



# Fetal liver and lung volume index of neonatal survival with congenital diaphragmatic hernia

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## Abstract

**Background** Magnetic resonance imaging (MRI) assesses pulmonary hypoplasia in fetal congenital diaphragmatic hernia (CDH). Neonatal mortality may occur with CDH.

**Objective** To quantify MRI parameters associated with neonatal survival in fetuses with isolated CDH.

**Materials and methods** Fetal MRI for assessing CDH included region of interest (ROI) measurements for total lung volume (TLV), herniated liver volume, herniated other organ volume and predicted lung volume. Ratios of observed lung volume and liver up volume to predicted lung volume (observed to predicted TLV, percentage of the thorax occupied by liver) were calculated and compared to neonatal outcomes. Analyses included Wilcoxon rank sum test, multivariate logistic regression and receiver operating characteristic (ROC) curves.

**Results** Of 61 studies, the median observed to predicted TLV was 0.25 in survivors and 0.16 in non-survivors ( $P=0.001$ ) with CDH. The median percentage of the thorax occupied by liver was 0.02 in survivors and 0.22 in non-survivors ( $P<0.001$ ). The association of observed to predicted TLV and percentage of the thorax occupied by liver with survival for gestational age (GA)  $>28$  weeks was greater compared to GA  $\leq 28$  weeks. The ROC analysis demonstrated an area under the curve of 0.96 (95% confidence interval 0.91–1.00) for the combined observed to predicted TLV, percentage of the thorax occupied by liver and GA.

**Conclusion** The percentage of the thorax occupied by liver and observed to predicted TLV was predictive of neonatal survival in fetuses with CDH.

**Keywords** Congenital diaphragmatic hernia · Fetus · Liver · Lung volume · Magnetic resonance imaging · Pulmonary hypoplasia · Survival · Thorax

## Introduction

Congenital diaphragmatic hernia (CDH) affects approximately 1–2 in 5,000 births [1–3]. Overall mortality frequencies

range from 61–68% [2, 4] and 44–47.9% for live born infants [1, 2, 4, 5]. There is a significant burden on the health care system due to associated morbidity, mortality and long-term sequelae [6–9].

In isolated CDH, mortality and morbidity have been shown to be related to pulmonary hypertension and the degree of pulmonary hypoplasia [10, 11]. Prenatal imaging has demonstrated utility in predicting lung volumes and may be used to predict the degree of pulmonary hypoplasia [12–16]. Ultrasound is the primary modality utilized in fetal imaging, and one of the first imaging parameters to predict pulmonary volume was the ultrasound lung–head ratio [10, 17–19]. However, studies have demonstrated variability in the utility of the lung–head ratio, and the lung–head ratio has been shown to increase with increasing gestational age (GA) [20–22]. Fetal magnetic resonance imaging (MRI) may provide a useful adjunct in the evaluation of lung volumes. With

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the advent of fast MRI sequences, MRI has increasingly been used in prenatal evaluation of CDH. Multiple MRI parameters to evaluate pulmonary hypoplasia in patients with CDH have previously been investigated [14, 18, 19, 23–26]. However, many of the previous studies evaluating fetal MRI in CDH relied on lung volume nomograms to generate observed to expected lung volume ratios, rather than calculating expected lung volumes within each fetus. Additionally, although previous studies have evaluated the presence of liver within the hernia, there are limited studies evaluating the quantified volume of liver herniation [19, 26–28]. We sought to combine both lung and liver volumes within the chest along with GA at the time of fetal MRI to offer prognostic findings, specifically, neonatal survival. Overall survival rates have not significantly changed over time [1, 2]. However, more recent studies suggest better neonatal outcomes, perhaps in improving morbidity, with more precise prenatal evaluation as well as referral to a tertiary care center [1, 23].

Our objective was to identify the MRI parameters associated with neonatal survival in isolated CDH. We predict that calculating the degree of liver herniation as well as actual lung volumes will improve the prediction of neonatal survival.

