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Fetal ultrasound markers of severity predict resolution of pulmonary hypertension in congenital diaphragmatic hernia

Leslie A. LUSK, MD[1], **Ms Katherine C. WAI, BS**[2], **Anita J. MOOD-GRADY, MD**[3], **Amaya BASTA, MD**[4], **Roy FILLY, MD**[4], and **Roberta L. KELLER, MD**[1,3]

[1]Department of Pediatrics, Division of Neonatology, Benioff Children's Hospital, University of California, San Francisco

[2]School of Medicine, University of California, San Francisco

[3]Fetal Treatment Center, University of California, San Francisco

[4]Department of Radiology and Biomedical Imaging, University of California, San Francisco Medical Center

Abstract

Objective—Congenital diaphragmatic hernia (CDH) results in morbidity and mortality due to lung hypoplasia and persistent pulmonary hypertension (PH). We sought to define the relationship between fetal ultrasound markers of severity in CDH and the time to resolution of neonatal PH.

Study design—We conducted a retrospective study of fetuses with an antenatal ultrasound and left-sided CDH cared for at the University of California San Francisco (2002–12). Fetal liver position was classified on ultrasound as abdominal (entire liver within the abdomen) or thoracic (any portion of the liver within the thorax). Fetal stomach position was classified from least to most aberrant: abdominal, anterior left chest, mid-posterior left chest, or retrocardiac (right chest). Lung-to-head ratio (LHR) was determined from available scans at 20–29 weeks gestational age (GA). Routine neonatal echocardiograms were performed weekly for up to 6 weeks or until PH resolved, or until discharge. PH was assessed by echocardiogram using a hierarchy of ductus arteriosus level shunt, interventricular septal position, and tricuspid regurgitant jet velocity. Days to PH-free survival was defined as the age at which pulmonary artery pressure was estimated to be <2/3 systemic blood pressure. Cox proportional hazards models adjusted for GA at birth, era of birth, fetal surgery, and GA at ultrasound (LHR model only), with censoring at 100 days.

Results—Of 118 patients, fetal markers were available as follows: LHR (n=53), liver position (n=112), and stomach position (n=80). Fewer infants resolved PH if they had LHR<1 (p=0.006),

CORRESPONDNG AUTHOR: Leslie A. Lusk, MD, Division of Neonatology, Box 0748, 533 Parnassus Ave., UC Hall, Room 503, San Francisco, CA 94143, Phone: 415-476-1888; Fax: 415-476-9976; Leslie.Lusk@ucsf.edu.

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thoracic liver position (p=0.001), or more aberrant stomach position (p<0.001). There was also a decreased rate of resolution of PH in infants with LHR <1 (hazard ratio 0.30, p=0.007), thoracic liver position (hazard ratio 0.38, p<0.001), and more aberrant stomach position (hazard ratios 0.28, p=0.002; 0.1, p<0.001; 0.07 p<0.001).

Conclusion—Fetal ultrasound markers of CDH severity are predictive not just of mortality but also of significant morbidity. LHR<1, thoracic liver, and aberrant stomach position are associated with delayed time to resolution of PH in infants with CDH and may be used to identify fetuses at high risk of persistent PH.

Keywords

Pulmonary vascular resistance; ultrasound; lung-to-head ratio

INTRODUCTION

Congenital diaphragmatic hernia (CDH) occurs in 1:4,000–5000 live births and is associated with significant morbidity and mortality.[1,2] Contemporary care strategies have dramatically improved the survival of these infants, particularly at referral centers.[3,4] Though this improvement is substantial, many of these infants are surviving with significant morbidity related to their pulmonary hypoplasia and pulmonary hypertension (PH) leading to prolonged need for assisted ventilation, home oxygen use, re-hospitalization, developmental delay, and complicated medication use.[5–9]

