Pulmonary hypertension in congenital diaphragmatic hernia: antenatal prediction and impact on neonatal mortality

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What's already known about this topic?

- Pulmonary hypertension (PAH) in the neonatal period puts congenital diaphragmatic hernia (CDH) infants at risk for mortality.
- In CDH, mortality can be predicted antenatally by biomarkers of lung hypoplasia.
- Biomarkers of lung hypoplasia provide a moderate prediction of PAH.
- The search for better predictors should continue.

What does this study add?

- PAH is a strong and independent risk factor for mortality that can be effectively combined with antenatal biomarkers in a dynamic model to predict mortality more accurately.

ABSTRACT

Objective: To determine the prevalence of pulmonary hypertension(PAH) in left-sided congenital diaphragmatic hernia(CDH); how we could predict it; and how PAH contributed to the model for mortality prediction.

Study Design: Retrospective analysis in three European centers. The primary outcome was the presence of PAH on postnatal day(d)1,7, and at discharge. Studied predictors of PAH were: observed/expected-lung/head-ratio(o/e LHR), liver-herniation, FETO, and gestational age(GA) at delivery. The combined effect of pre-and postnatal variables on mortality was modeled by Cox regression.

Results: Of the 197 neonates, 56(28.4%) died. At d1, 67.5%(133/197) had PAH and 61.9% (101/163) by d7. Overall, 6.4% (9/141) had PAH at discharge.

At d1, o/eLHR(OR 0.96) and FETO(OR 2.99) independently correlated to PAH(AUC:0.74). At d7, PAH significantly correlated only with the use of FETO (OR 3.9;AUC:0.65). None were significant for PAH at discharge.

Combining the occurrence of PAH with antenatal biomarkers improved mortality prediction(p=0.02), in a model including o/eLHR(HR:0.94), FETO(HR:0.35), liver herniation(HR:16.78), and PAH(HR:15.95).

Conclusions: Antenatal prediction of PAH was only moderate. The postnatal occurrence of PAH further increases the risk of death. Whereas this may be used to counsel parents in the postnatal period, our study demonstrates there is a need to find more accurate antenatal predictors for PAH.

Keywords: congenital diaphragmatic hernia, pulmonary hypertension, prediction, survival, outcome.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is associated with significant neonatal mortality and morbidity[1]. Postnatal outcome is mainly determined by the severity of neonatal impaired gas exchange, hypoxemia, cardiac ventricular dysfunction, and CDH related pulmonary hypertension (PAH)[2]. Personalized prediction of neonatal outcome aids in counselling parents and when based on antenatal biomarkers also guides antenatal management[2]. The concept of fetal therapy of pulmonary hypoplasia has boosted the search for antenatal predictors that would permit the selection of fetuses at the highest risk of neonatal mortality or severe morbidity. Antenatal ultrasound is currently most widely studied to assess the degree of pulmonary hypoplasia and to predict survival[3]. The combination of the observed-to-expected lung-to-head ratio (o/e LHR) measured by ultrasound and, for left-sided CDH, liver herniation, is a validated method to predict survival and has been used in clinical trials[4-6].

However, the prediction of CDH related morbidity has been far less studied. To our knowledge, no robust algorithm has been established to predict the occurrence of PAH[7]. A recent meta-analysis showed that several groups have assessed selected antenatal predictors of PAH, but with variable sample size and heterogeneous results[7]. This could be due to the lack of standardization in postnatal diagnosis and management, as well as in the time point of assessment of PAH[7]. Antenatal prediction of PAH remains however of great clinical value, since PAH increases the risk for postnatal death, morbidity, and poor quality of life of survivors[8] and several groups are currently investigating antenatal treatment methods[9]. The objectives of this study are first, to determine the prevalence of PAH and refractory-PAH (r-PAH) in infants managed according to our current standardized perinatal protocol; second, to examine the accuracy of predicting PAH and r-PAH in the antenatal period, and

third to investigate the potential increase in accuracy of prediction of mortality by adding the occurrence of PAH to antenatal biomarkers of severity.