## Materials and methods

We performed an institutional review board (IRB)-approved retrospective observational study of fetuses with CDH evaluated with fetal MRI in a single center.

### Patients

Inclusion criteria included patients undergoing fetal MRI for evaluation of left-side CDH between August 2000 and December 2018 with survival data available. This data was obtained from the fetal MRI clinical database at our institution. Exclusion criteria included right-side or bilateral CDH and/or antenatal diagnosis of aneuploidy or additional complex congenital anomalies that would preclude surgical correction. Data collected included GA at the time of MRI exam; side of diaphragmatic defect; MRI-based measurement of fetal lung volume, hernia volume and herniated liver volume; neonatal survival; and the use of extracorporeal membrane oxygenation (ECMO). Neonatal survival was defined as discharge from the neonatal intensive care unit.

### Management protocol

During the study period, CDH management did not significantly change at our institution. In general, management consisted of ventilation to support oxygenation followed by operative repair after the neonate demonstrated evidence of his or her ability to oxygenate blood. Surgical approach largely also did not change

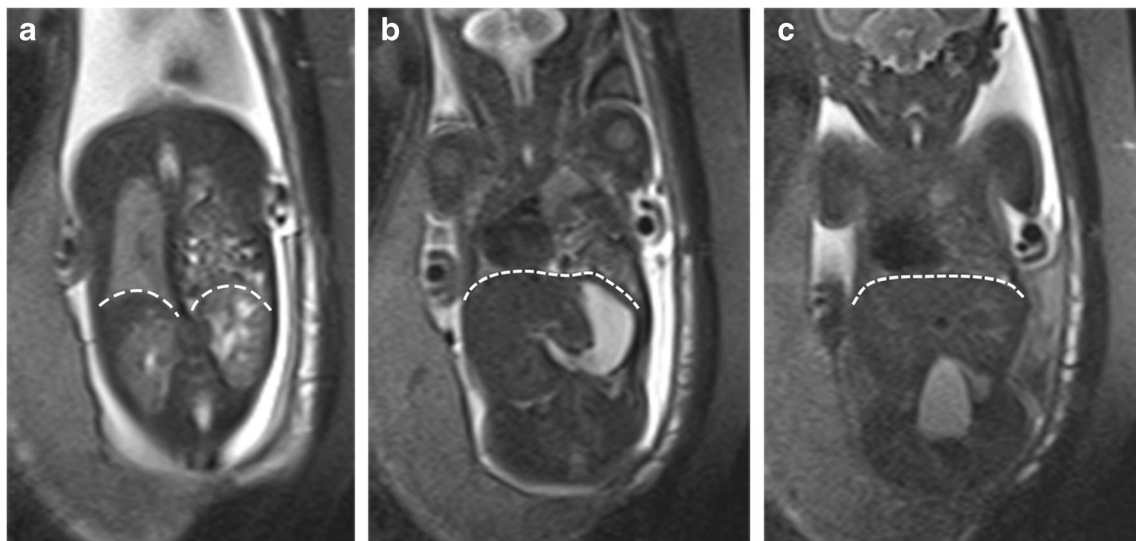
during the study period and consisted of reducing intrathoracic abdominal contents into the abdomen and closing the defect with either primary closure, muscle flap or mesh based on the size of the defect. Additionally, the decision to operate was based solely on the patient's hemodynamic stability.

