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Research Article

The Role of the Fetal MRI to Predict the Postnatal Survival in Fetuses with Congenital Diaphragmatic Hernia

Konjenital Diyafragma Hernili Fetüslerde Doğum Sonrası Sağkalımı Tahmin Etmede Fetal MRG'nin Rolü

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ABSTRACT

Objective: *To assess the role of the magnetic resonance imaging (MRI) to predict the postnatal survival in patients with congenital diaphragmatic hernia (CDH).*
Method: *25 patients with CDH who had fetal MRI between 2015 and 2020 were enrolled in this retrospective study. Patients were divided into two groups according to the postnatal survival at 30 days of age: alive and dead. The fetal MRI images were assessed to calculate the lung-to-liver signal intensity ratio (LLSIR), and the total lung volume (TLV). In addition, the site of the defect (right or left), accompanying liver herniation (present or absent), detectable-ipsilateral lung parenchyma at the apex (present or absent) were also recorded. MRI images were evaluated by two pediatric radiologists. A p value lesser than 0.05 was considered statistically significant.*
Results: *Among 25 fetuses, 6 were alive and 19 were dead within 30 days after birth. The detectable lung parenchyma had a relationship with the alive group (p = 0.023). Observed-to-expected TLV (p = 0.001) and LLSIR (p = 0.023) were significantly lower in the dead group. Using the cutoff values for the observed-to-expected TLV as 0.27 (a sensitivity of 84%, a specificity of 84%) and for the LLSIR as 2.02 (a sensitivity of 89%, a specificity of 67%) were found as predictors for death.*
Conclusion: *The postnatal survival in CDH may be predicted using the observed-to-expected TLV and LLSIR on the fetal MRI. The presence of the detectable-ipsilateral lung parenchyma at the apex may also be associated with the postnatal survival.*

Keywords: *congenital diaphragmatic hernia, fetal, magnetic resonance imaging, prognosis, total lung volume*

ÖZ

Amaç: *Çalışmamızın amacı konjenital diyafragma hernisi (KDH) olan hastalarda fetal manyetik rezonans görüntüleme (MRG)'nin doğum sonrası sağ kalımı öngörmedeki rolünü değerlendirmektir.*
Yöntem: *Çalışmaya 2015 ile 2020 yılları arasında KDH ön tanısıyla fetal MRG ile değerlendirilmiş olan 25 KDH hastası dahil edildi. Hastalar postnatal 30 günlük dönemde sağkalıma göre yaşayan ve yaşamayan olmak üzere iki gruba ayrıldı. Fetal MRG görüntüleri, akciğer-karaciğer sinyal yoğunluğu oranını ve total akciğer volümünü (TAV) hesaplamak için geriye dönük olarak değerlendirildi. Ek olarak, herni tarafı (sağ veya sol), eşlik eden karaciğer herniasyonu (var veya yok), herni tarafı ile ipsilateral apekste tespit edilebilir akciğer parankimi (var veya yok) kaydedildi. MRG görüntüleri iki pediatrik radyolog tarafından değerlendirildi. Prognozu tahmin etmek için duyarlılık-özgüllük analizleri kullanıldı. P değerinin <0.05 olması istatistiksel olarak anlamlı kabul edildi.*
Bulgular: *Postnatal 30 günlük dönemde 25 fetüsten 6'sı yaşayan ve 19'u ise yaşamayan gruptaydı. Herni tarafı ile ipsilateral apekste tespit edilebilir akciğer parankimi varlığı ile hastaların sağ kalımı arasında anlamlı ilişki saptandı (p=0.023). Yaşamayan grupta Gözlenen/beklenen TAV (p=0.001) ve akciğer-karaciğer sinyal yoğunluğu oranı (p=0.023) anlamlı olarak daha düşüktü. Gözlenen/beklenen TAV'nin <0.27 olması % 84 duyarlılık, % 84 özgüllük ve AKSO değerinin <2.02 olması % 89 duyarlılık, % 67 özgüllük postnatal ölümü öngörücü olarak bulundu.*
Sonuç: *Sonuçlarımıza göre KDH'de postnatal sağkalım, fetal MRG'de gözlenen/beklenen TAV ve akciğer-karaciğer sinyal yoğunluğu oranı kullanılarak tahmin edilebilir. İpsilateral apekste tespit edilebilir akciğer parankiminin varlığı doğum sonrası hayatta kalma ile ilişkilendirilebilir.*