METHODS

This is a retrospective analysis of data on consecutive fetuses with an antenatal diagnosis of left-sided CDH and who were assessed and managed in three different tertiary centers (UZ Leuven, Belgium; BCNatal, Spain; GOSH, United Kingdom) using the same antenatal management protocol[3, 4]. This includes eighty-two participants of the TOTAL-trial[5, 6]. Additional criteria were left-sided CDH, liveborn beyond 30 weeks between January 2008 and January 2019 when the Euro-CDH consortium neonatal management protocol was in use[10, 11]. During that period, FETO was offered to fetuses with severe (i.e., quotient of o/e LHR) under 25%) or moderate (o/e LHR of 25 to 34.9% (any liver position), or 35 to 44.9% with intrathoracic liver herniation) pulmonary hypoplasia[3, 4]. For the analysis, we excluded cases with associated major structural or genetic anomalies[12], either diagnosed in the antenatal or postnatal period, cases with diaphragmatic eventration, confirmed at autopsy or at postnatal surgery; and those in whom there was no early assessment (<24 hours) of PAH available.

Antenatal variables included the o/e LHR as determined the closest to 26-28 weeks, the presence of liver herniation as determined by 2-D ultrasound, and the use of FETO. Additional variables were gestational age (GA) at delivery, the occurrence of PAH within 24 hours of life defined as systemic to supra-systemic pulmonary pressures on echocardiography[13, 14]. The latter was assessed using three methods in descending order of importance as previously described[15]: Firstly, direction and velocity of the ductus arteriosus flow (Bernoulli equation)[16]; secondly, two-dimensional intraventricular septum position[17]; and thirdly, peak tricuspid regurgitant jet velocity with estimation of the right ventricular systolic pressure in the absence of right ventricular outflow tract obstruction by the modified Bernoulli equation, assuming 0 mmHg right atrial pressure[18] and estimation of the pulmonary systolic pressure with central venous pressure.

The presence of PAH from day two until recovery or discharge was diagnosed by fetal echocardiography, clinical signs, or a course of treatment with drugs such as inhaled Nitric Oxide (iNO), sildenafil, milrinone, prostacyclin[10, 11]. The occurrence of r-PAH was defined as PAH that required the use of two or more of the former pulmonary vasoactive drugs during NICU stay, or the use of one or more drugs for PAH at discharge. Other postnatal outcomes were the use of Extracorporeal Membrane Oxygenation (ECMO) and neonatal death during NICU admission.

This study is part of larger studies on the prediction of outcome of CDH as approved by the Ethics Committee of the University Hospitals Leuven (ML10784), Hospital Clínic and Hospital Sant Joan de Déu (2013-8445), Barcelona, and the Great Ormond Street Hospital (3126).

Statistical analysis

Continuous variables are presented as median and interquartile ranges; dichotomous variables are presented as numbers and percentages. The Mann-Whitney test and the Fisher`s exact test or chi-square test were used to compare continuous and dichotomous variables respectively. Analysis was stratified for each participating center.

First, the prevalence of PAH and r-PAH in our cohort was calculated. For the antenatal prediction of PAH and r-PAH, a fitted logistic regression model was designed. The discrimination of the model was assessed by receiver operating characteristic curves (ROC) and Areas under the Curve (AUC) computation. The detection rates at fixed False Positive Rates (FPR) of 20% and 10% were calculated.

We then investigated the correlation of neonatal *mortality* with antenatal as well as postnatal variables both as a separate model and in conjunction. We developed a Cox survival regression model to investigate the effect of the o/eLHR, liver herniation, FETO procedure, and GA at delivery. With Cox regression, the proportionality assumption has to be met; the hazards are proportional

over time which implies that the effect of a risk or a protective factor is constant over time. Diagnostics for the assumptions of the Cox model revealed that the effect of FETO and liver herniation violate the proportionality assumption and differ for the time variable. Therefore, we modeled them as time-varying coefficients meaning that the FETO procedure is a prenatal variable that has a different coefficient for different time points postnatally.

An extended Cox survival regression model was also developed that included the presence of PAH and rPAH in the neonatal period. Since PAH and r-PAH may occur or resolve at any point after delivery they were modeled as time-varying covariates. Additionally, PAH and r-PAH were treated as binary variables without any measurement error and independent of the survival model's failure definition (dead or alive at discharge). Therefore, they were modeled as time-varying exogenous covariates[19]. Observations on neonates that were discharged alive were censored for all the analysis. Concordance statistics and the Akaike information criterion were used to compare Cox regression models for their discrimination ability and fit respectively. The statistical software package R and MedCalc version 15.4 (MedCalc Software bvba, Ostend, Belgium) were used for the analysis[20, 21].

