# Value of prenatal magnetic resonance imaging in the prediction of postnatal outcome in fetuses with diaphragmatic hernia

J. JANI*†**, M. CANNIE†, P. SONIGO‡, Y. ROBERT§, O. MORENO¶, A. BENACHI‡, P. VAAST§,
E. GRATACOS¶, K. H. NICOLAIDES* and J. DEPREST†

*Radiology and Fetal Medicine Units of *King's College Hospital, London, UK, †University Hospital Gasthuisberg, Leuven, Belgium,
‡Hôpital Necker-Enfants Malades, Paris and §Hôpital Jeanne de Flandre, Centre Hospitalier Régional Universitaire de Lille, Lille, France
and ¶Hospital Clinic, Barcelona, Spain
**Currently working at Department of Obstetrics and Gynaecology, University Hospital Brugmann, Brussels, Belgium*

## ABSTRACT

*Objectives* To investigate the potential value of antenatally determined total fetal lung volume (TFLV) by magnetic resonance imaging (MRI) in the prediction of the postnatal survival in congenital diaphragmatic hernia (CDH).

*Methods* We examined fetuses with isolated CDH, in which MRI was used at 22–38 weeks of gestation to measure TFLV and assess intrathoracic herniation of abdominal viscera, that were liveborn after 30 weeks of gestation and had postnatal follow-up until death or discharge from hospital. Regression analysis was used to investigate the effect on survival of gestational age at diagnosis, observed to expected (o/e) TFLV, intrathoracic herniation of the liver, side of CDH, gestational age at MRI, institution, year and gestational age at delivery. In 76 fetuses measurements of o/e TFLV and the lung area to head circumference ratio (LHR) were performed within 2 weeks of each other; in these cases o/e TFLV and o/e LHR were compared for their prediction of postnatal survival.

*Results* In the 148 cases that fulfilled the entry criteria, multiple regression analysis demonstrated that significant predictors of survival were the presence or absence of intrathoracic herniation of the liver and o/e TFLV. The area under the receiver–operating characteristics curves for prediction of postnatal survival from o/e TFLV was 0.786 (standard error, 0.059; $P < 0.001$) and that from o/e LHR was 0.743 (standard error, 0.069; $P = 0.001$).

*Conclusions* In the assessment of fetuses with CDH, MRI-based o/e TFLV is useful in the prediction of postnatal survival. Copyright © 2008 ISUOG. Published by John Wiley & Sons, Ltd.

## INTRODUCTION

Congenital diaphragmatic hernia (CDH) is found in about one in 4000 births. In approximately 30% of cases of CDH there are associated chromosomal and major defects, and in this group the prognosis is poor[1]. In the group with apparently isolated CDH the overall survival rate is about 60%, with the remaining babies usually dying in the neonatal period from pulmonary hypoplasia and/or pulmonary hypertension[2,3]. Early experience shows that the prognosis may be improved by prenatal surgical intervention[4–6]. In order to counsel patients and to help them choose between options, assessment of the individual prognosis as well as potential indication for fetal surgery is a clinical necessity.

Because lung hypoplasia is the leading cause of death and the pathological diagnosis is based on the lung weight to body weight ratio[7–9], it seems logical that lung size should be useful as a prognostic indicator. The most extensively studied method is measurement of the area of the lung contralateral to the diaphragmatic defect, which can be obtained in a transverse section of the fetal thorax and is expressed as a ratio to the fetal head circumference (lung area to head circumference ratio, LHR)[10–12].

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**Table 1** Studies reporting on the value of fetal observed to expected (o/e) total fetal lung volume (TFLV) in the prediction of survival in isolated congenital diaphragmatic hernia

| Reference | n | Intrathoracic herniation of the liver (%) | Gestational age (weeks)* | o/e TFLV cut-off (%) | Survival (%) |
|---|---|---|---|---|---|
| Cannie et al. 2006[17] | 8 | 25 | 24–26 | < 35 | 50 |
| | | | | ≥ 35 | 100 |
| Gorincour et al. 2005[19] | 77 | Not stated | 24–37 | < 25 | 19 |
| | | | | > 25 | 60 |
| Williams et al. 2004[23] | 25† | Not stated | 21–36 | Not proposed | Not stated |
| Paek et al. 2001[21] | 11 | 73 | 21–28 | ≤ 40 | 25 |
| | | | | > 40 | 100 |
| Mahieu-Caputo et al. 2001[20] | 11 | 45 | 28–37 | < 35 | 0 |
| | | | | ≥ 35 | 67 |
| Walsh et al. 2000[22] | 41 | 51 | 20–39 | Not proposed | 59 |

*Gestational age at o/e TFLV measurement. †Of 28 at high risk for pulmonary hypoplasia, 25 had congenital diaphragmatic hernia.

