Fetoscopic endoluminal tracheal occlusion reverses the natural history of right-sided congenital diaphragmatic hernia: a European multicenter experience

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Contributions

What are the novel findings of this study? In right-sided CDH, survival can be predicted from prenatal lung size and, in cases with the worst prognosis, is improved by FETO.

What are the clinical implications? In cases with right-sided CDH and severe lung hypoplasia, defined by an o/eLHR<50%, FETO may be offered.

Abstract

Objective: To examine neonatal outcome of fetuses with isolated right-sided congenital diaphragmatic hernia (iRCDH) based on prenatal severity indicators and antenatal management.

Methods: Retrospective review of prospectively collected data on consecutive cases of iRCDH diagnosed prior to 30 weeks' gestation. Data on prenatal severity assessment, antenatal management, and perinatal outcome were retrieved. Univariate and multivariate logistic regression analysis were used to identify predictors of survival at discharge and early neonatal morbidity.

Results: Forty out of 265 assessed patients underwent termination of pregnancy (15%), while in two (0.7%) cases unexplained fetal death occurred. In the fetuses with iRCDH included in neonatal outcome analysis, 86 were managed expectantly during pregnancy and 128 underwent fetoscopic tracheal occlusion with a balloon (FETO). In the expectant management group, lung size measured by ultrasound or by magnetic resonance imaging was the only independent predictor of survival (observed-to-expected lung-to-head ratio, o/eLHR: OR 1.02, 95% CI 1.02-1.1;p=0.003). Till now, stratification was based on a cut-off of 45%. Survival rate was 15% (4/27) in those with o/eLHR <45% and 61% (36/59) for o/eLHR ≥45% (p=0.001). The best cut-off for o/eLHR however was 50% (78% sensitivity and 72% specificity). Survivors with severe pulmonary hypoplasia stayed longer in the neonatal intensive care unit (NICU). In fetuses with an o/eLHR<45% treated by FETO, survival was higher (41%, 49/120) than in the expectantly managed with similar lung size (p=0.014), despite higher prematurity rates (gestational age at birth: 34.4±2.7 vs 36.8±3.0;p<0.0001). In antenatally treated fetuses, gestational age at birth was the only predictor of survival (OR 1.25, 95% CI 1.04-1.50;p=0.02).

Conclusions: Antenatal measurement of lung size predicts survival in iRCDH. In fetuses with severe lung hypoplasia, FETO was associated with a significant increase in survival.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a developmental anomaly with a birth prevalence of about 2/10,000[1, 2] (ORPHA: 2140). In about 40% of cases, the condition is associated with chromosomal abnormalities, genetic syndromes and other major defects[3]. In fetuses with CDH there is compression of the developing lungs by the herniated abdominal viscera, so that 30-50% of neonates die due to respiratory insufficiency and persistent pulmonary hypertension[4-6]. In previous extensive studies in isolated (i) LCDH we have reported that, first, there is a high association between prenatally assessed lung size and postnatal survival[7], and second, in cases of severe disease the prognosis could be improved by fetoscopic endoluminal tracheal occlusion (FETO)[8]. Right-sided CDH (RCDH) is far less common than left-sided, accounting for only 15-20% of cases, and therefore solid data is rare. Available evidence is controversial on whether RCDH is a more severe condition and/or a separate entity with different outcomes[9-12]. In a previous study on 67 fetuses with iRCDH, we documented an overall survival rate of 53%, hence lower than that for left-sided CDH[13]. We also demonstrated a correlation between prenatal lung size and survival and a borderline significant improvement following FETO in cases with severe hypoplasia. The objectives of this extended series from four European FETO centers with standardized prenatal and postnatal management strategies[2, 14], are to examine the value of prenatal assessment, in particular fetal lung size, in the prediction of neonatal survival and morbidity, and second, the potential benefit of FETO on neonatal survival and morbidity.