### Magnetic resonance imaging protocol

All fetal MRI exams were performed on a 1.5-tesla (T) system (Siemens Magnetom Avanto; Siemens Healthineers, Erlangen, Germany; or GE Signa; GE Medical Systems, Waukesha, WI) utilizing a multi-channel body coil. Pregnant mothers were placed in a supine or decubitus position. No sedation or contrast administration was used during image acquisition. Free-breathing T2-weighted single-shot fast spin echo (SSFSE) sequences (repetition time [TR]/echo time [TE] 1,100/115 ms, flip angle 150°, matrix size 192×256 mm, section thickness 3 mm, no intersection gap) were obtained in transverse, sagittal and coronal planes. Free-breathing T2-weighted short tau inversion recovery (STIR) sequences (TR/TE 1,600/89 ms, flip angle 150°, matrix size 179×256 mm, slice thickness 5 mm, no intersection gap) were obtained in transverse, sagittal and coronal planes. Breath-hold T1-weighted gradient recalled echo (GRE) sequences (TR/TE 117/4.75 ms, flip angle 70°, matrix size 192×256 mm, slice thickness 5.5 mm, intersection gap 0.6 mm) were obtained in the coronal plane. Balanced steady-state free precession (bSSFP) free-breathing sequences (TR/TE 6.07/2.45 ms, flip angle 54°, matrix size 256×256 mm, slice thickness 5 mm, no intersection gap) were obtained in the coronal plane at 5-mm slice thickness.

### Magnetic resonance imaging assessment and interpretation

Images were evaluated by two investigators in concert: one fellowship-trained, board-certified radiologist (D.M.T.) with more than 25 years of experience in obstetrics imaging including antenatal ultrasound and fetal MRI and one fellowship-trained, board-certified radiologist (A.A.B.) with 5 years of experience in fetal MRI. All measurements were obtained on Philips IntelliSpace PACS Radiology version 4.4 workstations (Philips Healthcare, Brisbane, CA). Measurements obtained from MR images included actual observed lung volume, intrathoracic liver volume and herniated organ volume. The diaphragm location was estimated at the level of the defect to obtain these volumes (Fig. 1). Volumes of the visualized lung parenchyma (Fig. 2), herniated organs (Fig. 2) and intrathoracic liver (Fig. 3) were obtained by drawing a region of interest (ROI) measurement around the area of interest (i.e. visualized lung parenchyma, herniated organs or intrathoracic liver) for each slice, adding the ROI measurements, and then multiplying the summed measurements by the slice thickness. Mediastinum



**Fig. 1** Diaphragm location. **a–c** Sequential T2-W single-shot fast spin echo coronal images obtained at 32 weeks’ gestation through the posterior (**a**), mid (**b**) and anterior (**c**) fetal chest with left congenital diaphragmatic hernia demonstrating diaphragm location (*dashed lines*).

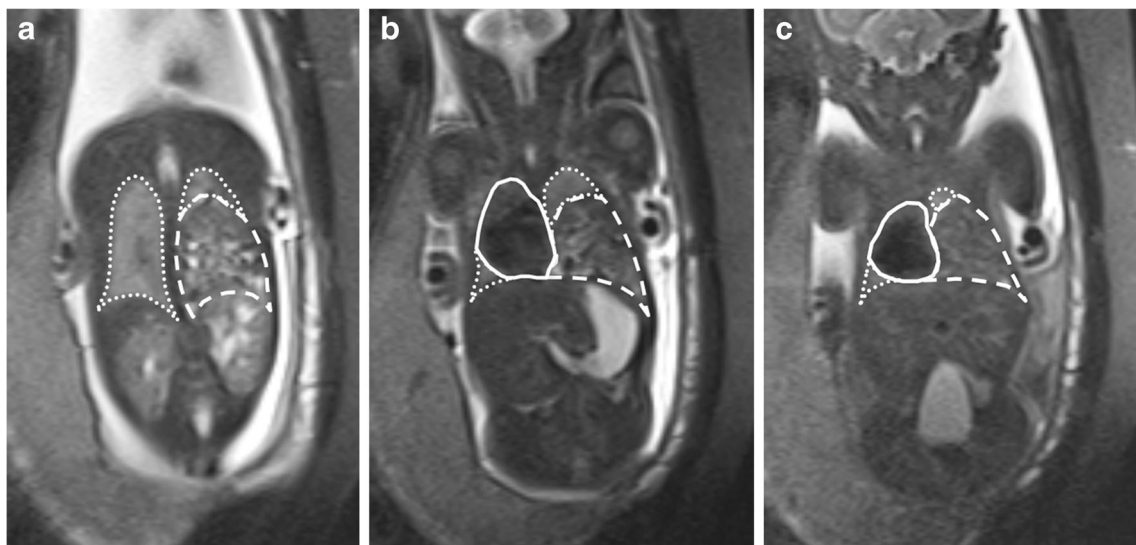
The diaphragm’s location on the side of the defect was estimated using the contralateral lung as reference. Although the hemidiaphragms are not necessarily at the same level, the contralateral diaphragm was favored to be the best approximation of diaphragm level on the side of the defect