Anahtar kelimeler: *konjenital diyafragma hernisi, fetal, manyetik rezonans görüntüleme, prognoz, total akciğer hacmi*

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INTRODUCTION

Congenital diaphragmatic hernia (CDH), which has a frequency of almost 1 in 2500 live births, is a severe anomaly that has the potential for mortality and morbidity [1,2]. Abdominal organs displace to the thoracic cavity by a defect in the diaphragm. Many important lung diseases like abnormal lung development, pulmonary hypoplasia, and pulmonary hypertension may occur due to the compression of the lungs [3-5]. The significative factors for the mortality in CDH are noted as the grade of pulmonary hypoplasia and the presence of incurable pulmonary hypertension [6].

Imaging has an essential role to evaluate the lung antenatally to estimate the prognosis and to decide the follow-up strategy. Although ultrasound plays an important role in the diagnosis of the CDH, it may give limited information due to many maternal, fetal, and technical factors. However, magnetic resonance imaging (MRI) provides more accurate and detailed information about fetal anatomy, as it is known. MRI has been considered as a potential method for identifying prognostic factors associated with the degree of pulmonary hypoplasia [2,7]. Many centers have adopted using the fetal total lung volume (TLV) which is calculated on MRI to determine the degree of pulmonary hypoplasia in CDH [9-12]. Besides, the lung-to-liver signal intensity ratio (LLSIR) [13], lung-to-spinal fluid signal intensity ratio [14], and liver position on MRI were also investigated to estimate the fetal prognosis in CDH.

The aim of this study was to assess the role of the fetal MRI to predict the prognosis in patients with CDH. For this purpose, the diagnostic performances of the LLSIR and TLV, as well as the qualitative MRI features were taken into consideration.

MATERIALS and METHODS

Patient selection

This study was approved by our institutional review board. Our radiology and obstetrics and gynecology archives were retrospectively reviewed to determine the fetuses who had been diagnosed with CDH by antenatal ultrasound and evaluated by fetal MRI between January 2015-December 2020. Two patients with motion artifacts on T2-weighted Half Fourier single-shot turbo spin-echo (HASTE) sequences were excluded. After the exclusion, 25 patients with CDH were enrolled in this study. Patients were divided into two groups according to the postnatal survival at 30 days of age: alive and dead. The alive group was defined for patients who lived after postnatal 30 days and the dead group was defined for patients who were not survived. The same management strategy was performed for all neonates after birth. Neonates were transferred to our neonatal intensive care unit after intubated nasally in the delivery room. Treatment strategies were performed according to the respiratory and hemodynamic issues. Surgical repair was performed on patients whose respiratory and hemodynamic conditions were stable.

MRI protocols

All examinations were performed on a 1.5-T MRI scanner (Siemens Aera, Germany). No maternal sedation was administered. Mothers were placed in the supine position. A torso phased array coil was wrapped around the mother's pelvis, centered at the area of the fetus. The MRI protocol included T2-weighted HASTE sequences in three orthogonal planes of the head and the body. For more details, true fast imaging with steady-state free precession, dixon T1-weighted and echoplanar sequences were also added in some of the patients. HASTE sequences of the fetal body were provided with no overlap or gap. HASTE sequence was acquired with the following parameters: HASTE sequence was acquired with the following parameters: time to repetition/time to echo, 1100/122 ms; slice thickness, 4-5 mm; field of view (FOV), 300-400 mm; matrix, 256×256; flip angle, 180; number of excitations, 1.