METHODS

Study population

This is a retrospective study on prospectively collected data on all patients with prenatally diagnosed iRCDH assessed in four fetal therapy centers (BCNatal, Barcelona, Spain; Hôpitaux Paris Sud, Clamart and Le Kremlin-Bicêtre, France; King's College Hospital London, UK and University Hospitals Leuven, Leuven, Belgium) between January 2008 and December 2018. To determine prenatal predictors of outcome, we included cases of iRCDH resulting in livebirth beyond 30 weeks' gestation. We excluded cases with prenatally diagnosed associated major structural or genetic anomalies, as defined according to the EUROCAT-coding guidelines[15]; patients undergoing termination of pregnancy or with intrauterine fetal demise and cases with diaphragmatic eventration confirmed at autopsy or at postnatal surgery.

Procedures

Antenatal assessment by fetal ultrasound and, in a proportion of cases, fetal magnetic resonance imaging (MRI) was performed to exclude major associated anomalies and determine the severity of lung hypoplasia. In all cases genetic testing by conventional karyotype or comparative genomic hybridization array analysis was performed. On the basis of the o/eLHR the parents were counselled by a multidisciplinary equipe (fetal medicine specialist, neonatologist and/or pediatric surgeon) as to the chance of neonatal survival[13] and they chose between expectant antenatal management, when indicated FETO or termination of pregnancy. In all participating centers the clinical protocol foresees offering FETO to cases with an o/eLHR <45% and without contraindications to fetal surgery, such as extreme obesity, increased risk of preterm delivery or major associated anomalies. In those choosing FETO this was carried out at 27-30 weeks' gestation as previously described[16]. Reversal of the

occlusion was performed electively between 34 and 35 weeks by either fetoscopy or ultrasound-guided puncture. In cases of threatened preterm labor or ruptured membranes, balloon removal was attempted earlier or, when this was not possible, it was performed during caesarean section under placental circulation or by postnatal tracheoscopy or postnatal puncture through the neck[17]. Patients undergoing FETO were asked to live near the FETO center throughout the duration of tracheal occlusion. After balloon removal, mothers either remained at the FETO center or were allowed to give birth in their tertiary referral center, as for pregnancies expectantly managed. After delivery, all newborns were managed according to the Euro-CDH consortium consensus protocol[14].

Perinatal predictors of neonatal outcome

Perinatal variables included the o/eLHR, presence or absence of intrathoracic liver herniation, presence of pleural effusion, pericardial effusion, ascites or hydrops, presence of polyhydramnios, o/e total fetal lung volume (o/eTFLV), liver-to-thorax ratio (LiTr) both in cases were MRI was performed, expectant antenatal management or FETO, gestational age at birth, occurrence of preterm premature rupture of membranes (PPROM), birthweight, center of antenatal management, delivery at or outside a FETO center and year of birth, categorized as until or after 2012. Fetuses were categorized into severity groups according to the o/eLHR. Lung hypoplasia was defined as severe if the ratio was <45%, and not severe if the ratio was ≥45%[13].

The LHR was measured by experienced operators by two-dimensional ultrasound using the tracing (center B and C) or longest-axis (center A and D) method[2, 18], and normalized for gestational age (o/eLHR)[19]. The TFLV was measured on MRI and expressed as a ratio over the expected pulmonary volume in a gestational age matched control (o/e TFLV)[20]. Liver herniation was determined on ultrasound and MRI and later confirmed at autopsy or at postnatal surgery. The LiTr was measured on MRI as the ratio between the intrathoracic liver volume and the total thoracic volume[21]. When more

than one US and MRI measurement was performed, the values reported between 26 and 28 gestational weeks were kept for analysis, as these were available for all study participants. Polyhydramnios was defined as a deepest vertical pocket of 8 cm or higher during any of the ultrasound assessments[22]. Hydrops was defined as the presence of ≥2 abnormal fetal fluid collections[23].

Outcome measures

The primary outcome was survival at discharge from the neonatal intensive care unit (NICU). Secondary neonatal outcomes were survival at 6 and at 12 months, the need of patch at postnatal repair, the need of any treatment for persistent pulmonary hypertension, the presence of pulmonary hypertension on day 28, the need for extracorporeal membrane oxygenation (ECMO) where available, and, for survivors, the length of NICU stay and the need for oxygen administration at discharge. Pulmonary hypertension was diagnosed by the presence of a preductal-postductal saturation difference >10%, and/or by echocardiographic evidence of systemic to supra-systemic pulmonary pressures[24, 25].