RESULTS

The initial cohort included 257 patients assessed for prenatally diagnosed CDH. Sixty of them were excluded for reasons displayed in Supplemental Figure 1. This left us 197 cases with isolated left-sided CDH for analysis. The characteristics of that study population are displayed in Table 1.

Prevalence of CDH-PAH and CDH-rPAH

On day one, the prevalence of PAH was 67.5% (133/197). Also, 10% (20/197) of newborns were started with one or more vasoactive drugs in addition to iNO (sildenafil (n=8), prostaglandins (n=1), milrinone (n=1), (n=10) had combined treatment of which (n=3) included ECMO) hence qualifying as r-PAH. Only 3% (n=5) of infants developed PAH beyond day one for the first time. By day seven, 61.9% (101/163) had PAH and 25% had r-PAH. Forty-one out of 163 newborns were treated with sildenafil (n=10), prostaglandins (n=1), milrinone (n=2) or had a combination of treatment (n=28) of which (n=16) included ECMO. Of those with PAH at day seven, 22/101 (21.8%) died, leaving 79 infants with PAH surviving, of whom 9/79 (11.4%) had PAH at discharge. None of the infants developed PAH beyond day seven, resulting in 9/141 (6.4%) of the surviving neonates having r-PAH and be discharged on treatment for PAH.

Prediction of CDH-PAH and CDH-r-PAH

Postnatal day one

Logistic regression analysis demonstrated that o/eLHR (OR: 0.96; 95%-CI: 0.94–0.99) and treatment with FETO (OR:2.99; 95%-CI: 1.34–6.65) independently correlated to the occurrence of PAH. The AUC was 0.74 with a detection rate of 56% and 42% at 20% and 10% FPR respectively (Figure 1a, Supplementary figure 2a). For r-PAH, both the o/eLHR (OR: 0.93; 95%-CI: 0.89–0.98) and GA at birth

(OR: 1.3; 95%-CI: 1.06–1.60) were predictive. The AUC was 0.75 with a detection rate of 55% and 25% at 20% and 10% FPR respectively (Figure 1b, Supplementary figure 2b).

Postnatal day seven

Logistic regression analysis demonstrated that the only significant predictor for PAH on postnatal day seven was the use of FETO (OR: 3.9; 95%-CI: 1.87–8.23). The AUC was 0.65 with a detection rate of 49% and 25% at 20% and 10% FPR respectively (Supplementary figure 3a). O/eLHR (OR: 0.95; 95%-CI: 0.92–0.98) and GA at birth (OR: 1.29; 95%-CI: 1.09–1.53) predicted r-PAH, with an AUC of 0.69 and a detection rate of 49% and 27% at 20% and 10% FPR respectively (Supplementary figure 3b).

At discharge from the NICU

In a multivariate approach, none of the variables remained significant for PAH at discharge, but the number of events was low (9/141).

Prediction of mortality

Mortality distribution

The overall mortality was 56/197 (28.4%) and as demonstrated in Figure 2, the vast majority occurred within 24h of birth (Figure 2). The characteristics of survivors and non-survivors groups are displayed in Table 1. A lower o/eLHR, liver herniation, PAH, and r-PAH were significantly more common in non-survivors. Of note, all infants who did *not* have PAH survived.

Survival analysis

In the *initial* Cox regression model based on prenatal variables, a higher o/eLHR is related to increased survival. Both the presence of liver herniation and having had FETO, violated the

proportionality assumption, meaning that the hazard ratio is not constant throughout the early neonatal period (Supplementary figures 4 and 5) . Liver herniation is associated with higher mortality but only during the first two days of life, and FETO is associated with a higher survival beyond day two of life (Table 2).