MRI interpretation

MRI images were evaluated by two pediatric radiologists in consensus. The site of the defect (right or left), accompanying liver herniation (present or absent), detectable-ipsilateral lung parenchyma at the apex (present or absent) were recorded (Figure 1). The LLSIR was calculated on T2-weighted HASTE

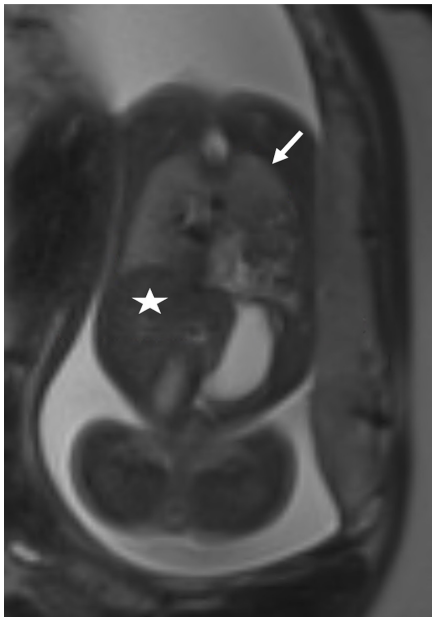

Figure 1. A 26-gestational week- fetus with left side herniation. A detectable-ipsilateral lung parenchyma at the apex was seen (arrow). Liver was in normal position (star).

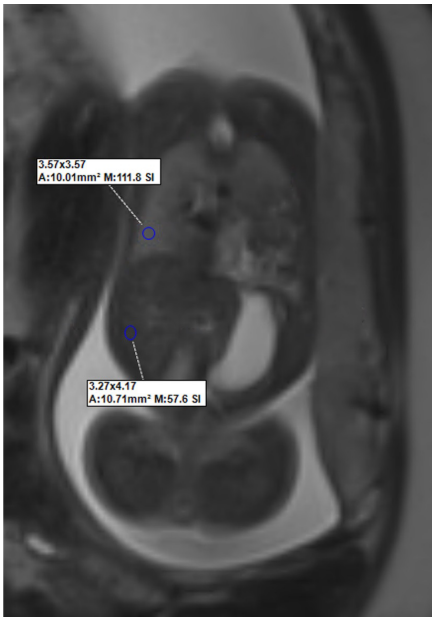

Figure 2. The calculation of the LLSIR. The ROIs are placed at the homogeneous zones of the lung parenchyma and the liver. LLSIR: Lung-to-liver signal intensity ratio, ROI: Region-of-interest.

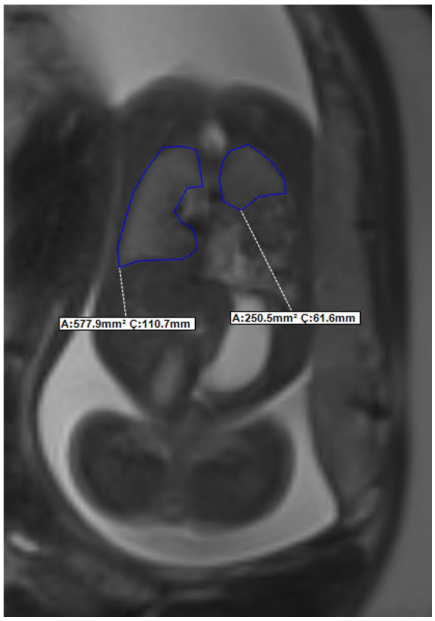

Figure 3. The measurement of the total lung volume. The freehand ROI on each contiguous slice was delineated to provide the lung area.

coronal sequences. The signal intensities of the lung and liver were obtained from the same section to avoid the signal changes on the different slices. The lung parenchyma signal intensity was measured on the homogeneous zone of the contralateral lung parenchyma according to the herniation site by a single region-of-interest (ROI). The portal vein and major branches were not included to the ROI when measuring the liver parenchyma signal intensity (Figure 2). Sizes of the ROIs were manually adjusted as approximately 1 cm^2.

For the calculation of the TLV, axial and coronal planes on HASTE sequences were used separately. First, the lung area was calculated using the freehand ROI on each contiguous slice to provide a sum of cross-sectional areas (in mm^2). Then, the total lung area was multiplied by slice thickness (in mm) to provide a volume (in mm^3) [15]. Subsequently, the TLV measured in axial and coronal planes was averaged to obtain the mean observed TLV (Figure 3). The observed-to-expected TLV was calculated by dividing the observed TLV by the expected TLV of a gestational age-matched healthy fetus. In our study, we considered the expected TLV values provided by Meyers et al. [16] that were provided from a large cohort.

