Original paper

Diagnostic Value of Lung-To-Liver Signal Intensity Ratio as An Indicator of Fetal Lung Maturity in Third-Trimester Pregnancy Using Magnetic Resonance Imaging.

Fatima Hasan Taqi [1], Mohammed Abd Kadhim [1,2]

[1]Department of radiology, Al-Imamain Al-Kadhemain medical city - Baghdad- Iraq.

[2]The Iraqi board for medical specialization, College of Medicine, Al-Nahrain University, Baghdad-Iraq.

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Correspondence: Fatima Hasan Taqi
Email: fatimahasan1010@gmail.com

Abstract

Background: fetal Magnetic resonance imaging (MRI) is effective and non-invasive, more accurate method for examining fetal lung development and predicting fetal respiratory outcomes.
Aims of the study: to study fetal lung-to-liver signal intensity ratio (LLSIR) using MR imaging T2-weighted images to indicate fetal lung maturity and predict neonatal respiratory outcome in third-trimester pregnancy and to establish an ideal LLSIR cut-off value
Patients and Methods: a prospective study was conducted on 40 fetuses from 39 pregnant women who delivered within 24 hours of an MRI scan during the period from January 2021 and January 2022 in AL-Imamain Al-Kadhimain Medical City/ Baghdad/ Iraq. LLSIR was evaluated using Half-Fourier acquisition single-shot turbo spin-echo (HASTE) MRI. An analysis of the receiver operating characteristic (ROC) curve was utilized to figure out the ideal cut-off value for the LLSIR to predict respiratory prognosis after delivery was determined.
Results: The gestational ages ranged from 28.1 to 40 weeks (mean 34.8 weeks). It was revealed that there was a correlation between magnetic resonance LLSIR and gestational age (p-value 0.001). The non-respiratory distress syndrome group had higher LLSIR compared with the respiratory distress syndrome group (2.81±0.32vs. 2.19±0.18, p-value 0.001). Compared to the preterm group, the term group exhibited a greater LLSIR. (2.87±0.34 vs 2.34±0.29, p-value 0.001). ROC curve analysis showed LLSIR at a cut-off value of LLSIR ≤ 2.32 and AUC=0.977, revealing high sensitivity (100%) and high specificity (88.9%).
Conclusions: The third- trimester LLSIR, as determined by T2-weighed images MRI, might be utilized as a prognostic marker for the neonatal respiratory prognosis if there is a strong correlation between these two parameters. 2.32 is the recommended cut-off number for forecasting newborn respiratory survival.
Keywords: fetal lung maturity, gestational age, third trimester, Lung-to-liver signal intensity ratio, Magnetic resonance imaging

Introduction

The fetal respiratory system might be regarded as the "key" to perinatal survival [(1)] An underdeveloped lung needs prompt intensive care after birth. As a result, it is critical to identify fetal lung growth and maturity before delivery precisely [(2)] Neonatal respiratory distress syndrome is the name for the respiratory impairment that happens right away upon delivery as a result of a pulmonary surfactant deficiency (RDS) [(3)] .1% of all infants born were impacted with neonatal RDS.; however, RDS babies are almost born prematurely (4) When compared to term newborns, An elevated risk of RDS is associated with even mild prematurity (specifically, the late preterm period of 35–37 weeks of gestation). If a reliable evaluation of fetal pulmonary development were available, therefore, any choice to deliver the baby before the 34 weeks of pregnancy would be boosted [(5)]
The lungs are one of the last embryonic organ systems to develop fully functionally [(5)] Attempts to determine the embryonic lung developing condition have always been of great concern [(6)] For a long time, the only way to confirm the maturity of the fetal lungs was to do an amniocentesis and then examine

the surfactant phospholipids that were released into the amniotic fluid in a lab. For this assessment, many assays are available, including the well-known lecithin-sphingomyelin ratio [7]. Despite the lecithin/sphingomyelin ratio being considered a definitive test for assessing fetal pulmonary maturity, the clinical utility of this test is limited by its unavailability in some medical centers. It is relatively expensive and time-consuming. Technically difficult and demands a lot of skill, making it inappropriate for point-of-care assessment [8]. Furthermore, amniocentesis for lung maturity is an intrusive operation with low (0.7%7) but occasionally significant morbidity; there is still a risk of infection, early labor, and potentially spontaneous abortion [9,10]. Furthermore, despite technological advancements, current research indicates that for fetal lung maturation utilizing any of these techniques after 36 weeks is neither dependable nor economical [11,12].