Subsequently, we added PAH and r-PAH as mortality predictors considering their temporal nature. We developed an *extended* Cox survival regression model, to describe the effect of prenatal fixed variables and PAH and r-PAH as postnatal time-varying covariates. The final model included o/eLHR, PAH FETO and liver herniation. GA at delivery and r-PAH were not significant in the initial analysis and were not included in the final multivariate model. The initial and the extended models are presented in Table 3. The addition of PAH in a model using prenatal variables alone improved both the model's discrimination (Concordance statistic: 0.830; 95%-CI: 0.07-0.86 vs. 0.90; 95%CI: 0.86-0.93), p-value= 0.020) and fit (Akaike information criterion: 617.63 vs. 578.36).

Dynamic prediction of mortality

Using the models above, one can construct individualized survival curves (Figure 3) and compute discrimination indices such as AUC, specific for any desired day of life (Table 4, Figure 4). We also obtained ROC curves for days 1,7, 14, 21, and 28 of life (Figure 4). The model shows that overall 40% of the infants stratified as high risk and would contain 90% of the neonatal deaths. This risk stratification is expressed by a continuous survival curve that can be updated at any point after delivery. Discrimination measures can be obtained at any time point after delivery. We found that at a fixed 90% sensitivity, FPR progressively decreased with increasing days after delivery; hence marginally improved discrimination (Table 4, Figure 4).

COMMENT

First, in our cohort, all infants who *did not* develop PAH, survived. In other words, mortality was confined to infants who developed PAH. Therefore, being able to identify which infants who will not develop PAH is clinically very relevant. Second, PAH is very common within the first seven days of life, but r-PAH is present only in one in five neonates. Third, the prenatal biomarkers currently used to predict survival also predict the occurrence of (r)PAH in the first seven days of life, though only moderately well. Fourth, we investigated the prediction of neonatal mortality by combining the *antenatal* factors (o/eLHR, liver herniation, FETO) with *early neonatal* variables (GA at birth and early occurrence of PAH) in a *dynamic* time-varying survival model. In that model, we considered the temporal nature of PAH and the time-dependent effect of FETO and liver herniation. The model that combined antenatal variables and (postnatal) occurrence of PAH improved mortality prediction compared to the model using prenatal predictors alone.

Several prenatal indicators are today widely used to predict survival, and these have also been considered in the prediction of PAH. These include measurement of lung size[22-25], herniation of the liver and position of the stomach into the chest[23, 26-29] as well as assessment of the pulmonary vasculature[23, 26-28, 30-32]. In the present study, we selected the former two because these are long-time part of our standardized assessment and prediction model and were used in several clinical trials[3, 5, 6]. Since pulmonary vascular development is closely related to airway development, it is no surprise that lung size measurements correlate with the postnatal occurrence of PAH. This is in line with previous reports[24, 28, 33, 34]. However, the correlation is only *moderate* (AUC=0.75). This is clinically acceptable but prediction needs to be interpreted with caution[35]. Using these predictors, one would only detect half of the babies that will eventually develop PAH and wrongly label one out of five fetuses as at risk for PAH. Even though vascular development parallels airway development,

the above predictors do not directly quantify the vascular compartment and/or degree of vascular remodeling typical for hypoplastic lungs[36]. Measurement of the characteristics of the pulmonary vasculature has been attempted by other investigators however without being very successful and/or using methods that are difficult to reproduce [7, 24, 32, 37].

We therefore proceeded with the prediction of PAH by adding GA at birth and could not find a better correlation. However, refractory-PAH was correlated with *later* GA at delivery. The relationship between PAH, pulmonary hypoplasia, and prematurity is a complex one[38] that we cannot explain.

We eventually moved again to *mortality* prediction and added the occurrence of PAH to the typical antenatal predictors (o/e LHR and liver herniation). In this cohort, PAH was an independent risk factor for mortality. This again confirms that the antenatal predictors we used, did not sufficiently capture the essence of what will postnatally lead to PAH, in addition to the consequences of ventilatory insufficiency. Again, several predictors for mortality have been explored with limited success[39]. One additional potential antenatal predictor for mortality may be the intrapulmonary artery Doppler[40], which can be measured by any trained sonographer[41].