Despite the high rates of morbidity, research in this population has thus far focused heavily on only mortality and need for extracorporeal membrane oxygenation (ECMO). As such, antenatal sonographic markers of severity in fetuses with CDH have primarily been used to predict mortality and the need for ECMO, as well as to select candidates for fetal intervention. The lung-to-head ratio (LHR), particularly LHR<1, [10–18] and thoracic liver position (as compared to abdominal position) have been shown to be predictors of both death and need for ECMO use.[11,14–16,18,19] More recently it has been demonstrated that increasingly abnormal stomach position is a strong predictor of not only death and ECMO, but also need for prolonged neonatal respiratory support.[20] This is likely due to the relationship of stomach position to liver position.[21,22]

We and others have shown that persistence of PH beyond 2 to 3 weeks of life is associated with poor neonatal outcomes and thus there may be benefits to early identification of these infants at high risk of morbidity for antenatal counseling, selection for fetal intervention, and targeting future early neonatal therapies.[8,23,24] This makes the prediction of persistent PH in infants with CDH an important and useful determination during fetal life. This study is the first to assess the ability of fetal LHR, liver position, and stomach position to predict both resolution of PH and the time required to achieve its resolution.

MATERIALS AND METHODS

Patient Data

We performed a retrospective cohort study of fetuses with antenatal ultrasound and left-sided Bochdalek-type congenital diaphragmatic hernia at our center, who were subsequently cared for after birth at the University of California San Francisco Benioff Children's Hospital (2002–12). Fetuses were included if they had ≥ 1 neonatal echocardiogram and excluded if they had multiple congenital anomalies or a known or suspected syndrome. Clinical data were collected by chart review. Echocardiograms were re-reviewed by a reader blinded to clinical data. The outcome of interest was days to resolution of pulmonary hypertension, defined as the chronological age at which the echocardiogram estimated <2/3 systemic systolic pulmonary arterial pressure. Chronic lung disease was defined as requirement for any respiratory support at 56d of age or home oxygen if discharged earlier than 56d.[25] Patients were managed using gentle ventilation and lung-sparing strategies as previously described.[23,24] The Institutional Review Board of the University of California San Francisco approved this study.

Imaging and echocardiographic data

Fetal sonographic markers of interest included the lung-to-head ratio (LHR), liver position and stomach position. LHR measurements were gathered from ultrasound reports or, if absent from the report, were directly measured from stored images, when available, by a single radiologist blinded to clinical outcome. LHR was only included in the analysis if the measurement was taken from a sonogram performed at 20–29 weeks gestational age (GA). All lung dimensions were measured on a transaxial view of the fetal chest at the level of the four-chamber view of the heart. The technique consistently used and reported at UCSF uses the aorta and lateral rib as landmarks for the lateral measurement, with the orthogonal anterior-posterior (AP) diameter measured from the cardiac atria to the posterior rib, then dividing by the head circumference.[15,26] All analyses were done first including scans from 22 through 27 weeks' GA [10,11] and then expanding to 20 to 29 weeks' GA. As results did not differ when using these two inclusion criteria, data from the broader range of ages are presented to increase the information provided in our analyses. Liver position was gathered from fetal ultrasound reports, and verified by operative report from CDH repair, if surgery was performed. Six infants, all with intrathoracic liver on fetal sonography, died prior to surgical repair and thus liver position could not be verified. Liver position was categorized as abdominal (defined as entire liver within the abdomen) or intrathoracic (defined as any portion of the liver herniated into the thoracic cavity).

A single radiologist blinded to neonatal outcomes reviewed the initial fetal sonogram performed at our institution to determine stomach position when adequate images were available. Stomach position was classified based on the degree of herniation into the thoracic cavity while viewing the fetal thorax in the true axial plane at the level of the four-chamber view of the heart. Positions included abdominal, anterior left chest (defined as a portion of the fetal stomach contacting the anterior chest wall), mid-to-posterior left chest (defined as not contacting the anterior left chest wall and either contacting or possibly

contacting the posterior left chest wall), or retrocardiac (defined as at least a portion of the stomach located posterior to the left atrium of the heart within the right chest).