Fetal lung development can be evaluated non-invasively using noninvasive imaging techniques, including magnetic resonance imaging and ultrasound, which are preferable [13]. The vast majority of clinically important prenatal abnormalities are detected by ultrasound; however, even in experienced hands, predicting lung development and maturity is difficult and affected by operator experience [14]. MRI provides eminent tissue contrast, a broader field of view, and the absence of bone shadowing. In addition, maternal weight or the fetal position has little effect on MRI imaging of the fetus. Furthermore, MRI allows for multiplanar imaging. The fetus is deemed safe throughout the second or third trimester of pregnancy [15]. Therefore, creating a noninvasive, simple-to-use, and more accurate test for fetal lung maturity would be useful.

Aims of this study to study the role of fetal lung-to-liver signal intensity ratio (LLSIR) using MR imaging T2-weighted images to indicate fetal lung maturity and predict neonatal respiratory outcome in third-trimester pregnancy and establish an optimal cut-off value of LLSIR.

Patients and methods

The study was a prospective study conducted on 40 fetuses from 39 pregnant women who delivered within 24 hours of an MRI scan during the period from January 2021 and January 2022 in Baghdad, Iraq's AL-Imamain Al-Kadhimain Medical City.MR imaging was performed for various reasons (suspected placental, fetal, or uterine anomalies). There were 40 uncomplicated fetuses (38 singleton pregnancies and one dichorionic twin gestation). Monitoring the outcomes of every fetus scanned was accomplished. According to gestational age, fetuses were categorized into two groups; preterm fetuses (28—36w6/7wk) and term fetuses (37 0/7 weeks through 41 6/7 weeks). The most precise gestational age when the MRI scan was performed depended on Ultrasound (US) scans performed during the first trimester or last menstrual period. The scanning US was also done to exclude fetal malformation and growth retardation. Each fetus was regarded as a unique instance in a case of multiple gestations.

Inclusion Criteria: pregnant ladies in their third trimester and giving birth within 24 hours of an MRI scan.

Exclusion Criteria: patients given corticosteroids, the presence of a fetus, cardiac, liver, and renal abnormality, presence of fetal lung and/or diaphragm abnormality, gross fetal anomaly, and patients with general contraindications to MRI.

The scientific board of the Iraqi Board of Diagnostic Radiology granted its approval. Verbal approval was obtained from all participating women before fetal MR imaging, the MR exam was explained to all mothers before the exam according to the regulations of the Ethical Board at our institution.

MR Imaging and interpretation: all cases were examined using a 1.5 T MR unit (MAGNETOM Aera, Siemens medical system, Erlangen, Germany) with an 18-channel phased-array surface coil during this period. MRI examination was done in the supine or left lateral position to confirm the mother's comfort during the scan. During the examinations, no breath-hold was applied, no sedative was administered, and no contrast agent has applied.

All patients were examined using a Half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence of the fetal chest and abdomen in the coronal, axial, and sagittal planes. the images were taken using the following settings (FOV 400x400mm, matrix 512x512, TR/TE 2000-1300/100-92; flip angle 180°; slice thickness 3mm; gap 1.2mm, partial Fourier factor 5/8. The acquisition time was about 45 sec /sequence per patient.

The imaging plane that captured the liver and lung in a single frame was chosen for analysis. Using an ellipse, an area of interest (ROI) was defined in this slice within the homogenous lung and liver without considering the organ's boundaries, bronchi, arteries, or surrounding structures. Measurements were made in each lung and liver, and the average of these signals was used. The LLSIR is calculated by dividing the mean signal intensity value of the lung by the mean signal intensity value of the liver.