There are several limitations to our study. Firstly, its retrospective design which inherently creates bias. Secondly, our findings may not be extrapolated to other centers or case-mix or neonatal management protocol. Our cohort arises from fetal medicine centers that offer in prenatal therapy, hence it included proportionally more fetuses with severe hypoplasia and more infants were born prematurely secondary to having FETO. Thirdly, we included both cases treated in-utero and cases managed expectantly. FETO on itself may reduce the risk for PAH [42, 43]. For that reason, we added FETO as a variable in our multivariate model to offset this limitation. Fourthly, we did not review echocardiographic images to assess image quality. Fifthly, given there is no widely accepted

definition for PAH, let be for r-PAH , which we based on a given clinical treatment protocol[10]; it may be difficult to compare our results with other studies. Sixthly, for the prediction of PAH and r-PAH beyond day one of life, only survivors were included. Finally, we did not include other potential prenatal predictors of survival such as the o/e total lung volume[34], as well as typically used postnatal variables such as Apgar or oxygenation parameters[44, 45].

Our study also has some strengths. First, all observations were made under a standardized prenatal assessment and neonatal management protocol. We stratified our analysis for each of the participating centers and no significant differences were found (data not shown). Second, prenatal measurement methods were typically done in a narrow time window, i.e., the gestational age period that is relevant to fetal therapy[46, 47]. Third, our data include a population undergoing FETO, a procedure for which there is now level I evidence, hence is an additional factor of relevance in prediction studies. Fourth, the outcome measures were precisely defined. Fifth, a robust statistical methodology was used. Finally, this is to our knowledge, the largest series assessing prenatal predictors of CDH related to PAH.

CONCLUSIONS

This study confirms that in CDH, PAH is very common and usually occurs as early as the first day of life. The o/e LHR andliver herniation, as well as eligibility for FETO only provide a moderate prediction of PAH. In neonates with an antenatally predicted poor outcome, the postnatal occurrence of PAH further increases the risk of neonatal death. Whereas this may be used to counsel parents postnatally, our study demonstrates there is a need to find a predictor for PAH.

TABLES

Variables	Survivors (N=141)	Non-Survivors (N=56)	p value
o/e LHR	36 (28 - 49)	26.6 (21 - 32)	<0.001
GA at o/e LHR measurement	26.2 (22.8 – 28.5)	25.6 (22 – 27.2)	0.106
Liver herniation	73 (51.8%)	45 (80.3%)	0.001
FETO	53 (37.6 %)	30 (53.6 %)	0.064
GA at delivery in weeks	38 (35 - 38.7)	37.2 (33.2 - 39.0)	0.317
PAH	82 (58.1%)	56 (100%)	<0.001
Refractory PAH	39 (27.7%)	30 (53.6%)	0.001
Delivery to discharge interval in days	36 (22 - 61)	2 (1 - 13)	<0.001

Table 1: Characteristics of the neonates who survived and those who did not survive. Abbreviations: o/e LHR, observed-to-expected lung-to-head ratio; GA, gestational age FETO, Fetoscopic endoluminal tracheal occlusion; CDH, congenital diaphragmatic hernia; PAH, pulmonary hypertension.

Outcome: Mortality		
Variable	**HR (95%CI)**	**p value**
o/e LHR	0.93 (0.89 - 0.96)	<0.001
Liver herniation		
Effect < 2 days of life	10.7 (1.4 - 82.9)	0.022
GA at delivery	NA	
FETO		
Effect > 2 days of life	0.35 (0.14 - 0.89)	0.026

Table 2: Cox survival regression model for mortality based on prenatal variables. FETO and the presence of liver herniation are modeled with varying coefficients. The final model with significant parameters is presented. Abbreviations: o/e LHR, observed-to-expected lung-to-head ratio; GA, gestational age; FETO, Fetoscopic endoluminal tracheal occlusion; HR, hazard ratio.