Statistical analysis

Continuous variables are presented as mean (standard deviation) or median (25^{th}-75^{th} percentile) when normally or not normally distributed, respectively; dichotomous variables are presented as percentages. Student's t-Test or Mann-Whitney test and the Fisher`s exact test were used to compare continuous and categorical variables, respectively. Stepwise logistic regression analysis with backward variable selection (variables entered only if $p<0.1$) was used to assess the relationship between perinatal variables and neonatal survival. As both the o/eLHR and the o/eTFLV are proxies of lung size, only the o/eLHR was included in the logistic regression analysis. To determine the predictive value of the o/eLHR and o/eTFLV for survival, Receiver Operating Characteristic (ROC) curve analysis was performed using the DeLong method[26]. The best cut-off was automatically generated according to the Youden index[27]. ROC curves were compared using the DeLong method[26]. A p value <0.05 was considered statistically significant. We used GraphPad PRISM version 8.0 (GraphPad Software, La Jolla, CA 92037 USA) and MedCalc statistical software version 15.4 (MedCalc Software bvba, Ostend, Belgium) for statistical analysis.

RESULTS

Study population

A total of 265 patients with prenatally iRCDH were assessed during the study period (Figure 1). We excluded 40 (15%) cases who underwent termination of pregnancy (Supplementary Table 1), 2 (0.7%, Supplementary Table 2) cases of unexplained fetal death, 2 (0.7%) cases that were lost to follow up, 1 (0.3%) case where no antenatal assessment of lung hypoplasia was available and 6 (2.3%) cases thought to be isolated on prenatal assessment but found to have major associated anomalies or syndromes after birth (Supplementary Table 2). In 14 (6%) cases minor associated abnormalities were detected prenatally (Supplementary Table 2). These cases were included in the analysis, because the associated findings did not affect antenatal or postnatal management and were assumed not to contribute independently to the primary outcome.

The 214 cases used for outcome analysis included 86 (40%) that were managed expectantly prenatally and 128 (60%) treated by FETO. All patients had at least one ultrasound evaluation, while fetal MRI was performed in 83 (39%) patients. Intrathoracic liver herniation was present in 209 (98%) cases; in all fetuses without liver herniation the o/eLHR was ≥45%. Pleural effusion, pericardial effusion and/or ascites were observed in 46 (21%) fetuses and hydrops in 22 (10%); in two of these, a thoraco-amniotic shunt was placed. Hydrops was equally present in fetuses with an o/eLHR below (18/147; 12%) or above 45% (4/67; 6%; p=0.22).

Expectantly managed fetuses

The overall survival of the expectantly managed cases was 46% (40/86). Survival rate was 15% (4/27) in those with o/eLHR <45%) and 61% (36/59) for o/eLHR ≥45% (p=0.001; Figure 2A) None of the 10 fetuses with o/eLHR <30% survived.

On univariate analysis, larger lungs (either by o/eLHR on ultrasound or by o/eTFLV on MRI) and a lower LiTr significantly correlated with survival (Table 1). Survival was not affected by the place of antenatal management and delivery and did not change over time. Using logistic regression, the only predictor of survival was lung size on US (o/eLHR: OR 1.06, 95% CI 1.02-1.11). The area under the curve (AUC) of the o/eLHR for the prediction of survival was 0.77, with a best cut-off of 50% (78% sensitivity and 72% specificity, Figure 2B). Of interest, the currently used cut-off to define severe pulmonary hypoplasia (o/eLHR 45%) had the same sensitivity (78%) but lower specificity (64%). The AUC of the o/eTFLV was similar (0.86, p=0.09, Figure 2B), with a best cut-off of 70% (83% sensitivity and 87% specificity).