Recently, it has become possible to measure fetal lung volume by either three-dimensional (3D) ultrasound examination or magnetic resonance imaging (MRI)[13–17]. The advantage of MRI is that both the ipsilateral and contralateral lungs can be visualized and measured reliably, whereas with 3D ultrasound imaging it is not possible to examine the ipsilateral lungs in nearly half of cases[18]. Relatively few studies have examined the potential value of total fetal lung volume (TFLV), as measured by MRI, in the prediction of outcome (Table 1)[17,19–23]. So far, the number of patients examined has been too small to draw definitive conclusions, let alone allow assessment of confounding factors, such as intrathoracic herniation of the liver or gestational age at delivery, which have a profound impact on survival.

The purpose of this multicenter study, involving 148 cases of isolated CDH that were liveborn after 30 weeks of gestation and had postnatal follow-up until death or discharge from the hospital, was to investigate the potential value of prenatal MRI in the prediction of postnatal outcome.

## METHODS

### Study subjects and design

This was a retrospective multicenter study of the antenatal findings and postnatal outcome of fetuses with CDH examined in fetal medicine and radiology units. The participating centers provided the necessary data, which were entered into a central antenatal-CDH-Registry. In all cases the patients were assessed by, and received counseling from, a multidisciplinary team composed of fetal medicine specialists, neonatologists and pediatric surgeons. Patients were offered the following management options: expectant management and timed delivery in a tertiary center with optimal postnatal care or, for severe cases (i.e. LHR < 1.0 and intrathoracic liver), either fetal surgery or termination of pregnancy. The study was approved by the Institutional Review Board.

For patients who opted for expectant management, we searched the database to identify all consecutive fetuses with CDH diagnosed from the year 1995 onwards that fulfilled the following criteria: first, no major associated abnormalities diagnosed either prenatally or postnatally; second, live birth after 30 weeks of gestation and postnatal follow-up until death or discharge from hospital; third, assessment of the presence or absence of intrathoracic liver herniation and measurement of fetal TFLV by MRI.

In some of the fetuses an ultrasound examination was carried out and the LHR was measured within 2 weeks of MRI; in these cases TFLV and LHR were compared for their ability to predict postnatal survival.

### Magnetic resonance imaging

MRI was performed on a clinical 1.5-T whole-body unit. Patients were positioned in a left lateral position to prevent supine hypotension syndrome, with a combined six-channel phased-array body coil and a two-channel spine coil positioned over the lower pelvic area. The MRI protocol comprised only T2-weighted images. Geometric parameters of the T2-weighted images according to the machine used have been described previously[15,17]. T2-weighted images were obtained using a single-shot half-Fourier turbo spin echo (HASTE) sequence in orthogonal transverse, coronal and sagittal planes according to the fetal orientation. No breath-hold was requested of the patient.

In each center, the radiologist adjusted the field of view and the number of sections and image orientation for each fetus as required for optimal measurement of lung volumes[24]. Sequences that were degraded by fetal motion were repeated with the same parameters. Mean ± SD examination time was 15 ± 5 min. In all examinations, the side of CDH as well as the intrathoracic position of the liver was noted, as reported by MRI.