was excluded from the volume measurements. Visualized lung parenchyma (observed total lung volume [TLV]) was defined as the volume of lung parenchyma present. Herniated organ volume (mass) was defined as the volume of herniated contents in the thoracic cavity (e.g., stomach and bowel). Intrathoracic liver volume (liver up) was defined as the volume of liver present within the thoracic cavity. ROI measurements were completed in the coronal plane. The total thoracic cavity volume, not including the mediastinum, was the summation of observed TLV, volume of herniated liver, and volume of herniated organs, referred to as the predicted TLV. This was

preferred over nomograms of expected TLV because of the large variability of fetal weights and, therefore, lung volume measurements. The measurements were then used to calculate the percentage of the thoracic cavity occupied by lung (observed to predicted TLV) and the percentage of thoracic cavity occupied by liver (% of thorax occupied by liver).

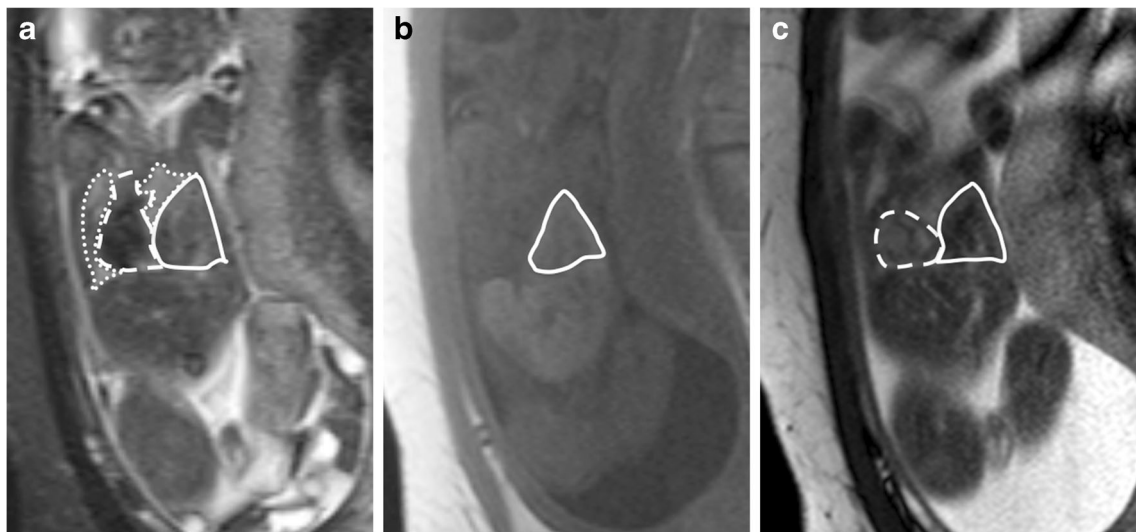
**Statistical analysis**

Statistical analyses included the Wilcoxon rank sum test for continuous measures, receiver operating characteristic (ROC)



**Fig. 2** Region of interest (ROI) measurements of a left congenital diaphragmatic hernia. **a–c** Sequential T2-W single-shot fast spin echo coronal images obtained at 32 weeks’ gestation through the posterior (**a**), mid (**b**) and anterior (**c**) fetal chest demonstrate a left congenital

diaphragmatic hernia. The *dotted line* indicates ROI of residual lung, the *dashed line* indicates ROI of hernia contents and the *solid line* indicates ROI of the mediastinum. The liver is located in the right upper quadrant of the abdomen, and no intrathoracic liver is identified