	Initial Model		Extended Model	
Variable	**Hazard ratio (95% CI)**	**p value**	**Hazard ratio (95% CI)**	**p value**
Prenatal variables				
o/eLHR	0.93 (0.91 - 0.96)	<0.001	0.94 (0.91 - 0.96)	<0.001
Liver herniation	16.91 (6.32 – 45.22)	<0.001	16.78 (6.27 - 44.88)	<0.001
Effect < 2 days of life				
FETO	0.35 (0.18 - 0.69)	0.000254	0.35 (0.17 - 0.68)	0.0023
Effect > 2 days of life				
Postnatal variables				
GA at delivery	1.01 (0.92 - 1.09)	0.8092	NA	
PAH	14.51 (4.16 – 50.61)	<0.001	15.95 (4.86 - 52.33)	<0.001
r-PAH	1.14 (0.65 – 2.01)	0.6284	NA	

Table 3: Extended Cox survival regression model, combining prenatal and postnatal variables. PAH and r-PAH are treated as time-varying covariates. FETO and the presence of liver herniation are treated as variables always present but with time-varying coefficients. Abbreviations: CDH, congenital diaphragmatic hernia; PAH, pulmonary hypertension; r-PAH, refractory pulmonary hypertension; o/eLHR, observed-to-expected lung-to-head ratio; FETO, Fetoscopic endoluminal tracheal occlusion; GA, gestational age; NA, not applicable.

Time (Days after delivery)	AUC	FPR % for 90% sensitivity
1	0.79	44.2
7	0.82	41.2
14	0.83	39.9
21	0.84	38.4
28	0.85	37.5

Table 4: False Positive Rate to achieve 90% sensitivity for the prediction of mortality for different time intervals after delivery by the extended Cox model. Abbreviations: AUC, area under the curve; FPR, false-positive rate.

FIGURES LEGENDS

Figure 1: Receiver operating characteristic (ROC) curve for the prediction of pulmonary hypertension (PAH, Figure 1a) and refractory-PAH, Figure 1b), on postnatal day one. Abbreviations: AUC, area under the curve.

Figure 2: Distribution of deaths (cumulative frequency) by day after delivery.

Figure 3: Predicted individualized survival curve according to the extended Cox survival model for a high-risk case (red solid line, observed-to-expected lung-to-head ratio [o/e LHR] of 20%, pulmonary hypertension [PAH] occurrence at day one and having fetoscopic endoluminal tracheal occlusion [FETO]; and a low-risk case (blue solid line, o/e LHR of 20%, no PAH occurrence, and having FETO), with 95% confidence intervals (interrupted lines).

Figure 4: Receiver operating characteristic (ROC) curves for the time-dependent prediction of mortality until day one (black solid line), first week after delivery (black interrupted line), second week after delivery (gray solid line), third week after delivery (gray interrupted line), fourth week after delivery (black dotted line).

SUPPLEMENTARY FIGURES LEGENDS

Supplementary Figure 1: Flow-chart of the study population.

Supplementary Figure 2: Receiver operating characteristic (ROC) curve with partial area under the curve at a fixed 10 to 20 % false-positive rate for the prediction for pulmonary hypertension (PAH) Figure 2A, and refractory-PAH, Figure 2B, on postnatal day one.

Supplementary Figure 3: Receiver operating characteristic (ROC) curve for the prediction of pulmonary hypertension (PAH, Figure 3A) and refractory-PAH, Figure 3B) on postnatal day seven.

Supplementary Figure 4: Proportionality violation of Fetoscopic endoluminal tracheal occlusion (FETO). Effect in relation to days after delivery.

Supplementary Figure 5: Proportionality violation of the presence of liver herniation. Effect in relation to days after delivery.

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Table 1. Characteristics of the neonates who survived and those who did not survive. Abbreviations: o/e LHR, observed-to-expected lung-to-head ratio; GA, gestational age FETO, Fetoscopic endoluminal tracheal occlusion; CDH, congenital diaphragmatic hernia; PAH, pulmonary hypertension.

Variables	**Survivors (N=141)**	**Non-Survivors (N=56)**	**p value**
o/eLHR	36 (28 - 49)	26.6 (21 - 32)	<0.001
GA at o/eLHR measurement	26.2 (22.8 – 28.5)	25.6 (22 – 27.2)	0.106
Liver herniation	73 (51.8%)	45 (80.3%)	0.001
FETO	53 (37.6 %)	30 (53.6 %)	0.064
GA at delivery in weeks	38 (35 - 38.7)	37.2 (33.2 - 39.0)	0.317
PAH	82 (58.1%)	56 (100%)	<0.001
Refractory PAH	39 (27.7%)	30 (53.6%)	0.001
Delivery to discharge interval in days	36 (22 - 61)	2 (1 - 13)	<0.001

Table 2. Cox survival regression model for mortality based on prenatal variables. FETO and the presence of liver herniation are modeled with varying coefficients. The final model with significant parameters is presented. Abbreviations: o/eLHR, observed-to-expected lung-to-head ratio; GA, gestational age; FETO, Fetoscopic endoluminal tracheal occlusion.