Echocardiogram Protocol

Beginning in 2002, all infants with CDH underwent echocardiograms (Acuson Sequoia C256 and C512 and SC2000, Mountain View CA), per routine clinical protocol, within the first 48 hours of life and then weekly for the first 6 weeks of life or until resolution of pulmonary hypertension, death, or discharge. Standard clinical views were obtained to estimate the degree of elevation of pulmonary arterial pressure relative to systemic systolic blood pressure. Echocardiograms were classified into one of two categories: less than 2/3 systemic systolic pressures (no/mild PH) and greater than or equal to 2/3 systemic systolic pressures (PH). Classifications were made using a hierarchy of measurements involving (1) direction and velocity of flow via the ductus arteriosus (2) interventricular septum position and (3) peak tricuspid regurgitant (TR) jet velocity, by the modified Bernoulli equation and assuming right atrial pressure as 0 mmHg, as previously described.[23,24]

Statistical Analysis

Between groups univariate comparisons were made using Chi squared, Student's t-test, Mann Whitney rank-sum, Kruskal Wallis, and ANOVA tests where appropriate. Kaplan Meier curves were compared using Log-rank tests. Cox proportional hazards multivariate models were created to assess the relationship between fetal markers of CDH severity and time to resolution of PH. Infants were censored at 100 days; infants who died were treated as being alive and never having resolved their PH and were censored at 100d of age to avoid informative censoring. We adjusted for GA at birth, era of birth (2002–2005, 2006–2008, and 2009–2012), history of fetal tracheal occlusion, and, for the LHR model only, GA at sonography. Finally, a Harrell's C statistic was generated for each model to assess the predictive accuracy of each fetal marker in predicting time to resolution of PH (Stata 12.0 software; College Station, TX).

RESULTS

We identified 118 infants with left-sided CDH who had fetal sonography at UCSF. Cohort characteristics are described in Table 1. The cohort was predominantly term, with an overall mortality of 19% (23/118). Seventy-three percent (86/118) resolved their PH prior to death or discharge (Figure 1), with a median time to resolution, among those who resolved, of 14d (IQR 9, 20). Lung-to-head ratio was available in 89 (75%) patients, 53 of which were obtained from 20–29 weeks GA and thus included in the final analysis. There were 29 subjects in whom LHR was not noted in the fetal ultrasound report and original images were unavailable for primary review. Of the 118 subjects, 80 (68%) had adequate images available for determination of stomach position. Liver position was documented in 112 fetuses. The distribution of these measurements is shown in Table 2. There were no obvious differences in newborn characteristics between sub-cohorts, as determined by fetal measurement (Table 1). Additionally, there was no difference in proportion of subjects with available measurements by era across the 10-year study period for liver position, stomach

position, or LHR and thus no suggestion of bias introduced by differential missing data by era.

Infants with an LHR<1 had increased death prior to discharge (58% versus 18%, p=0.001), increased need for ECMO (32% versus 6%, p=0.012), and increased incidence of chronic lung disease (75% versus 14%, p=0.001) compared to infants with an LHR≥1. Additionally, a lower proportion of infants with LHR<1 had resolution of their PH prior to death or discharge (42% versus 76%, p=0.012, Figure 2) as well as a longer time to resolution of PH among those who ultimately resolved (median 22d versus 14d, p=0.003). After adjusting for GA at birth and GA at the time of fetal ultrasound, fetal tracheal occlusion, and era of birth, infants with LHR<1 continue to have a prolonged time to resolution (Table 3). However, LHR is only a moderate predictor of rate of resolution of PH with a C statistic of 0.68.