**Fig. 3** Region of interest (ROI) measurements of the intrathoracic liver. **a–c** Coronal T2-W short tau inversion recovery (**a**), breath-hold T1 gradient recalled echo (**b**) and balanced steady-state free precession (**c**) images obtained at 27 weeks' gestation through the fetal thorax

demonstrate left congenital diaphragmatic hernia with the intrathoracic liver. The *dotted line* indicates ROI of residual lung, the *dashed line* indicates ROI of mediastinum and the *solid line* indicates ROI of liver

curves, area under the curve (AUC) and multivariate regression analysis. The Wilcoxon rank sum test was chosen because of the size of the statistical sample.

## Results

One hundred and ten MRI studies were performed for CDH from 2000 to 2018. Neonatal survival data were available for 61 of these exams. Eleven patients were found to have additional complex fetal anomalies and were excluded from evaluation (Table 1). Ten patients were found to have either right-side CDH (8) or bilateral CDH (2) and were also excluded from evaluation. Forty patients with survival data met inclusion criteria. Of the study patients, there were 21/40 male fetuses (52.5%) and 19/40 female fetuses (47.5%). There were

21/40 survivors for a survival frequency of 52.5%. The median GA at the time of MRI exam was 32 weeks; 30 exams were performed after 28 weeks' GA, and 10 exams were performed before or at 28 weeks' GA. The observed to predicted TLV ranged from 0.06 to 1.00 and the % of thorax occupied by liver ranged from 0 to 0.67. Eleven patients required ECMO.

The medians and quartiles of observed to predicted TLV and % of thorax occupied by liver were compared between survivors and non-survivors (Table 2). Medians and quartiles were compared due to the nonstandardized distribution of the patient population. Using the Wilcoxon rank sum test, there was a significantly higher observed to predicted TLV for survivors compared to non-survivors ( $P=0.001$ ), and there was a significantly lower % of thorax occupied by liver for survivors compared to non-survivors ( $P<0.001$ ). The data were further evaluated based on GA at the time of study (Table 3). For

**Table 1** Patients excluded due to additional complex anomalies detected on antenatal imaging or amniocentesis

Patient	Additional anomalies detected
1	Ambiguous genitalia, bilateral grade 4 hydronephrosis, polyhydramnios
2	Aqueductal stenosis
3	Clenched hands, rocker bottom feet, kyphosis of the thoracic spine
4	Trisomy 18
5	Agenesis of the corpus callosum, bilateral clenched fists
6	Cerebellar hypoplasia and obstructive hydrocephalus
7	Dandy-Walker malformation
8	Endocardial cushion defect
9	Wolf-Hirschhorn syndrome with dysgenesis of the corpus callosum, bilateral cleft lip and severe underdevelopment of the globes
10	Ventriculomegaly, Chiari II, agenesis of the corpus callosum
11	Severe oligohydramnios



**Table 2** Comparison of observed to predicted total lung volume (TLV) and percentage of thorax occupied by liver between survivors and non-survivors

		Survivors	Non-survivors	P-value
<i>n</i>		21	19	
Observed to predicted TLV	Minimum	0.09	0.06	0.001
	Q1	0.17	0.10	
	Median (Q2)	0.25	0.16	
	Q3	0.42	0.20	
	Maximum <sup>a</sup>	1.00	0.30	
% of thorax occupied by liver	Minimum	0.00	0.00	<0.001
	Q1	0.00	0.16	
	Median (Q2)	0.02	0.22	
	Q3	0.13	0.41	
	Maximum	0.29	0.67	

Q1 first quartile, Q2 second quartile, Q3 third quartile

<sup>a</sup> Observed to predicted TLV maximum value of 1.00 was in a patient with congenital diaphragmatic hernia containing only a small portion of stomach. The measured volume of the intrathoracic stomach (0.26 mL) and the measured volume of lung parenchyma (69.6 mL) gave an observed to predicted TLV of 0.996, rounded up to 1.00

exams performed after 28 weeks' GA, the *P*-values decreased for both observed to predicted TLV and % of thorax occupied by liver.