The ROI area ranged from 1.3 -2 cm2 depending on the size of the lungs and fetus. After delivery, the feedback based on the status of the evaluated newborns and fetal outcome was determined by the Pediatrician depending mainly on the Apgar score at 1-, 5-, and 10-minutes data, as follows: RDS neonate if a case of the low Apgar score and respiratory disorder required Nursing Care Unit admission or respiratory assistance. All neonates with normal APGAR scores and unremarkable postnatal respiratory assessment were considered non-RDS normal fetuses.

Statistical analysis: was performed with the Statistical Package for the Social Sciences (IBM SPSS v.28). Descriptive data were expressed as mean and standard deviation and ranges by the distribution. Both the relationships between LLSIR and neonatal RDS for each gestational age group and the relationships between LLSIR and gestational weeks instances were explored. To compare statistically two similar

groups (preterm and term MRI), linear regression analysis was used to determine the effects of LLSIR (y-axis) and gestational age (x-axis). The data were evaluated using an analysis of variance and the Pearson correlation coefficient. The level of statistical significance was fixed at P 0.05. To determine the best cut-off value for LLSIR, the accuracy or power of each prognostic variable for survival prediction was evaluated by the area under the ROC curve (AUC), sensitivity, and specificity. The analytical method employed was a receiver operating characteristic (ROC) curve.

Results

The current study included 40 fetuses of 39 pregnant mothers (1 woman with twin pregnancies). The mean age of mothers is 27.48±6.04 years. The gestational age of included fetuses ranged from 28.1 to 40 weeks, with a mean of 34.8 ±3.54 weeks. On average, the infant lung-to-liver signal intensity ratio (LLSIR) was 2.56±0.41. The gestational ages included in this study compass 17 term fetuses (42.5%) and 23 preterm fetuses (57.5%). Of the 40 infants, 16 (40%) developed RDS, whereas 24 infants (60%) had no RDS.

A substantial positive connection between LLSIR and growing gestational age was found by regression analysis (p=0.001).

The validity criteria of LLSIR at a cut-off value of LLSIR ≤ 2.32 and AUC=0.977 revealed high sensitivity (100%) and acceptable specificity (88.9%). as clarified in table 1 and figure 1.

Table 1. Validity criteria of LLSIR of the study sample.

The cutoff value for LLSIR	Sensitivity	Specificity	NPV	PPV	Accuracy
≤ 2.32	100	88.9	100	81.3	92.5

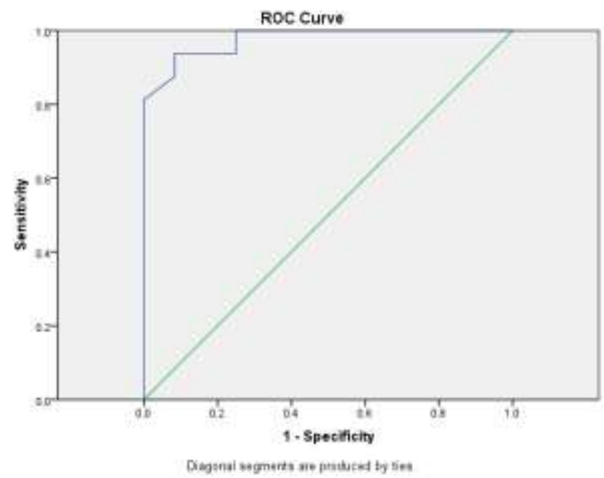

Figure 1. High sensitivity and good specificity were found in the receiver operating characteristic curve for the fetal lung-to-liver signal intensity ratio for determining postnatal pulmonary prognosis.

When the data were analyzed, it was discovered that there was a very statistically significant difference between the mean LLSIR of RDS newborns and non-RDS normal infants (p=0.0001). Additionally, the mean LLSIR of term infants differed statistically significantly from preterm infants (p=0.0001), as seen in table 2.