Infants with an intrathoracic liver had increased death prior to discharge (37% versus 2%, p<0.001), increased need for ECMO (25% versus 0%, p<0.001), and increased incidence of chronic lung disease (40% versus 10%, p<0.001) as compared to those with an abdominal liver position. A lower proportion of those with an intrathoracic liver had resolution of their PH (60% versus 88%, p=0.001, Figure 3) as well as a longer time to resolution (median 17d versus 11d, p=0.001), among those who ultimately resolved. After adjusting for GA at birth, fetal tracheal occlusion, and era of birth, infants with intrathoracic liver position continued to have a prolonged time to resolution (Table 3). Liver position is also only a moderate predictor of rate of resolution of PH with a C statistic of 0.66.

Increasing herniation of stomach into the thoracic cavity (abdominal versus anterior left chest versus mid-to-posterior left chest versus retrocardiac/right chest) was also associated with increasing risk of death (0%, 6%, 29%, and 60%, respectively, p<0.001), increasing need for ECMO (0%, 0%, 15%, and 47%, p=0.001), and increasing incidence of chronic lung disease (8%, 18%, 38%, and 67%, p=0.03). Furthermore, the proportion of those who ultimately resolved their PH decreased with progressive malposition of the stomach (100%, 94%, 62%, and 47%, p<0.001, Figure 4) while the time to resolution increased (median 9d, 15d, 17d, and 22d, p=0.002). After adjusting for GA at birth, fetal tracheal occlusion, and era of birth, infants with progressively abnormal stomach position continued to have a prolonged time to resolution (Table 3). Stomach position is a somewhat better predictor of rate of resolution of PH with a C statistic of 0.73.

In a sensitivity analysis, evaluations of the effect of fetal markers on time to resolution of PH were repeated with censoring at the time of death for those infants who expired at < 100d of age. There were no substantial effects on the estimated Hazard Ratios (data not shown).

COMMENT

Despite recent improvements in care strategies, congenital diaphragmatic hernia remains a challenging problem for providers both pre- and postnatally. Not only are providers faced with the challenge of predicting mortality, but as survival improves, we must begin to consider the significant morbidities faced by this population. Persistent pulmonary hypertension is a commonly seen in this population and, when persistent, it is well known to

be a major cause of mortality and morbidity among infants with CDH. Despite this, fetal sonographic markers that are routinely used in evaluation of CDH have not been used to predict persistent PH in these infants. In this study, we demonstrate that fetal ultrasound markers previously found to be associated with neonatal survival, including LHR ≥1, abdominal liver position and less abnormal stomach position, are also strongly associated with a decreased time to resolution of PH.

As treatment strategies evolve, the survival rate for CDH continues to improve, from 50% in previous eras, to 75–90% in single center reports.[3,4,27] However, among survivors, pulmonary hypertension remains a major cause of morbidity [5,6,8,23,28]. We have recently confirmed, in a large cohort, that the persistence of PH, as defined in the current study, was itself a biomarker of severe disease in infants with CDH, predicting prolonged ventilation, prolonged respiratory support of any level, need for supplemental home oxygen, and death.[24] The current study extends these findings to quantitative antenatal measurements, showing that resolution of PH, as well as the timing of resolution, can be predicted from fetal ultrasound markers already being widely employed. Progressively abnormal fetal measurements are associated with a delay in the usual neonatal fall in pulmonary vascular resistance. Healthy term newborns achieve an estimated pulmonary arterial pressure < 2/3 systemic pressure by 24 hours of life,[29] yet infants with CDH with even the best outcomes do not achieve this milestone until 1–3 weeks of age.[24] Infants with CDH with estimated pulmonary arterial pressures that remain elevated beyond this time are those at highest risk for poor outcomes and thus may benefit from early identification. As fetal intervention and treatment strategies continue to develop, fetuses and infants may be specifically targeted for antenatal or early neonatal intervention based on unfavorable fetal markers, making these even more valuable for patient and provider decision-making over time.