Outcome: Mortality		
Variable	**HR (95%CI)**	**p value**
o/eLHR	0.93 (0.89 - 0.96)	<0.001
Liver herniation Effect < 2 days of life	10.7 (1.4 - 82.9)	0.022
GA at delivery	NA	
FETO Effect > 2 days of life	0.35 (0.14 - 0.89)	0.026

Table 3. Extended Cox survival regression model, combining prenatal and postnatal variables. PAH and r-PAH are treated as time-varying covariates. FETO and the presence of liver herniation are treated as variables always present but with time-varying coefficients. Abbreviations: CDH, congenital diaphragmatic hernia; PAH, pulmonary hypertension; r-PAH, refractory pulmonary hypertension; o/eLHR, observed-to-expected lung-to-head ratio; FETO, Fetoscopic endoluminal tracheal occlusion; GA, gestational age;

	Initial Model		**Extended Model**	
Variable	**Hazard ratio (95% CI)**	**p value**	**Hazard ratio (95% CI)**	**p value**
Prenatal variables				
o/eLHR	0.93 (0.91 - 0.96)	<0.001	0.94 (0.91 - 0.96)	<0.001
Liver herniation Effect < 2 days of life	16.91 (6.32 – 45.22)	<0.001	16.78 (6.27 - 44.88)	<0.001
FETO Effect > 2 days of life	0.35 (0.18 - 0.69)	0.000254	0.35 (0.17 - 0.68)	0.0023
Postnatal variables				
GA at delivery	1.01 (0.92 - 1.09)	0.8092	NA	
PAH	14.51 (4.16 – 50.61)	<0.001	15.95 (4.86 - 52.33)	<0.001
r-PAH	1.14 (0.65 – 2.01)	0.6284	NA	

Table 4. False Positive Rate (FPR) to achieve 90% sensitivity for the prediction of mortality for different time intervals after delivery by the extended Cox model. Abbreviations: AUC, area under the curve; FPR, false-positive rate.

Time (Days after delivery)	**AUC**	**FPR % for 90% sensitivity**
1	0.79	44.2
7	0.82	41.2
14	0.83	39.9
21	0.84	38.4
28	0.85	37.5

FIGURE LEGENDS

Figure 1: Receiver operating characteristic (ROC) curve for the prediction of pulmonary hypertension (PAH, Figure 1a) and refractory-PAH, Figure 1b), on postnatal day one.

Figure 2: Distribution of deaths (cumulative frequency) by day after delivery.

Figure 3: Predicted individualized survival curve according to the extended Cox survival model for a high-risk case (red solid line, o/e LHR=20, Pulmonary hypertension (PAH) occurrence at day 1 and having FETO) and a low-risk case (blue solid line, o/e LHR=20, no PAH occurrence, and having FETO), with 95% confidence intervals (interrupted lines).

Figure 4: Receiver operating characteristic (ROC) curves for the time-dependent prediction of mortality until day 1 (black solid line), first week after delivery (black interrupted line), second week after delivery (gray solid line), third week after delivery (gray interrupted line), fourth week after delivery (black dotted line)

Supplementary Figure 1: Flow-chart of the study population.

Supplementary Figure 2: Receiver operating characteristic (ROC) curve with partial area under the curve at a fixed 10 to 20 % false-positive rate for the prediction for pulmonary hypertension (PAH) Figure 2A, and refractory-PAH, Figure 2B, on postnatal day one.

Supplementary Figure 3: Receiver operating characteristic (ROC) curve for the prediction of pulmonary hypertension (PAH, Figure 3A) and refractory-PAH, Figure 3B), on postnatal day seven.

Supplementary Figure 4: Proportionality violation of FETO. Effect in relation to days after delivery.

Supplementary Figure 5: Proportionality violation of the presence of liver herniation. Effect in relation to days after delivery.