### Magnetic resonance planimetry

Planimetric measurements of lung volumes were all performed by radiologists in each of the participating
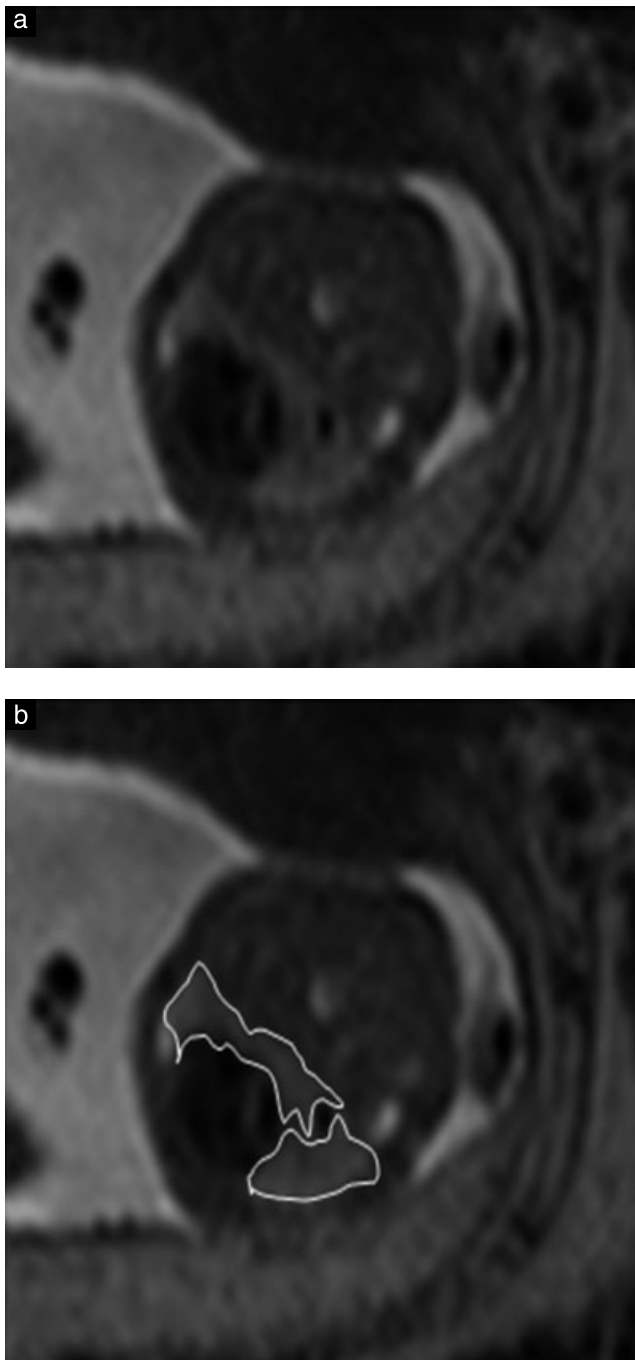
**Figure 1** Fetus with a left-sided congenital diaphragmatic hernia at 29 weeks of gestation. T2-weighted magnetic resonance image (echo time 88 ms, slice thickness 4 mm, field of view 300 × 300 mm, matrix 173 × 256) showing an axial view at the thoracic level without (a) and with (b) delineation of both lungs.

centers. Lung volumes were calculated on the T2 HASTE sequences in the transverse plane, using sequences that allowed complete imaging of both lungs and volume without motion-induced artifacts.

Lung areas were determined on each section by using free-form regions of interest on PACS (Impax, Agfa-Gevaert, Mortsel, Belgium). The measured areas were added and multiplied by the slice thickness to determine the entire volume of the right and left lungs. Volumes of right and left lungs were added to obtain the total lung volume of the fetus (Figure 1). The time required to perform these measurements ranged between 5 and 10 min for both lungs. The radiologist who performed these measurements was not aware of the two-dimensional (2D) ultrasound LHR findings.

## Lung area to head circumference ratio measurement

In all centers measurement of the lung area was as previously described. It involved, first, obtaining a transverse section of the fetal chest demonstrating the four-chamber view of the heart and, second, multiplying the longest diameter by the longest perpendicular of the contralateral lung (Figure 2)[10]. The LHR was derived by dividing the lung area by the head circumference measurement.



**Figure 2** Measurement of the lung area in a section through the four-chamber view in a fetus with a left-sided congenital diaphragmatic hernia and intrathoracic liver, at 31 weeks of gestation. The contralateral lung area is measured by multiplying the longest axis and that perpendicular to it.

## Data and statistical analysis

In each case the measured TFLV or LHR was expressed as a percentage of the previously reported respective appropriate normal mean for gestational age (observed to expected (o/e) ratio)[15,25].

Univariate regression analysis was used to investigate the effect on survival of gestational age at diagnosis of the CDH, o/e TFLV, gestational age at MRI, gestational age at delivery and date of delivery (year) as numerical variables, and intrathoracic herniation of the liver (yes or no), side of CDH (left or right) and institution in which the patient was managed as categorical variables. Multiple logistic regression analysis was subsequently performed to determine the significant independent contribution of variables with $P < 0.05$ in the univariate analysis. Regression analysis was used to investigate the effect on survival of o/e TFLV separately in fetuses with and those without intrathoracic herniation of the liver.