Table 2. Association of mean LLSIR with the severity of RDS and gestational period.

Variables	Categories	Total	LLSIR (mean± SD)	P-value
Infant status	Normal	24	2.81±0.32	< 0.001
	RDS	16	2.19±0.18	
Gestational period	Term	17	2.87±0.34	< 0.001
	Preterm	23	2.34±0.29	

*Independent t-test was used with a significant P value of less than 0.05.

The data analysis also revealed that 87.5% of preterm infants had a mean LLSIR equal to or less than 2.32 compared to 37.5% mean LLSIR of more than 2.32. This difference between the two groups was statistically significant (p=0.002), as shown in Table 3 and figure 2.

Table 3. Association of LLSIR and gestational period of the study sample.

Independent variables	Gestational period		P-value
	Term No. (%)	Preterm No. (%)	
	(n=17)	(n=23)	
LLSIR (mean± SD)			
≤2.32	2(12.5)	14(87.5)	0.002*
>2.32	15(62.5)	9(37.5)	

The data analysis showed that 87.5% of infants with RDS had a mean LLSIR equal to or less than 2.32 compared to 8.3% mean LLSIR of more than 2.32. This difference between the two groups was statistically significant (p=0.0001), as clarified in Table 4.

Table 4. Association of LLSIR and Infant status of the study sample.

Independent variables	Normal No. (%)	RDSNo. (%)	P-value
	(n=24)	(n=16)	
LLSIR (mean± SD)			
≤2.32	2(12.5)	14(87.5)	0.0001*
>2.32	22(91.7)	2(8.3)	< 0.001

Discussion

Neonatal prognosis is significantly impacted by fetal lung maturity. Over the past 40 years, and to date, the prediction of fetal lung maturity using different imaging methods has been attempted. Because Different tissues' chemical and structural makeup can be determined using MRI, researchers have attempted to examine developmental alterations related to biochemical lung maturation processes using signal intensity on different sequences [16]. LLSIR is straightforward to acquire from MRI without any specialist procedures, and there is no requirement for trained examiners, which is one of the benefits of LSSIR as an accurate marker to identify fetal lung maturity compared to other parameters [17] In this study, at more advanced gestational ages, the normal lungs showed a higher LLSIR; this finding was identical to the results of Ogawa et al. [6], Brewerton et al. [18], Moshiri et al. [19], Sakuma et al. [20], Yamato et al. [21], Gorincour et al. [22] Kuwashima et al. [23], and Dutemyer et al. [24].

T2-weighted MR images of the fetal lungs show the signal intensity and relaxation times. Investigators thought that higher LLSIR values could be related to fluid accumulation in the lungs during fetal lung development with increasing gestation [25]. Oka et al. [2] previously reported a positive correlation between LLSIR and gestational age but did not correlate with the values with gestational age.