Our results support recent studies concluding that lower LHR, o/e LHR, o/e total fetal lung volume, and intrathoracic liver position were predictive of an increased incidence of PH.[30–32] The current study utilizes our validated approach to the definition and the timing of the assessment of PH in newborns with CDH, [23,24] and thus it expands the findings from other groups by evaluating PH as an outcome *over time*, in relationship to fetal measurements. A major strength of our study is the use of routine weekly echocardiograms for all infants with CDH. With this clinical protocol, we have not only added the ability to assess resolution of PH over time, but we have also removed the potential selection bias in studies using data from echocardiograms obtained only for clinical indications.[8,28,32] Thus, we have determined not only the ultimate resolution of PH, but also an unbiased quantification of the time to its resolution.

Currently, fetal assessment of diaphragmatic hernia is done through measurement of various fetal parameters by both magnetic resonance imaging (MRI) and ultrasonography. While MRI assessment of fetal lung volume has utility, it may be limited due to cost, availability, and expertise required for interpretation. Sonographic measurements that are frequently used include the lung-to-head ratio (with or without use of the observed-to-expected LHR), liver position, and more recently, stomach position. Our current data confirm the results of previous studies showing increased mortality and use of ECMO in patients with LHR <1, liver herniated into the thorax and more aberrant stomach position.[10–18,32] This is despite

the previously noted limitations of these measurements, which include challenges in accurate determination of liver position due to difficulties in distinguishing liver from lung by fetal ultrasound,[11,14–16,18,19,22] the difficult learning curve to achieve competency,[33] moderate inter-observer agreement and change in LHR with GA (which may or may not be improved by the use of observed-to-expected LHR),[16,18,32] and the variability in classification of stomach position, from current proposals in the literature.[20,21,34,35]

Our study was limited in its ability to accurately measure pulmonary arterial pressures. Cardiac catheterization is the gold standard for the assessment of pulmonary arterial pressures, though this procedure is invasive so not repeatedly used in this population. Previous work in infants with congenital heart disease has shown Doppler echocardiography to produce accurate estimates of pulmonary arterial pressures.[36] In infants with chronic lung disease (including infants with CDH), Mourani and colleagues found TR jet alone did not accurately predict PH by cardiac catheterization; however, multiple echocardiographic parameters together did predict PH.[37] Similarly, our previous work shows that utilizing the hierarchy of echocardiographic measurements employed in this study, echocardiographic findings are related to important clinical outcomes, despite the lack of confirmation by cardiac catheterization.[24]

Another limitation of our study concerns the accuracy and availability of the LHR measurement as it is dependent on GA. Since just over half of our study population had available LHR measurements within our defined GA window, there could be bias in our analysis related to LHR. However, we found no difference in the demographics or clinical outcomes of infants based on available sonographic measurements (Table 1). Further, we have shown that there is no difference in the proportion of subjects with missing data across the study period. It is known that LHR increases in a non-linear fashion as GA increases[38] and as such, a variety of ranges for GA have been analyzed to assess ability to predict outcome. Yang et al. found that LHR was more accurate when measured at 24–34 weeks' GA, and less so at 20–24 weeks' GA, while Jani et al. showed that LHR at 22–28 weeks' GA in fetuses with intrathoracic liver position was strongly predictive of neonatal outcome. Other studies have suggested using an observed-to-expected (o/e) LHR since it may be independent of GA,[38,39] though recent evidence by Quintero et al. call this into question.[40] Their results demonstrate that o/e LHR is not independent of GA and should also be interpreted with caution. In this study, we have focused on LHR rather than o/e LHR and included only measurements from fetuses at 20–29 weeks' GA. Of note, the majority of included measurements lie within previously accepted ranges, with a median gestational age of 24.2 weeks (IQR 22, 26). As noted, our results did not change with this wider inclusion period in comparison to measurements obtained from 22–27 weeks' GA. Further, despite this potential limitation, we found that an LHR <1 is associated with a decreased survival and an increased use of ECMO, as previously shown by others.