In cases in which both MRI and ultrasound examination were carried out within 2 weeks of each other, receiver–operating characteristics (ROC) curves were constructed to examine the prediction of survival by o/e TFLV and o/e LHR.

The data were analyzed using the statistical software packages SPSS 13.0 (Chicago, IL, USA) and Excel for Windows 2000 (Microsoft Corp., Redmond, WA, USA). Two-sided $P < 0.05$ was considered statistically significant.

## RESULTS

### Characteristics of the study population

The search of the antenatal-CDH-Registry identified 148 patients who fulfilled the entry criteria for the prediction based on MRI images, and 76 patients in whom both ultrasound and MRI data were available. These patients were examined antenatally in one of the following units: University Hospital Gasthuisberg (Leuven, Belgium), Hôpital Necker Enfants Malades (Paris, France), Hospital Clinic (Barcelona, Spain) and Hôpital Jeanne de Flandre (Lille, France).

### Regression analysis in the prediction of postnatal survival

Univariate regression analysis demonstrated that significant predictors of survival were the presence or absence of intrathoracic herniation of the liver, side of the CDH, o/e TFLV and place of neonatal management (Table 2). Multiple regression analysis demonstrated that the only significant independent predictors of survival were liver herniation and o/e TFLV.

Of the 63 cases with intrathoracic herniation of the liver, 29 (46.0%) infants survived after delivery at 32–41 (median, 39) weeks and the rate of survival increased with o/e TFLV ($P = 0.004$) (Table 3 and Figure 3). Among the 34 infants that died, the primary cause of death was pulmonary hypoplasia and/or hypertension. Of the 85 cases in which the liver was confined to the abdomen, 66 (77.6%) infants survived after delivery at 34–41 (median, 39) weeks and the rate of survival increased with o/e TFLV ($P = 0.001$) (Table 3 and Figure 3). In 17/19 infants without liver herniation who died the primary cause of death was pulmonary hypoplasia and/or hypertension, and in two it was sepsis.

### Receiver–operating characteristics curve analysis

For the 76 cases that had both MRI and ultrasound measurements the area under the ROC curve for prediction of postnatal survival from o/e TFLV was 0.786 (standard error, 0.059; $P < 0.001$) and that from o/e LHR was 0.743 (standard error, 0.069; $P = 0.001$) (Figure 4).

**Table 3** Survival rate according to fetal observed to expected (o/e) total fetal lung volume (TFLV) in fetuses with and without intrathoracic herniation of the liver

| o/e TFLV (%) | Intrathoracic liver herniation | | No liver herniation | |
|---|---|---|---|---|
| | n | Survival (n (%)) | n | Survival (n (%)) |
| ≤ 25 | 17 | 2 (11.8) | 15 | 6 (40) |
| 26–35 | 16 | 6 (37.5) | 13 | 11 (84.6) |
| 36–45 | 14 | 9 (64.3) | 21 | 18 (85.7) |
| > 45 | 16 | 12 (75.0) | 36 | 31 (86.1) |
| Total | 63 | 29 (46.0) | 85 | 66 (77.6) |

**Table 2** Regression analysis for prediction of survival in fetuses with isolated diaphragmatic hernia managed expectantly

| | | Survival | | | |
|---|---|---|---|---|---|
| | | Univariate analysis | | Multivariate analysis | |
| Variable | n (%) or median (range) | OR (95% CI) | P | OR (95% CI) | P |
| Intrathoracic herniation of liver | | | | | |
| No | 85 (57.4) | 1 | | 1 | |
| Yes | 63 (42.6) | 0.25 (0.12–0.50) | < 0.0001 | 0.29 (0.12–0.67) | 0.004 |
| Side of CDH | | | | | |
| Left | 127 (85.8) | 1 | | 1 | |
| Right | 21 (14.2) | 0.36 (0.14–0.92) | 0.032 | 0.94 (0.30–2.96) | 0.915 |
| o/e total fetal lung volume (%) | 38 (6–92) | 1.07 (1.04–1.11) | < 0.0001 | 1.07 (1.04–1.10) | < 0.0001 |
| Gestational age at diagnosis (weeks) | 23 (16–37) | 0.99 (0.92–1.06) | 0.780 | | |
| Gestational age at MRI (weeks) | 31 (22–38) | 0.93 (0.85–1.02) | 0.112 | | |
| Gestational age at delivery (weeks) | 39 (32–41) | 1.04 (0.84–1.30) | 0.695 | | |
| Place of neonatal management | | | | | |
| Paris | 77 | 1 | | | |
| Leuven | 33 | 2.64 (1.02–6.83) | 0.045 | 1.96 (0.68–5.62) | 0.211 |
| Lille | 27 | 0.77 (0.32–1.85) | 0.553 | | |
| Barcelona | 11 | 7.11 (0.87–58.36) | 0.068 | | |
| All centers other than Leuven | 115 | | | 1 | |
| Year of management | 2003 (1996–2007) | 1.05 (0.92–1.19) | 0.452 | | |