Three cases were lost to follow up after hospital discharge. All the other infants were alive at 6 and 12 months. Survival rate at these time points was 11% (3/26) and 60% (34/56) for fetuses with an o/eLHR < or ≥45% respectively (p<0.001)

Fetuses managed by FETO

FETO was performed at a mean gestational age of 28.2±1.9 weeks. Balloon dislodgement or deflation occurred in 2 (1.6%) cases and in one of these a new balloon was inserted at 33.3 weeks. The average interval between balloon insertion and removal was 34±15 days. Reversal of occlusion took place at a mean gestational age of 33.1±1.7 weeks; this was performed electively in 86 (67%) cases and as an emergency in 42 (33%) cases. In one case balloon removal was unsuccessful. That patient went into precipitous labor at 30.4 weeks. Postnatal puncture failed and the baby died a few minutes after birth.

One patient developed complete chorionic membrane separation at 33 weeks and was hospitalized for increased risk of cord entanglement. She went into labor the day after and the balloon was removed during cesarean section on placental circulation. That baby survived until discharge.

The characteristics of fetuses undergoing FETO, as compared to those managed expectantly, are summarized in Table 2. The former had more frequently severe pulmonary hypoplasia (94% vs 31%; p<0.0001) and a higher LiTR (31±10% vs 19±12%; p=0.02). FETO was associated with an increased risk of PPROM (24% vs 2%; p=0.0001) and with a lower gestational age at delivery (34.4 ±2.7 weeks vs 36.8±3.0 weeks, p<0.0001). Despite that, fetuses with severe hypoplasia survival undergoing FETO were more likely to survive as compared to fetuses of similar severity managed expectantly (41% vs 15%, p=0.014, Figure 2A). Apparently, FETO was also performed in 8 cases with milder pulmonary hypoplasia at ultrasound (o/eLHR range 45.5 to 58%). Of note, four of these had severe lung hypoplasia on MRI (o/eTFLV range 24 to 32%). Survival at discharge in those eight fetuses with milder hypoplasia was 50% (4/8). When taking all fetuses with an o/eLHR <50% into account, FETO significantly improved survival (p 0.028, Figure 2B).

Gestational age at birth was the only predictor of survival at discharge in cases treated in utero (OR 1.25, 95% CI 1.04-1.50, Table 2). Similar results were obtained when excluding the eight cases with milder pulmonary hypoplasia from the analysis (gestational age at birth: OR 1.27, 95% CI 1.05-1.53). All fetuses with ascites, hydrothorax and a third location of fluid collection, did not survive. As in the expectantly managed cases, survival was not affected by the center of antenatal and postnatal management or by the year of birth.

One FETO case died at 8 months of age because of respiratory insufficiency. Four cases with o/eLHR <45% operated in utero were lost to follow up after hospital discharge. In the remaining cases, FETO significantly increased survival at 6 (38% vs 11%, p 0.01) and 12 months (37% vs 11%, p 0.01).

Neonatal morbidity

Tables 3A and 3B summarize the neonatal morbidity indicators based on the severity of pulmonary hypoplasia and on antenatal management. In expectantly managed fetuses with severe hypoplasia and

surviving till discharge, NICU stay was longer (71 (IQR 47-119) days vs 22 (IQR 14-51) days in fetuses with mildly hypoplastic lungs; p=0.02). In fetuses with severe pulmonary hypoplasia treated by FETO, there was no change in neonatal morbidity (Table 3B). In two of these infants bronchoscopy performed during admission revealed the presence of tracheomalacia.

DISCUSSION

This study has four main findings. First, in fetuses with iRCDH expectantly managed during pregnancy, neonatal survival and duration of stay in NICU are related to the fetal lung size, measured either as o/eLHR or as o/eTFLV. Second, in fetuses with iRCDH and o/eLHR <45%, antenatal treatment with FETO, is associated with a substantially improved neonatal survival (41% vs. 15%) and, third, similar neonatal morbidity, despite earlier birth. Fourth, the best cut off in o/eLHR to define severe pulmonary hypoplasia with ultrasound in this series is 50%, rather than the currently used 45%.

