure for standardization. Balassy *et al.* reported that the
267 liver is a more accurate reference structure compared to gastric fluid because
268 of its sufficient size, when assessing fetal lung maturation.[7] In most previous
269 studies, liver is used as the reference structure because it is homogenous
270 during gestation, sufficiently-sized, and close to lung. [6,8-16]

271 In this study, the intervals between MRI and delivery were not
272 unified. As described above, the fetal lung starts to produce lung fluid, but

there could be a time lag between the gestational age when fetal lung starts to produce lung fluid, and become filled with enough fluid to be detected by LLSIR. Further studies with unified protocols that determine when MRI should be performed are needed. In this study, lung volume examinations were not performed because of the heterogonous indications of MRI. A future study may discuss a combined LLSIR and lung volume examination for more accurate evaluation methods of pulmonary hypoplasia.

In conclusion, we remark that low o/e LLSIR might reflect the histological characteristics of hypoplastic lung structures; furthermore, o/e LLSIR promises to be a useful MRI parameter for the screening of functional pulmonary hypoplasia.

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Disclosure: No authors have any conflict of interest to report.

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Appendices

None.

Figure legends

Figure 1) We calculated both the lung and liver signal intensities using region of interest (ROI) analysis. LLSIR was defined as the ratio of lung signal intensity to liver signal intensity.

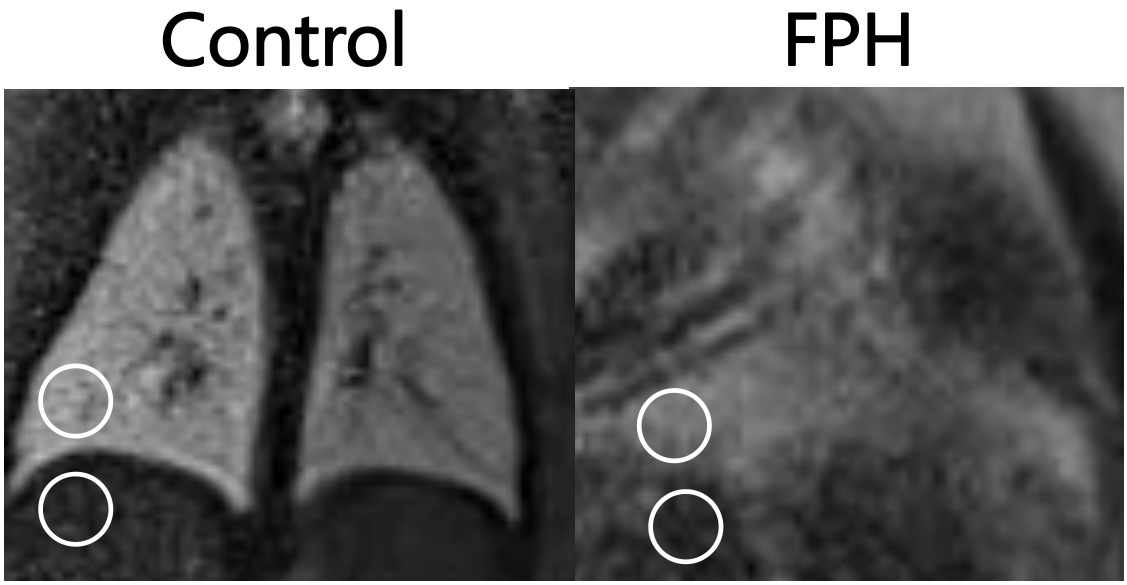
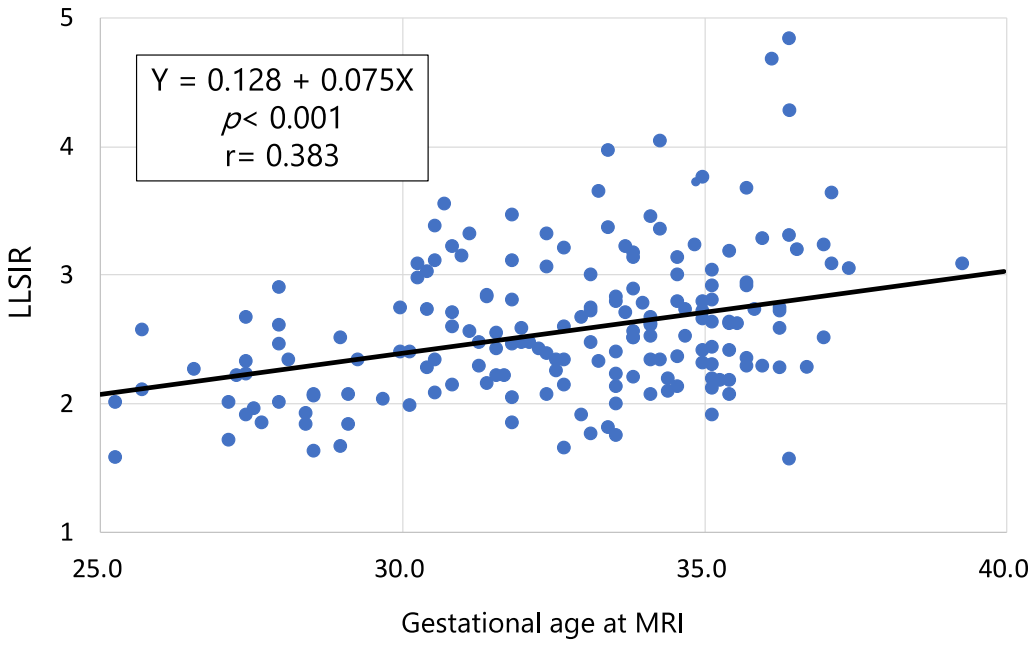