An ROC curve was generated to predict neonatal survival using GA, MRI-derived observed to predicted TLV and % of thorax occupied by liver (Fig. 4). ROC analysis demonstrated an AUC of 0.96 (95% confidence interval [CI]: 0.91, 1.00). ROC curves were also generated to predict survival using observed to predicted TLV only or % of thorax occupied by liver only (Fig. 5). ROC analysis for observed to predicted TLV demonstrated an AUC of 0.80 (95% CI: 0.66, 0.94). ROC analysis for % of thorax occupied by liver demonstrated

an AUC of 0.88 (95% CI: 0.77, 0.99). Comparing the three ROC curves demonstrated that a combination of factors (GA, observed to predicted TLV and % of thorax occupied by liver) generated the largest AUC and had the greatest strength of prediction. Multivariable analysis evaluating observed to predicted TLV, % of thorax occupied by liver and GA at the time of MRI exam demonstrated significant differences between survivors and non-survivors (Fig. 6).

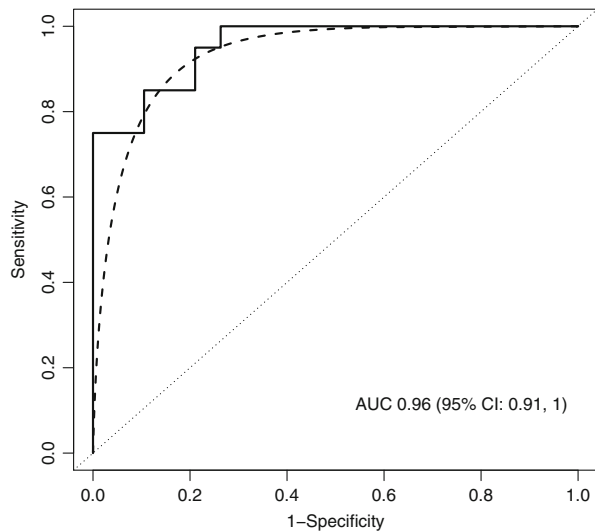
About one-fourth of our patient population received ECMO (11/40; 27.5%). An ROC curve generated to predict the need for ECMO based on observed to predicted TLV, % of thorax occupied by liver and GA demonstrated an AUC of

**Table 3** Comparison of observed to predicted total lung volume (TLV) and percentage of thorax occupied by liver between survivors and non-survivors subdivided based on gestational age at the time of MRI

		Gestational age					
		≤28 weeks (n=10)			>28 weeks (n=30)		
		Survivor	Non-survivor	P-value	Survivor	Non-survivor	P-value
<i>n</i>		2	8		19	11	
Observed to predicted TLV	Minimum	0.17	0.09	0.03	0.09	0.06	0.003
	Q1	0.29	0.11		0.17	0.10	
	Median (Q2)	0.42	0.16		0.24	0.13	
	Q3	0.51	0.27		0.32	0.16	
	Maximum	0.59	0.30		1.00	0.12	
% of thorax occupied by liver	Minimum	0.00	0.00	0.15	0.00	0.19	<0.001
	Q1	0.00	0.16		0.02	0.31	
	Median (Q2)	0.08	0.20		0.12	0.41	
	Q3	0.18	0.28		0.09	0.06	
	Maximum	0.20	0.50		0.17	0.10	