This study shows that iRCDH is a highly lethal condition, with survival rates that are comparable to those described a decade ago by our group[28], and that did not change during the study period. Though a comparison with iLCDH was not the purpose of this study, the lower survival rates in this and our previous experience[28] further support the hypothesis that RCDH constitutes a separate entity with different biology and different mortality and/or morbidity[9, 29-31]. As such, RCDH might also need specific prediction models. In line we previous observations on RCDH[7, 13] and similar to the contralateral form, lung size measured by US or MRI predicts the natural history. Of interest, ultrasound and MRI had similar predictive value. However, MRI was only available in 39% of cases, which might have biased the comparison between the two techniques. Based on this series, the best o/eLHR cut off to define severe hypoplasia was 50%, which is higher than what was earlier proposed empirically[7]. This should be taken into consideration when counselling parents and selecting fetuses for antenatal therapy.

As in iLCDH[32], the severity of lung hypoplasia also predicts the length of NICU stay, suggesting a higher morbidity. There was no correlation with other early morbidity indicators, but this may be the consequence of the sample size and high early mortality rates in newborns with severe lung hypoplasia. Obviously, liver herniation was not predictive, as it was present in 98% of cases. On univariate analysis, the amount of liver into the chest correlated with survival, but it did not predict survival independently from lung size. Similarly, we could not identify other independent prognostic factors.

If RCDH is a different biological entity, response to FETO cannot be extrapolated to what is reported in iLCDH. Notwithstanding the not randomized design, this study provides evidence of a survival benefit by FETO in severe iRCDH. Findings are in line with those in a previous smaller series[13]. Despite the consistent side effect of fetal intervention, i.e. an increased risk of prematurity, which offsets to some extent the benefit of FETO, survivors had similar morbidity and NICU stay, as cases managed expectantly. This experience suggests, therefore, that in iRCDH the benefits of antenatal treatment overcome its prematurity risks

The main strengths of this study are first, the large population of fetuses with iRCDH including the so-called hidden mortality by terminations, stillbirths and immediate neonatal deaths[33]. Second, the antenatal and neonatal management in the four participating centers was standardized[34, 35]. Third, we provide data on the neonatal outcome of cases of severe iRCDH treated by FETO. The conclusion that FETO is beneficial in cases of severe iRCDH is limited by the fact that this was not a randomised trial. However, the rarity of the condition makes it very unlikely that such a trial will ever be feasible. The value of FETO in iLCDH has been investigated in a trial which has just been completed, but it has taken almost 10 years to recruit the necessary patients[36]. Another limitation relates to the generalisability of our findings in the expectantly managed group. In our series, the mortality rate was 60%, which is similar to what was described in series from two decades ago[7, 13]. Often it is claimed

that advances in neonatal and surgical care lead to substantial improvement in outcome[37]. Although in our study population survival was not affected by the center of antenatal or postnatal management, we do not claim that our findings can be extrapolated to other settings, with different postnatal management, including the wide use of ECMO[38].

In conclusion, this study shows that for iRCDH survival can be predicted by antenatal measurement of lung size. In fetuses with o/eLHR <45% FETO is associated with a significant increase in survival without an associated increase in neonatal morbidity.

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Conflict of interest

The authors report no conflict of interest

Contribution to authorship

FMR and JD conceived the study. FMR, JD, AGC and DB contributed to the analysis and interpretation of data. FMR, AGC, LS, EL, OG, AD, MA, EG, KN and AB provided substantial contributions to data acquisition. FMR, JDP and KN drafted the article, which was critically revised by all co-authors. All authors approved the final version of the manuscript.

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Details of ethics approval

This report is part of a larger study on outcomes of CDH that was approved by the Ethics Committee of the University Hospitals Leuven (ML10784), Hospital Clínic and Hospital Sant Joan de Deu (2013-8445). No specific ethics approval was necessary in France for the analysis of retrospective data.

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Figures legend

Figure 1: Overview of the study population. RCDH: right-sided congenital diaphragmatic hernia; IUFD: intrauterine fetal death; TOP: termination of pregnancy; o/eLHR: observed-to-expected lung-to-head ratio.