Figure 2) Relation between LLSIR and gestational age at MRI in control group.

LLSIR increased with correlation with gestational age by the regression line Y=0.128 + 0.075X (r=0.383, p<0.001, Y is LLSIR and X is gestational age.)



435 Figure 3) Comparisons of LLSIR between FPH group and control group.

436 In the FHP group, o/e LLSIR was significantly lower than that in the control

437 ($p = 0.001$).

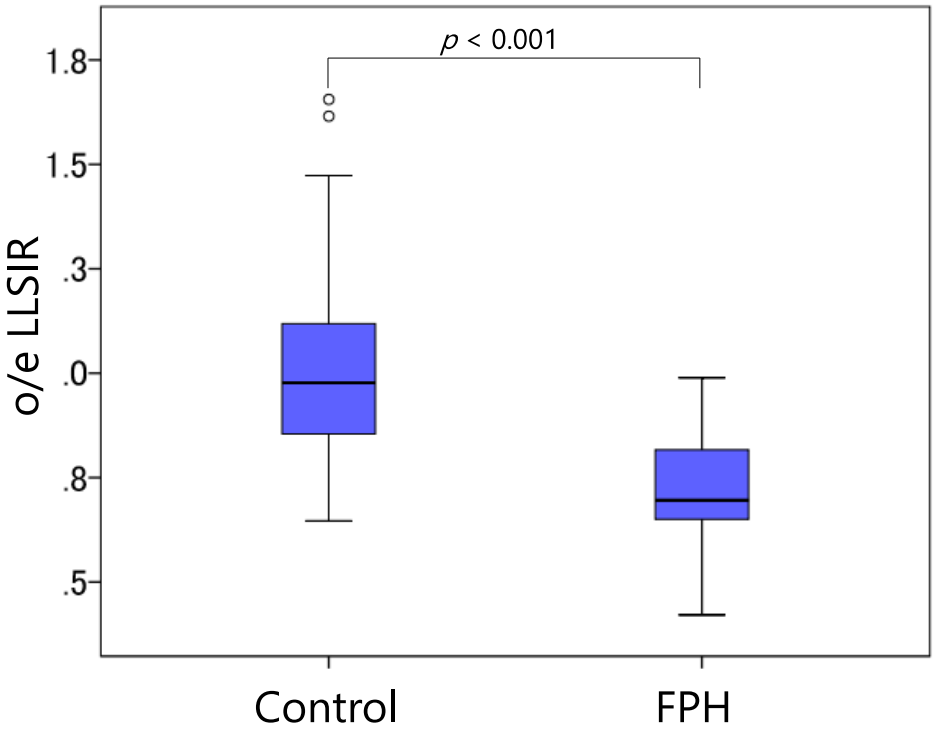


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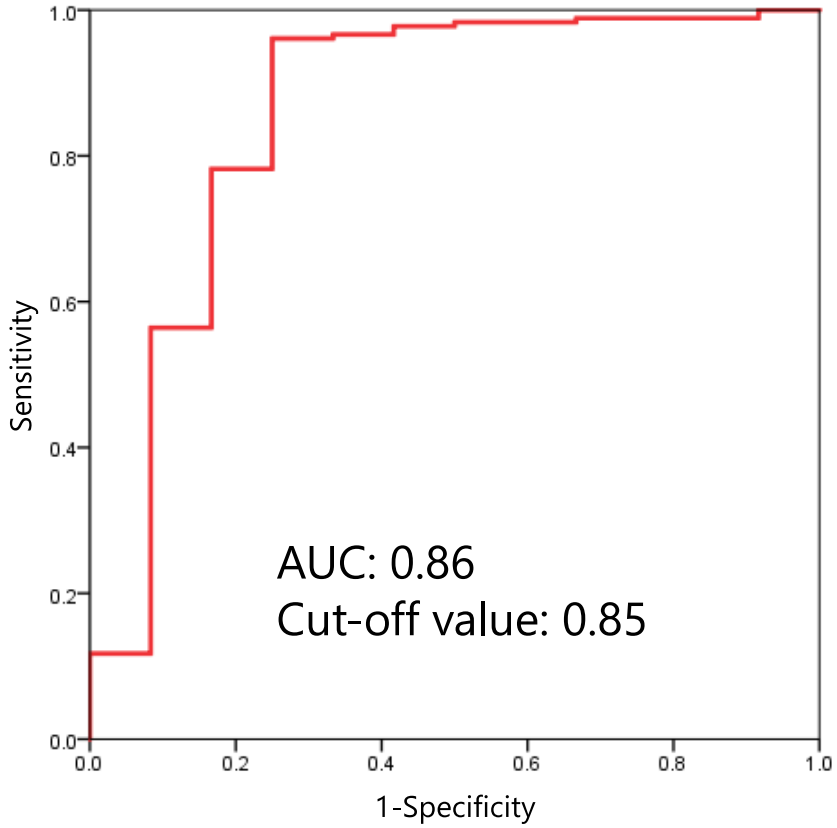
Figure 4) ROC curve analysis for o/e LLSIR to predict FPH

The area under curve was 0.86. Using this ROC curve analysis, the optimal cut-off value for o/e LLSIR was 0.85. The high negative predictive value indicated that o/e LLSIR was excellent for examining functional pulmonary hypoplasia.



453 Table 1) Comparisons of perinatal data between FPH group and control group.

	Control (n=179)	FHP (n=12)	*p* value
Maternal age	35.0 (24-45)	34.5 (30-41)	0.420
GA at MRI	33.3 (25.3-39.3)	31.8 (27.1-37.1)	0.752
GA at delivery	37.4 (28.1-41.4)	37.6 (29.7-40.7)	0.793
Birth weight	2702 (581-4048)	2483 (339-3299)	0.078

454 FPH: functional pulmonary hypoplasia, GA: gestational age, MRI: magnetic

455 resonance imaging.

456 There was no significant difference between these groups in terms of their

457 background.