Statistical analysis

Statistical analyses were done using IBM SPSS ver. 22.0 (IBM Corp.). Categorical variables were summarized with frequency counts and percentages and the continuous features were summarized with means and standard deviations. Continuous variables were compared by the Mann-Whitney U test. Chi-square and Fisher's exact tests were performed to analyze the association between the categorical variables and prognosis. Receiver operating characteristic (ROC) curve analyses were performed for each statistically significant parameter to evaluate the ability to predict the prognosis. A p-value lesser than 0.05 was considered as statistically significant.

RESULTS

Twenty-five patients were included in this study. The mean gestational week at the fetal MRI was

Table 1. The patients' characteristics.

	Ssurvived group (n = 6)	Non-survived group (n = 19)	p value
Gestational week at fetal MRI	26.17±7,2	24.74±5.3	0.733
Maternal age	24.33±2.5	28.47±5.8	0.138
Birth weight*	2935.0±538.5	2736±553.5	0.319
Apgar score at 1 minutes*	5.67±2.3	3±1.4	0.010

MRI: Magnetic resonance imaging
** Birth weight and Apgar score were calculated in 23 fetuses because of the terminations of the two pregnancies.*

25.08± 1.1 (18-36). Among 25 fetuses, 6 were alive and 19 were dead within 30 days after birth. The demographic characteristics of the patients were shown in Table 1. Two pregnancies underwent termination in terms of the parents' decision and these fetuses were classified under the dead group. Apgar score at 1 minute was significantly lower in the dead group (p=0.010).

The MRI features were shown in Table 2. The left side herniation (23 of 25 patients) was dominant in both groups (83.3% of the alive group and 94.7% of the dead group). 14 of 25 patients had liver herniation and among them, 12 patients had left liver lobe herniation due to the left-sided diaphragmatic defect. The detectable lung parenchyma was found in 83.3% of the alive group (p=0.023).

The observed-to-expected TLV values were significantly lower in the dead group (0.42±0.12; 0.20±0.09, p=0.001). The LLSIR values were also found lower in the dead group (2.31±0.79; 1.7±0.31, p=0.025). The ROC curve analysis showed that the observed-to-expected TLV had a larger area under the curve (0.930) than LLSIR (0.807) to predict death. Using the cutoff value for the observed-to-expected TLV as 0.27 had a sensitivity of 84% and a specificity of 84% for predicting death in fetuses with CDH. The optimal cutoff value for the LLSIR was 2.02, with a sensitivity of 89% and a specificity of 67% for death within 30 days after birth.

DISCUSSION

We evaluated the role of the fetal MRI to estimate the postnatal survival in CDH. According to our results, the observed-to-expected TLV and LLSIR may help to predict the postnatal survival. An observed-to-expected TLV value lower than 0.27 and an LLSIR value lower than 2.02 were the significant predictors for death within 30 days after birth. In addition, the detectable lung parenchyma on the ipsilateral side was associated with survival.

MRI allows more accurate information about fetal TLV since it is not limited by a fetal lie or maternal body habitus [9,11]. Different methods can be used for the measurement of the fetal TLV on MRI. The lung parenchyma can be outlined on each slice by the freehand ROI and multiplied by the slice thickness [7,16]. Moreover, the sequences can be exported to a 3-D workstation for segmentation and can be measured by manual or automated delineation of ROI [16]. Fetal TLV is also estimated by subtracting the mediastinal volume from the total thoracic volume [12]. The formulas for the prediction of expected fetal TLVs adjusted for gestational age (GA) by MRI measurements have been provided by Rypens

Table 2. Magnetic resonance imaging findings.

	Ssurvived group (n=6)	Non-survived group (n=19)	p value
Herniation site (Right/left)	1/5	1/18	0.430
Presence of the liver herniation	3 (50%)	11 (57.9%)	1.000
Presence of the detectable lung parenchyma	5 (83.3%)	5 (26.3%)	**0.023**
TLV	18961.6±19110.3	7422.68 ±6381.2	0.069
Observed-to-expected TLV	0.42 ± 0.12	0.20 ± 0.09	**0.001**
Lung signal intensity	329.5 ± 113.2	282.7 ± 175.8	0.598
Liver signal intensity	147.6 ± 57.3	166.7 ± 104.0	0.733
LLSIR	2.31 ± 0.79	1.7 ± 0.31	**0.025**

TLV: Total lung volume, LLSIR: lung-to-liver signal intensity ratio

et al. [7] and Meyers et al. [16] as follows:

According to Rypens et al. [7] (2001): $TLV=0.0033x(GA)^{2.86}$, in 2001. Recently, Meyers et al [16] suggested a formula according to a larger cohort of fetuses with gestational ages ranging from 18 to 38 weeks as follows: $TLV=0.000865x(GA)^{3.254}$. In cases of pulmonary hypoplasia, observed-to-expected fetal TLV should be used regardless of the measuring method of the TLV.