Conclusions

In conclusion, we have shown that fetal ultrasound markers of survival in CDH are also strongly associated with time to resolution of pulmonary hypertension. LHR ≥1, abdominal liver position, and less abnormal stomach position are favorable antenatal prognostic signs

for short-term morbidity. Incorporation of these findings can be useful during prenatal counseling and may identify individual high-risk fetuses who might benefit from intrauterine or early neonatal interventions, as PH is both a major cause of morbidity and a marker of illness severity in CDH. Given the close relationships of various fetal markers, future studies with a larger sample size might define an antenatal decision algorithm to identify combinations of findings yielding prediction of the fetuses at highest risk for neonatal morbidity or mortality.

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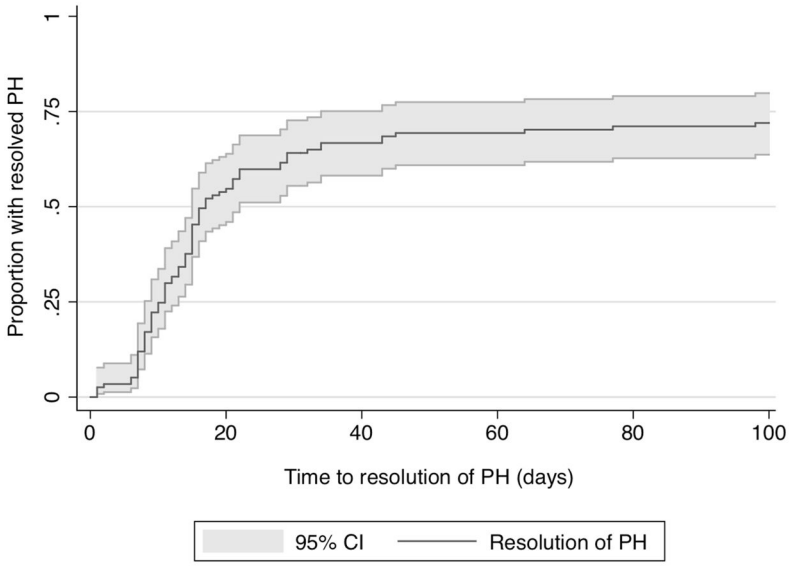

Figure 1. Time to resolution of pulmonary hypertension

Kaplan Meier curve of time to resolution of pulmonary hypertension in all patients, with 95% confidence interval.

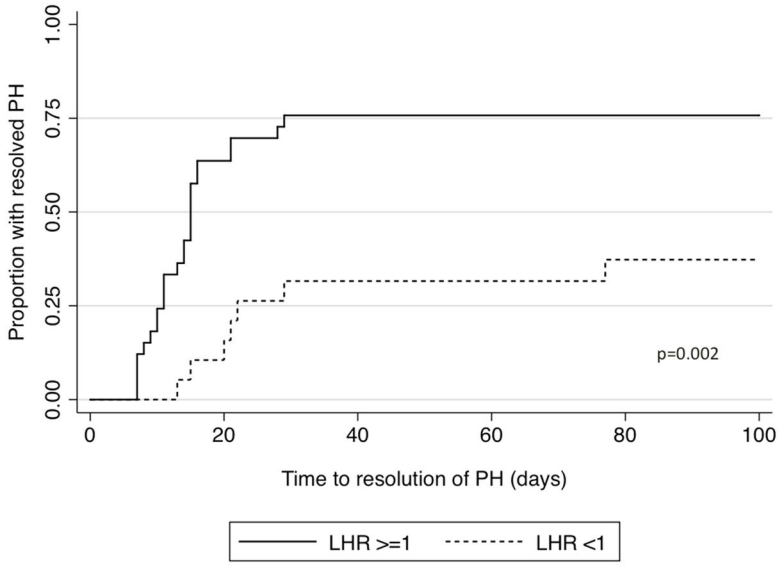

Figure 2. Time to resolution of pulmonary hypertension by lung-to-head ratio

Kaplan Meier curve of time to resolution of pulmonary hypertension by LHR. (Black solid) LHR ≥1 and (black dash) LHR <1. Curves differ significantly by logrank test, p=0.002.