Figure 2: Survival rates in fetuses stratified based on the degree of pulmonary hypoplasia, either managed expectantly (grey bars) or with FETO (black bars); in A a 45% cut off is used, in B a 50% cut off. C: ROC curve for prediction of survival at discharge in the expectantly managed fetuses by o/eLHR an o/eTFLV measurement. n: total number, o/eLHR: observed-to-expected lung-to-head ratio

Supplementary Table 1: Characteristics of cases undergoing termination of pregnancy

Supplementary Table 2: Case description and postnatal outcome of cases with intrauterine demise, major anomalies detected postnatally and associated minor anomalies. o/eLHR: observed-to-expected lung-to-head ratio; FETO: fetoscopic endoluminal tracheal occlusion

Table 1: Univariate analysis on potential predictors of survival in cases of iRCDH managed expectantly or with FETO. o/eLHR: observed-to-expected lung-to-head ratio; o/eTFLV: observed-to-expected total fetal lung volume; LiTR: liver-to-thorax ratio; PPROM: preterm premature rupture of membranes; OR: odds ratio, CI: confidence interval

	Expectant management (n=86)		**FETO (n=128)**	
	OR (95% CI)	p value	OR (95% CI)	p value
o/eLHR	**1.07 (1.01-1.12)**	**0.003**	1.01 (0.96-1.01)	0.83
o/eTFLV	**1.16 (1.03-1.30)**	**0.009**	1.07 (0.99-1.14)	0.06
LiTR	**0.78 (0.59-0.97)**	**0.01**	0.93 (0.85-1.02)	0.11
≥1 fetal fluid collection	1.16 (0.49-2.74)	0.52	1.46 (0.49-4.37)	0.49
≥2 fetal fluid collection	1.09 (0.14-8.48)	0.93	0.38 (0.11-1.32)	0.13
Polyhydramnios	1.05 (0.45-2.48)	0.75	0.96 (0.33-2.83)	0.94
PPROM	0.53 (0.02-8.55)	1	0.65 (0.23-1.84)	0.42
Gestational age at birth	1.10 (0.91-1.33)	0.33	**1.25 (1.04-1.50)**	**0.02**
Interval balloon removal-delivery >24 hours	-	-	0.64 (0.22-1.82)	0.40
Tracheal occlusion days	-	-	1.17 (0.85-1.63)	0.32
FETO center				
A (n=96)	0.71 (0.19-2.68)	0.61	0.93 (0.40-2.18)	0.87
B (n=43)	2.29 (0.57-9.22)	0.24	1.06 (0.32-3.45)	0.92
C (n=34)	0.82 (0.26-2.59)	0.73	0.15 (0.02-1.31)	0.09
D (n=41)	0.70 (0.11-4.61)	0.71	1.70 (0.62-4.65)	0.30
Born at FETO center (n=84)	0.45 (0.13-1.52)	0.20	0.58 (0.21-1.60)	0.30
Born after 2012 (n=83)	0.98 (0.31-3.07)	0.97	1.14 (0.47-2.73)	0.80

Table 2: Comparison of perinatal characteristics of fetuses managed expectantly or with FETO. o/eLHR: observed-to-expected lung-to-head ratio; o/eTFLV: observed-to-expected total fetal lung volume; LiTR: liver-to-thorax ratio; PPROM: preterm premature rupture of membranes; n: number; NC: not calculated as PPROM occurred in only two patients; NA: not applicable.

	Expectant management (n=86)	**FETO (n=128)**	**P value**
o/eLHR (%)	51±20	32±8	**<0.0001**
o/eTFLV (%)	33±22	26±9	**0.04**
o/eLHR <45% (n(%))	27 (31%)	120 (94%)	**<0.0001**
Liver herniation (n(%))	81 (94%)	128 (100%)	**0.01**
LiTR (%)	19±12	31±10	**0.02**
≥1 fetal fluid collection	13 (15%)	29 (23%)	0.16
≥2 fetal fluid collection	4 (5%)	12 (9%)	0.29
Gestational age at birth (weeks)	36.8±3.0	34.4 ±2.7	**<0.0001**
PPROM (n(%))	2 (2%)	31 (24%)	**0.0001**
Gestational at PPROM	NC	32.9±1.7	NC
Antepartum bleeding	1 (1%)	1 (1%)	1
Antepartum maternal infection	0	0	NA
Abnormal antenatal cardiotocography	0	1 (1%)	**NA**

Table 3: Early neonatal morbidity indicators according to the severity of pulmonary hypoplasia and to antenatal management. o/eLHR: observed-to-expected lung-to-head ratio; ECMO: extracorporeal membrane oxygenation; NICU: neonatal intensive care unit; n: number; IQR: interquartile range