Cannie et al. [17] showed that the observed-to-expected TLV was an independent predictor of postnatal survival in CDH patients. They showed that fetuses with CDH who had 25% of expected TLV had a survival rate of 25%. Barnewalt et al. [12] demonstrated that patients with observed-to-expected TLV ratio of less than 15% had a higher risk for mortality in their small study population. Our results were compatible with the literature. We found that patients who could not survive had an observed-to-expected TLV ratios of lower than 0.27. In other words, the TLV less than approximately 25% of expected value was associated with high mortality.

There have been several studies that assessed fetal lung maturity by using LLSIR [18-20]. Brewerton et al. [18] showed that the LLSIR ranged from 1.52 to 4.31 between 21st and 34th gestational weeks. Moshiri et al. [19] manifested a normal mean value of LLSIR as 2.5. Oka et al. [20], found that a cut-off value of ≤2.0 for LLSIR was a good indicator for predicting respiratory outcome after birth. These studies have demonstrated that the fetal LLSIR increases with gestational age. The investigators thought that higher LLSIR values could be related to fluid accumulation in the lungs during fetal lung development with increasing gestational age.

Contralateral lung maturity evaluated with the LLSIR provided important prognostic information. Yamato et al. [21] investigated the LLSIR in the unaffected contralateral lungs of patients with isolated left-sided CDH detected on MRI. They observed that the LLSIR increased in parallel with advanced gestational age in the healthy control group but did not in the CDH group with good or bad prognosis. They suggested cut-off values of 2.16, and 2.22 with the aim to identify the fetuses in the early and late stages of CDH with good or bad prognosis. Our results were compatible with the literature.

We also examined the association between the detectable lung parenchyma in the herniation side and survival. We showed a relationship between the presence of a detectable lung parenchyma on the ipsilateral side and survival. We thought that this finding may help to predict the survival along with other specific parameters. Yokoi et al. [22] proposed a risk stratification using both the detectable lung parenchyma at the apex and the contralateral LLSIR with a cut-off value of 2 on MRI. They reported that all fetuses with detectable lung parenchyma had survived.

Although liver herniation is accepted as a prognostic factor for survival and severity of the pulmonary hypoplasia by many authorities, there have been controversial results in the literature. Ruano et al. [23] could not demonstrate any significant association between either the mortality or the need for ECMO and liver herniation. Nevertheless, they found significant differences in the amount of the liver harniation between the groups with good and bad prognosis. In our study, there was no significant relationship between liver herniation and survival. We considered the liver herniation as a dichotomous variable (either absent or present) and did not use it in the quantification of liver herniation. This may be the reason for this incompatibility.

Our study had several limitations. Firstly, the study had a retrospective design, and the number of our patient population was rather small. Secondly, we did not use three-dimensional MRI sequences for volumetric analysis since they were not performed routinely due to the long acquisition time in fetal MRI. Although we used the same method with the literature, three-dimensional MRI sequences might provide more accurate results. Thirdly, the interpretation of the MRI findings was performed by two pediatric radiologists in consensus which might limit to reproducibility of our results. Fourthly, morbidities were not considered in this study, and we grouped the patients as survived and non-survived cases. We did not evaluate other outcome parameters due to the insufficient information about patients in our archives.

CONCLUSION

In conclusion, fetal MRI is an important tool for evaluating patients with CDH. Based on our results, we established that the postnatal survival in CDH may be predicted using the observed-to-expected TLV and LLSIR on the fetal MRI. The presence of the detectable-ipsilateral lung parenchyma at the apex may also be associated with the postnatal survival. To achieve more definitive results of the prognostic value of the fetal MRI, more studies including larger numbers of patients are needed.

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