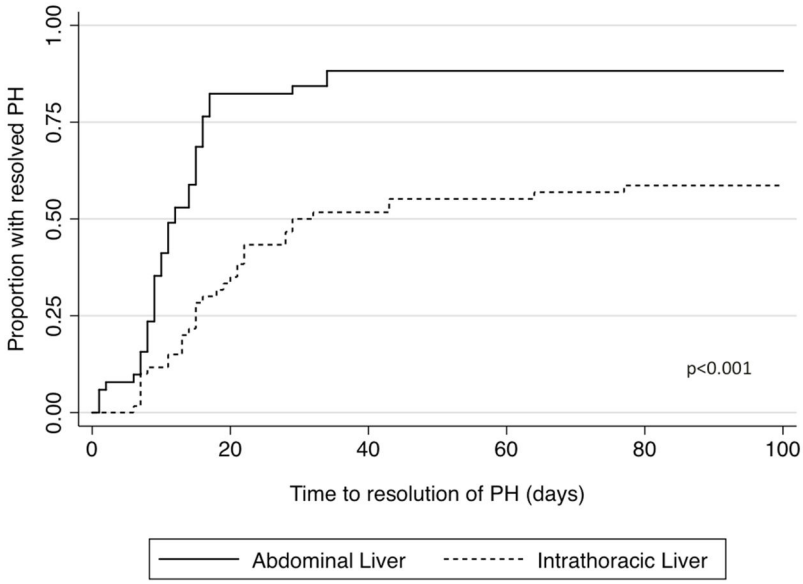

Figure 3. Time to resolution of pulmonary hypertension by liver position

Kaplan Meier curve of time to resolution of pulmonary hypertension by liver position. (Black solid) Abdominal liver position and (black dash) intrathoracic liver position. Curves differ significantly by logrank test, p<0.001.

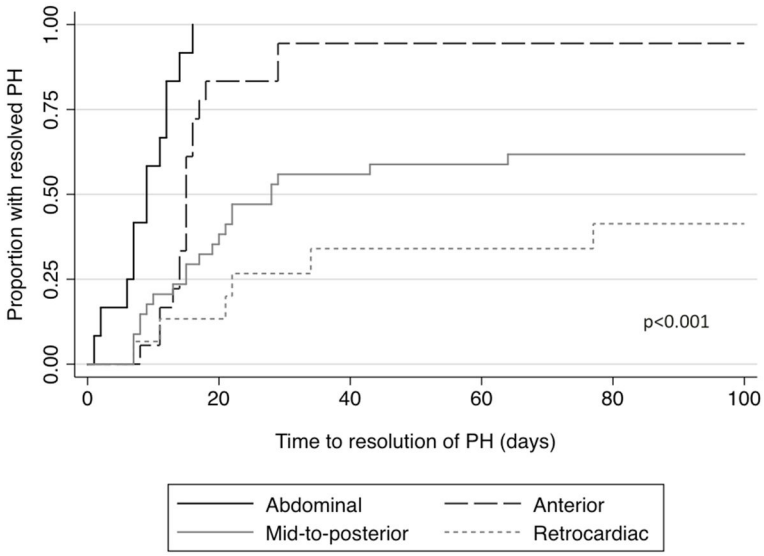

Figure 4. Time to resolution of pulmonary hypertension by stomach position

Kaplan Meier curve of time to resolution of pulmonary hypertension by stomach position. (Black solid) abdominal, (black dash) anterior, (grey solid) mid-posterior, and (grey dash) retrocardiac stomach position. Curves differ significantly by logrank test, p<0.001.