CDH, congenital diaphragmatic hernia; MRI, magnetic resonance imaging; o/e, observed to expected; OR, odds ratio.
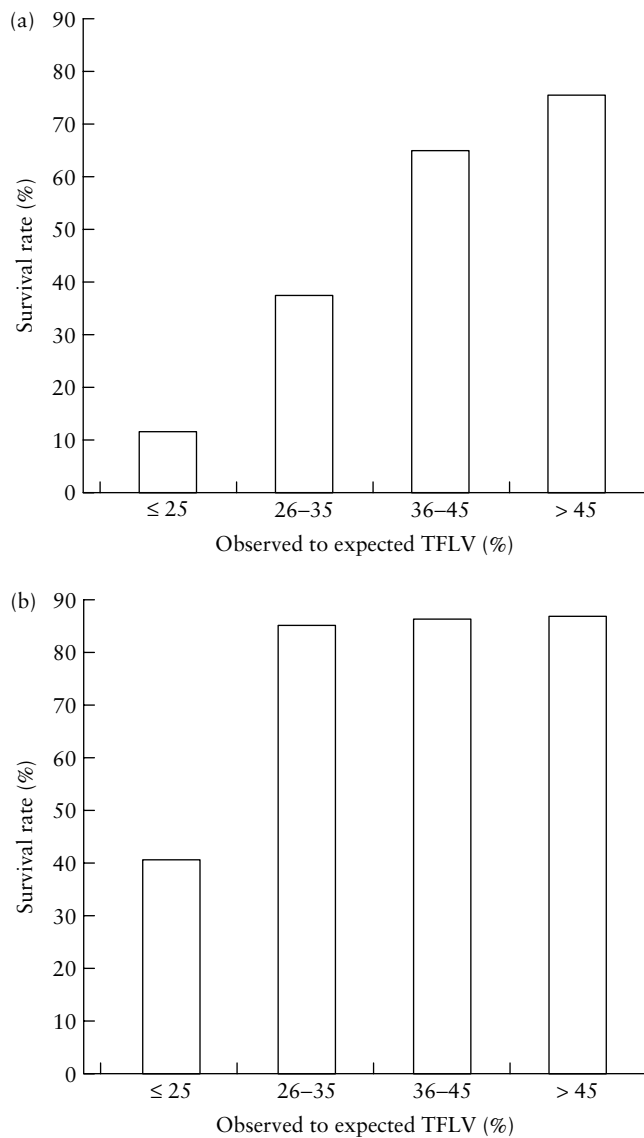
(a)


(b)


**Figure 3** Survival rate according to the fetal observed to expected total fetal lung volume (TFLV) in fetuses with isolated diaphragmatic hernia with (a) and without (b) intrathoracic herniation of the liver.

In view of the small number of cases examined it was not possible to test the significance of differences between the areas under the curves. A minimum of 565 patients would be needed to provide a probability of 80% of detecting a difference between the area under the ROC curve for MRI and that for ultrasound examination[26].

## DISCUSSION

The findings of this study demonstrate that in isolated CDH managed expectantly the rate of postnatal death is about 40%, primarily due to pulmonary hypoplasia and/or hypertension. Furthermore, the data show that lung size and intrathoracic herniation of the liver as determined by MRI provide independent prediction of subsequent postnatal survival at discharge from hospital, whereas side of the CDH, gestational age at diagnosis and
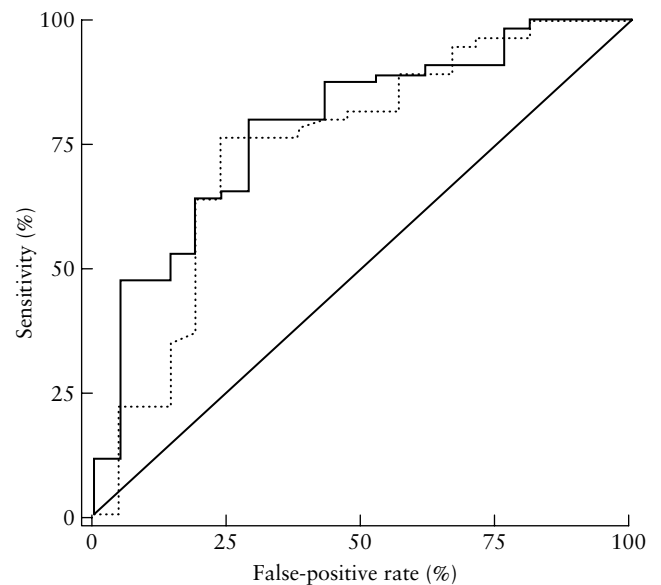