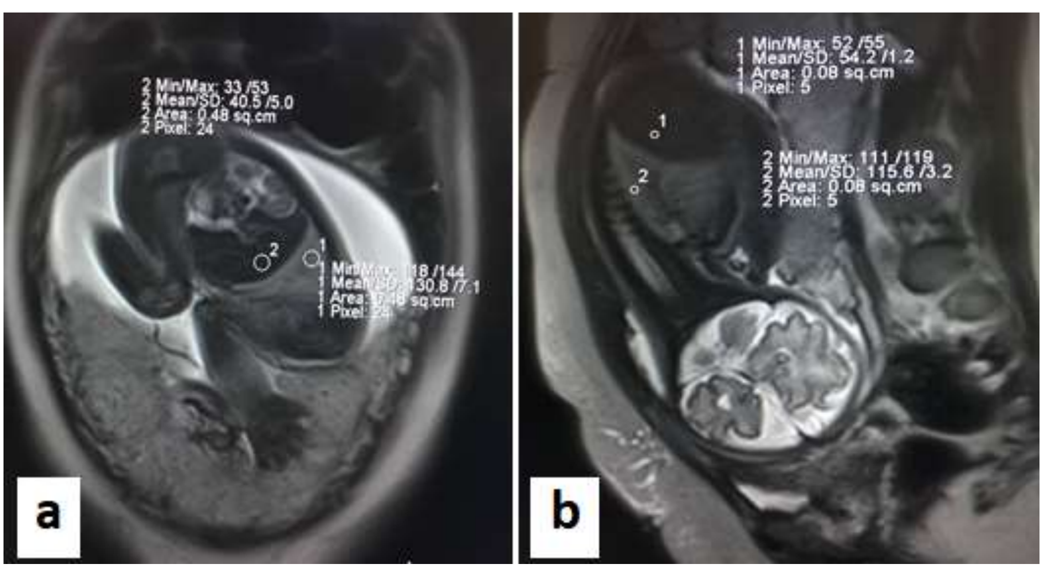

Figure 2a. 39 weeks Term infants with LLSIR 3.2. **figure 2b**: image obtained in a preterm infant (32 weeks pregnancy), LLSIR=2.1.

The findings of this study demonstrate a significant linear incremental association between the LLSIR value and gestational age. Moshiri M et al. [19] showed identical findings. Their outcome showed a significant link between LLSIR and gestational age at fetal MRI. Also, Gorincour et al. [22] found an exponential association between lung-liver HASTE ratios and expected gestational age. Similarly, Perrone et al. [26] demonstrate that lung/liver size increases with fetal lung development and looks to be a valuable way to gauge fetal growth inside the womb. However, Brewerton et al. [18] showed that LLSIR and gestational age have a quadratic relationship. This discrepancy's origin is uncertain.

A previous research by Keller et al. [27] used single-shot fast spin-echo ratios to measure the signal intensities of the fetal lung, liver, amniotic fluid, muscle, and liver in 35 healthy fetuses hypothesized neither gestational age relationship nor clinical relevance for fetal lung signal intensity values; they postulated that the liver, whose signal intensities change with age, might not be a good reference structure.

Perkins NJ et al. [28] studies demonstrated that the nearest point on the curve where specificity and sensitivity are both 1 is typically the best cut-off point. With the help of this cut-off number, we may divide all fetuses into two groups: those with diseases projected to occur and those without. High sensitivity (100%) and adequate specificity (88.9%) were found in the current study's validity criteria of LLSIR to detect the respiratory outcomes at a cut-off value of LLSIR 2.32 and AUC=0.977, Oka Y et al. [2].

With a sensitivity of 100% (95% CI = 52-100%) and a specificity of 73% (95% CI = 54-88%), the cut-off level of LLSIR on 2.0 was found to be the most effective. Brewerton et al. [18] showed that the LLSIR ranged from 1.52 to 4.31 between the 21st and 34th gestational weeks. Moshiri et al. [19] manifested a normal mean value of LLSIR as 2.5.

The current study clarifies that LLSIR is higher in the non-RDS group in comparison to the RDS group and predicts good respiratory maturity and function, which is consistent with the research of Oka Y et al. [2]. When compared to the non-RDS group at comparable gestational ages, the RDS group had a much lower signal intensity due to its low LLSIR throughout pregnancy; these results were similar to that of Oka Y et al. [2] and Sakuma J et al. [20] studies. Brewerton et al. [18] found that LLSIR was lower in RDS fetuses as compared to fetuses with normal lungs.

Undoubtedly depending on LLSIR, and as agreed by Cannie et al. [29], The study shows a significant reasonable difference in RDS incidence between preterm and term fetuses, and this can be explained by the developmental changes in the fetal lung, which impact both lung architecture and content, as well as possibly additional still unknown alterations factors such as maturation occurs.

Conclusions

There is a significant relationship between fetal lung maturation and the LLSIR during the third trimester, as measured by T2-weighed MRI, and this has the potential to be used as a prognostic indicator for neonatal respiratory outcome in both preterm and term infants. The best cut-off value that predicts the neonatal respiratory outcome is ≤ 2.32.

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