Table 1

Characteristics of 118 Infants with CDH and Fetal Imaging

Neonatal characteristics	All infants N= 118	LHR available* N=53	Liver position available N=112	Stomach position available N=80
Gestational age (weeks)	38 (±2.3)	37 (±2.6)	38 (±2.3)	38 (±2.2)
Male sex	58% (68)	53% (28)	59% (66)	55% (44)
Fetal tracheal occlusion surgery	8% (9)	15% (8)	8% (9)	10% (8)
Year of birth				
2002 – 2005	30% (35)	26% (14)	29% (33)	29% (23)
2006 – 2008	25% (29)	23% (12)	25% (28)	25% (20)
2009 – 2012	46% (54)	51% (27)	46% (51)	46% (37)
Time to resolution of PH (median days, IQR)†	14 (9, 20)	15 (10, 21)	14 (9, 18)	15 (9, 21)
Death	19% (23)	32% (17)	21% (23)	25% (20)
ECMO	13% (15)	15% (8)	13% (15)	15% (12)
Chronic lung disease	23% (22)	28% (10)	22% (20)	28% (17)

Data reported as mean (± SD) or %(N) unless otherwise stated

*Patients only included if fetal ultrasound was performed between 20 and 29 weeks gestational age. Three infants excluded for scan under 20 weeks; 33 excluded for scan 29 weeks and over.

†Time to estimated pulmonary arterial pressures <2/3 systemic systolic pressures among those who resolved prior to death/discharge

Table 2

Fetal Ultrasound Characteristics

Ultrasound Parameter	
Lung to head ratio (LHR) (n=53)	1.2 (±0.5)
Gestational age (weeks) at US[§]	24 (±2.4)
LHR <1	36% (19)
Liver position (n=112)	
Abdominal	46% (52)
Intrathoracic	54% (60)
Stomach position (n=80)	
Abdominal	16% (13)
Anterior left chest	23% (18)
Mid-to-posterior left chest	43% (34)
Retrocardiac (right chest)	19% (15)

Data reported as mean (± SD) or %(N) unless otherwise stated

Table 3

Resolution of pulmonary hypertension by fetal ultrasound parameter

	Survival to DC	Resolved PH prior to death or DC	Time to resolution of PH (days) *	Adjusted† Hazard Ratio	95% CI	P value
	N (%)	N (%)	Median (IQR)			
Lung-to-head ratio (n=53)						
>=1 (n=34)	28 (82%)	26 (76%)	14 (9, 15)	Ref	Ref	n/a
<1 (n=19)	8 (42%)	8 (42%)	22 (18, 30)	0.3	(0.13, 0.72)	0.007
Liver position (n=112)						
Abdominal (n=52)	51 (98%)	46 (88%)	11 (8, 15)	Ref	Ref	n/a
Intrathoracic (n=60)	38 (63%)	36 (60%)	17 (12, 28)	0.38	(0.24, 0.61)	<0.001
Stomach position (n=80)						
Abdominal (n=13)	13 (100%)	13 (100%)	9 (6, 12)	Ref	Ref	n/a
Anterior left chest (n=18)	17 (94%)	17 (94%)	15 (14, 16)	0.28§	(0.13, 0.62)	0.002
Mid-to-posterior left chest (n=34)	24 (71%)	21 (62%)	17 (9, 22)	0.1§	(0.04, 0.23)	<0.001
Retrocardiac (n=15)	6 (40%)	7 (47%)	22 (11, 34)	0.07§	(0.02, 0.20)	<0.001

Abbreviations: PH - pulmonary hypertension; DC - discharge; IQR - interquartile range

Lower hazard ratios represent a decreased chance of resolution of pulmonary hypertension

* Time to estimated pulmonary arterial pressures <2/3 systemic systolic pressures among those who resolved prior to death/discharge

† After adjusting for gestational age, history of fetal surgery, birth era, and (for LHR model) gestational age at fetal ultrasound using Cox proportional hazards models