**Figure 4** Receiver–operating characteristics curves for prediction of postnatal survival according to cut-off values of observed to expected total fetal lung volume measured by magnetic resonance imaging (——) and lung area to head circumference ratio measured at ultrasound examination ( · · · · · · ) in fetuses with isolated congenital diaphragmatic hernia. The diagonal line is the reference line.

delivery, year and institution in which the patient was managed do not.

In the group with intrathoracic herniation of the liver there was a direct correlation between higher o/e TFLV at 22–38 weeks of gestational age and higher survival rates. Essentially, the survival rate increased from 12% for those with an o/e TFLV of $\leq 25\%$, to about 40% for an o/e TFLV of 26–35%, 60% for an o/e TFLV of 36–45% and more than 70% for an o/e TFLV of $\geq 46\%$. In the group with no intrathoracic herniation of the liver, the survival rate was around three times higher in the group with an o/e TFLV of $\leq 25\%$, with a 40% survival rate; however, this was substantially smaller than the survival rates of at least 80% in all groups with an o/e TFLV > 25%. These findings are compatible with a recent large multicenter study on 354 fetuses with isolated CDH assessed by o/e LHR[25].

In a recent study comparing prediction of postnatal survival in 47 fetuses with isolated CDH using o/e LHR calculated by the longest-axis method (as used in the present study), o/e LHR acquired by the tracing method, and o/e contralateral lung volume measured by 3D ultrasound examination, it was shown that the best prediction was provided by the 2D measurement of LHR with the tracing method and that 3D measurement of contralateral lung volume was no better than o/e LHR calculated by the longest-axis method[27]. The lung volume measurement did not take into account the ipsilateral lung volume because it was shown previously that reliable measurement of the ipsilateral lung is not possible by 3D ultrasound examination, but only by MRI[18]. In another study we showed that the contralateral

lung area measurement acquired using the longest-axis method provided a good estimate of the TFLV measured by MRI[28]. In the latter study, ipsilateral lung volume could be measured by MRI in all 191 cases. However, there were inconsistencies between the two methods and such inconsistencies were dependent on the relative contribution of the ipsilateral lung volume.

In the present study, 76 fetuses were assessed with both methods within 2 weeks of each other. Comparison of prediction of postnatal survival by o/e LHR using the longest-axis method and o/e TFLV by MRI showed that there was a trend towards a better prediction with total lung volume measurement by MRI, but the numbers were too small to show a significant difference between the methods. These findings are interesting and need to be confirmed in prospective studies using the most reliable method of 2D measurement of lung area, namely the tracing method[29,30].

We acknowledge that our study has some limitations. First, it was a retrospective analysis. On the other hand, at the moment it represents the largest study on isolated CDH assessed prenatally by MRI. Second, intrathoracic liver position was assessed in a non-quantitative way. In a study that has quantified intrathoracic liver in 43 expectantly managed cases of isolated CDH using a single dimension measurement, the resulting liver/diaphragm ratio was shown to be predictive of postnatal outcome[22]. It would therefore certainly be of interest to explore the latter parameter further.

In conclusion, we have shown in fetuses with isolated CDH that o/e TFLV and intrathoracic liver herniation, as determined by MRI at 22–38 weeks, are independent predictors of postnatal survival at discharge from hospital. We have also shown a trend towards a better prediction with o/e TFLV by MRI rather than with o/e LHR measured by 2D ultrasound examination; this should be validated in further studies. Finally, we have calculated survival rates in empirically chosen subgroups of o/e TFLV with and without intrathoracic liver herniation, which may be used when counseling patients carrying fetuses with isolated CDH.

## ACKNOWLEDGMENTS

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