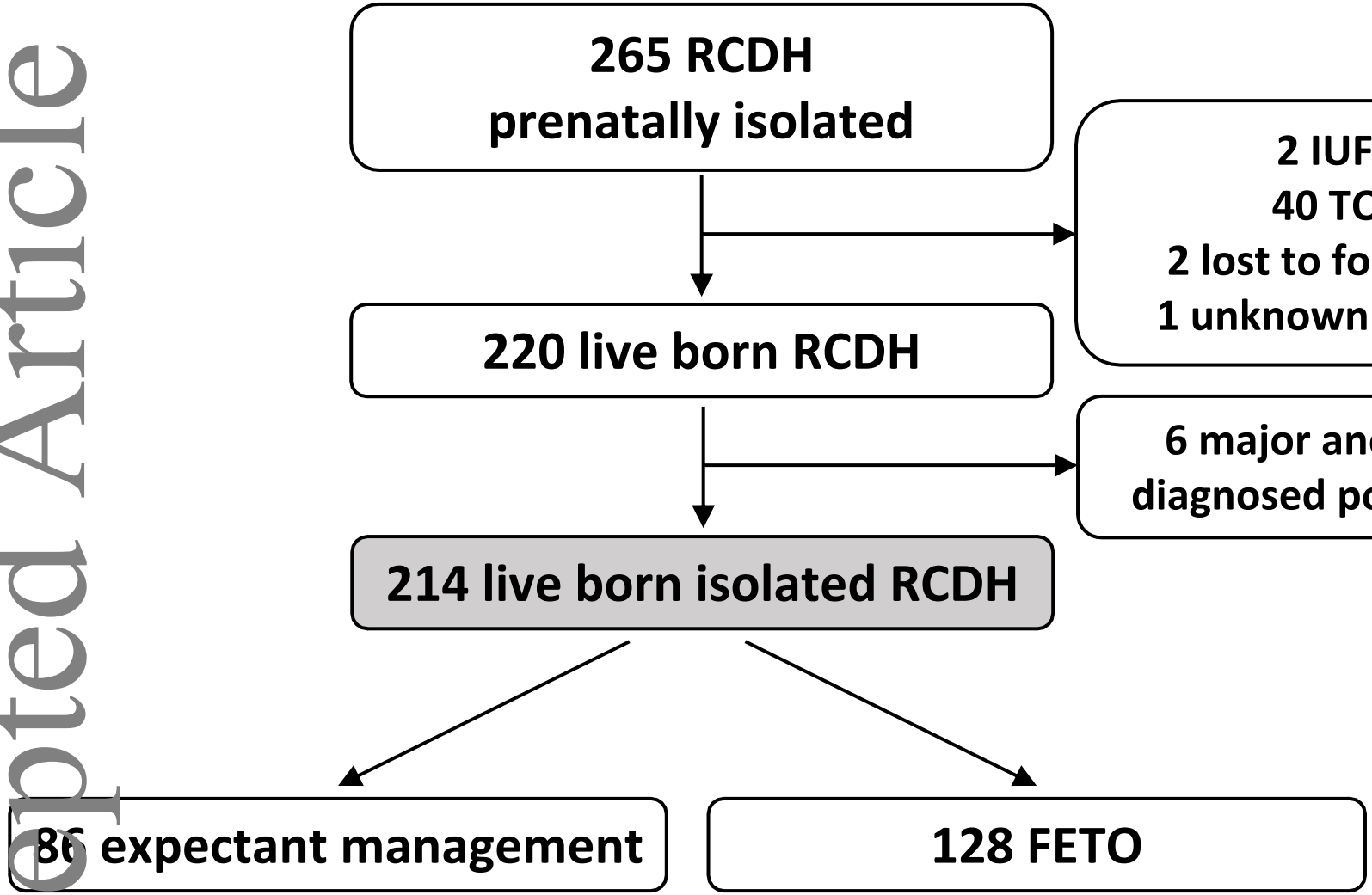
3A: Outcomes in expectantly managed fetuses based on the degree of pulmonary hypoplasia.