Q1 first quartile, Q2 second quartile, Q3 third quartile

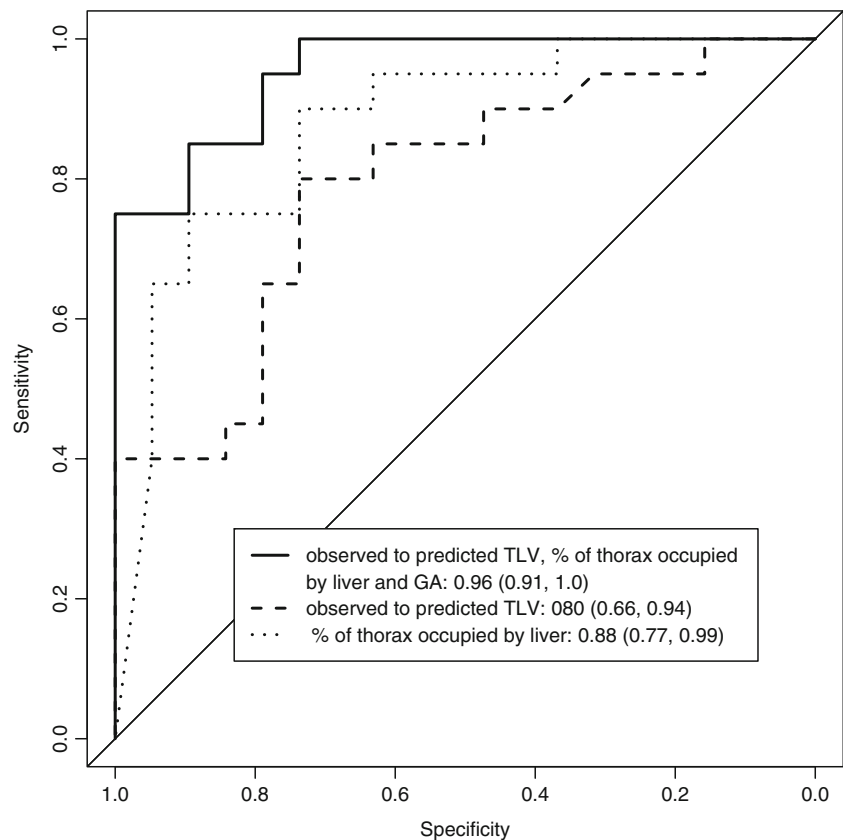
ROC curve for observed to predicted TLV, % of thorax occupied by liver and GA



**Fig. 4** The receiver operator characteristic (ROC) curve predicts neonatal survival using gestational age, MRI-derived observed to predicted total lung volume (TLV) and percentage of thorax occupied by liver. ROC analysis demonstrates the value of using observed to predicted TLV, percentage of thorax occupied by liver and gestational age at the time of the exam in predicting survival in isolated congenital diaphragmatic hernia. *AUC* area under the curve, *CI* confidence interval, *GA* gestational age

0.67 (95% CI: 0.51, 0.83). Both observed to predicted TLV and % of thorax occupied by liver were not significantly

**Fig. 5** Receiver operator characteristic (ROC) curves compare a combination of factors with observed to predicted total lung volume (TLV) alone or percentage of thorax occupied by liver alone. ROC analysis demonstrates that a combination of factors generated the largest area under the curve (AUC) with the greatest strength of prediction. Ninety-five percent confidence intervals are given in parentheses. *GA* gestational age

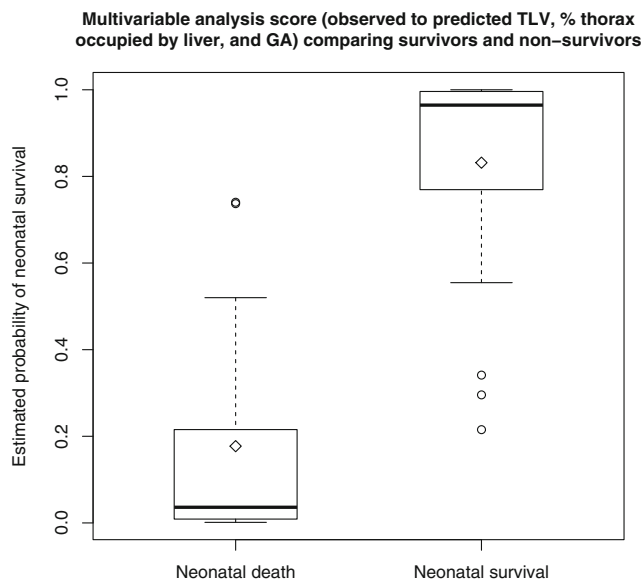


different in predicting the need for ECMO. Patients requiring ECMO had higher mortality with 10/11 (90.9%) dying.