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467 Table 2) Indications for MRI.

Indications for MRI	Numbers of cases
Malposition of the placenta	77
Fetal anomaly	37
pregnancy-complicated uterine fibroma	35
TTTS	25
Other maternal complications	9
MCDA twin with other complications	8

468 MRI: magnetic resonance imaging, TTTS: twin-to-twin transfusion syndrome,

469 MCDA twin: monochorionic diamniotic twin.

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480 Table 3) Details of 12 FPH cases.

481 Of the FPH group, 58% related to oligohydramnios.

482

Indications for MRI	GA at MRI	GA at delivery	LLSIR	o/e LLSIR	Outcome	Oligohydramnios
TTTS	27.4	29.7	1.6	0.721	NO inhalation	+
ARPKD	37.0	37.4	1.2	0.428	NO inhalation	+
CDH	36.4	37.6	1.9	0.667	death	-
Thacatophoric dysplasia	37.1	37.6	1.9	0.654	NO inhalation	-
CDH	32.3	38.1	1.7	0.681	NO inhalation	-
Potter syndrome	27.1	40.7	1.8	0.850	death	+
Posterior urethral valve	31.3	36.4	1.7	0.700	NO inhalation	+
TTTS	30.0	31.0	2.3	0.953	NO inhalation	+
Potter syndrome	33.9	37.6	1.7	0.648	NO inhalation	+
sIUGR	28.0	31.7	2.8	1.281	NO inhalation	-
MCDK	30.4	37.7	1.6	0.652	NO inhalation	+
CDH	36.4	38.0	1.9	0.660	NO inhalation	-

483 TTTS: twin-to-twin transfusion syndrome, ARPKD: autosomal recessive
484 polycystic kidney disease, CDH: Congenital diaphragmatic hernia, sIUGR:
485 selective intrauterine growth restriction, MCDK: multicystic dysplastic
486 kidney.