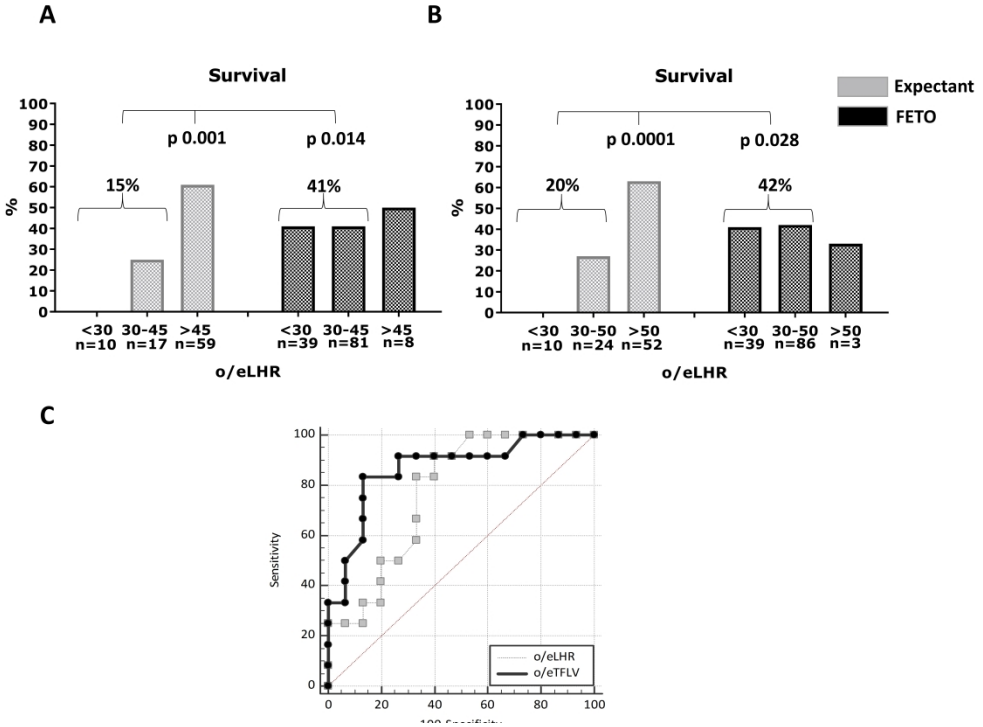
	o/eLHR<45%	**o/eLHR>45%**	**p value**
Need of patch at surgery, n (%)	5/7 (71%)	10/22 (45%)	0.39
Treatment for pulmonary hypertension, n (%)	10/13 (77%)	16/24 (67%)	0.71
Pulmonary hypertension on day 28	1/7 (14%)	5/18 (27%)	0.64
Need of ECMO, n (%)	0/13 (0%)	1/24 (4%)	1
NICU days in survivors, median (IQR)	71 (47-120)	22 (14-51)	**0.02**
Oxygen at discharge in survivors, n (%)	1/9 (11%)	1/20 (5%)	0.53

3B: Effect of FETO on morbidity in fetuses with severe pulmonary hypoplasia

	Expectant management	**FETO**	**p value**
Need of patch at surgery, n (%)	5/7 (71%)	25/28 (89%)	0.25
Treatment for pulmonary hypertension, n (%)	10/13 (77%)	38/49 (77%)	0.63
Pulmonary hypertension on day 28	1/7 (14%)	3/33 (9%)	0.55
Need of ECMO, n (%)	0/13 (0%)	7/49 (14%)	0.32
NICU days in survivors, median (IQR)	71 (47-120)	42 (31-69)	0.14
Oxygen at discharge in	1/9 (11%)	4/14 (29%)	0.61

survivors, n (%)			





Survival rates in fetuses stratified based on the degree of pulmonary hypoplasia, either managed expectantly (grey bars) or with FETO (black bars); in A a 45% cut off is used, in B a 50% cut off. C: ROC curve for prediction of survival at discharge in the expectantly managed fetuses by o/eLHR an o/eTFLV measurement. n: total number, o/eLHR: observed-to-expected lung-to-head ratio

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