## Discussion

CDH is a complex medical problem with significant societal cost [6, 8, 11] and stagnant survival rates over the past several decades despite advances in both detection and management [1, 2, 9]. Studies have demonstrated that outcomes in isolated CDH are related to both the degree of pulmonary hypoplasia and the presence of pulmonary hypertension [10, 11]. Imaging provides assessment of pulmonary hypoplasia [14, 29]. Further research into the imaging parameters has the potential to significantly impact management of this disease.

The present study demonstrated that observed to predicted TLV and % of thorax occupied by liver evaluated in conjunction with GA at the time of the exam were most predictive of neonatal survival in isolated left-side CDH. Furthermore, both the % of thorax occupied by liver and the observed to predicted TLV were independent predictors of neonatal survival in isolated CDH. The strength of prediction (e.g., greater differences in medians and lower *P*-values) improved with MRI exams performed after 28 weeks' GA. This may indicate weaker evidence when the MRI exam is performed earlier than 28 weeks and, furthermore, more confidence of



**Fig. 6** A box plot compares the multivariable analysis score between survivors and non-survivors. The two groups are significantly different without overlap. *GA* gestational age, *TLV* total lung volume

prediction of survival when the exam is performed at a later GA [3, 30]. However, fewer fetuses were evaluated before 28 weeks in our study, and therefore, higher *P* values may be related to the smaller sample size and weaker power. This may influence practice guidelines regarding when fetal MRI for CDH should be performed.

The observed to predicted TLV, % of thorax occupied by liver and the GA at the time of the exam were not found to predict the need for ECMO use in our study. However, only a small number of patients required ECMO use ( $n=11$ ), and smaller sample size may result in weaker, more limited data.

Our study had several limitations. Evaluation was retrospective and our patient population was predominantly from outside referents. Therefore, despite having a large total number of patients who were evaluated with CDH, outcome data were not available in a percentage of patients. GA at birth was not available for a large percentage of our imaged patients, including study participants. Planning a prospective evaluation would improve this aspect of the study. The sample size was small, in part due to the lack of outcome data, specifically for evaluations before 28 weeks' GA. Additionally, as a referral center, it may not be possible to extrapolate results to the general population. Ultrasound imaging parameters were not included in evaluation or comparison. Additionally, other parameters, such as GA at delivery, birth weight, Apgar scores and the time of CDH repair were also not included in the evaluation.

The use of antenatal imaging in the management of CDH is variable across centers. This is, in part, due to differences in access and resources available to centers [31]. Furthermore, most of the current data about CDH are related to single-center experiences. Single-center experiences are difficult to

generalize and reproduce as outcomes are variable due to differences in center protocols, experience and resource availability. Theoretically, antenatal imaging data may better triage patients to centers capable of managing CDH as well as select the appropriate patients for fetal intervention. However, this does not consistently occur.

Antenatal imaging parameters generally do not dictate postnatal management of CDH. The ultimate goal is to use antenatal data to initially identify those potentially high-risk fetuses requiring care in a tertiary referral center, aid in delivery management, more expeditiously effect bedside decision-making after delivery and possibly reduce mortality and morbidity related to delays in care. Standardized management guidelines in CDH have not been developed, largely due to differences in the resources available to centers. However, limited work has been initiated to develop practice guidelines [32, 33]. Future directions include a large multicenter trial to improve sample size and power of the study as well as reproducibility. Prospective analysis using data from our study and additional data comparing ultrasound with MRI would be useful to further extrapolate and validate study outcomes.

## Conclusion

Fetal MRI in the setting of CDH provides discriminating quantitative evaluation of actual lung volumes and liver up in association with survival during the neonatal period. This data may assist prenatal counseling and clinical decisions regarding delivery, surgery and neonatal intervention.

## Declarations

**Conflicts of interest** None

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