Accepted: 14 March 2023

DOI: 10.1111/1471-0528.17497

BJOG An International Journal of Obstetrics and Gynaecology

RESEARCH ARTICLE

Survival in very preterm infants with congenital diaphragmatic hernia and association with prenatal imaging markers: A retrospective cohort study

Emily J. J. Horn-Oudshoorn[1] | Francesca M. Russo[2,3] | Jan A. Deprest[2,3] | Florian Kipfmueller[4] | Annegret Geipel[5] | Thomas Schaible[6] | Neysan Rafat[6] | Anne-Gael Cordier[7,8] | Alexandra Benachi[7,8] | Nimrah Abbasi[9] | Priscilla P. L. Chiu[10,11] | Willem P. de Boode[12] | Esther Sikkel[13] | Nina C. J. Peters[14] | Bettina E. Hansen[15,16,17] | Irwin K. M. Reiss[1] | Philip L. J. DeKoninck[14]

[1]Division of Neonatology, Department of Paediatrics, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

[2]Clinical Department of Obstetrics and Gynaecology, University Hospitals Leuven, Leuven, Belgium

[3]Academic Department of Development and Regeneration, Cluster Woman and Child, KU Leuven, Leuven, Belgium

[4]Department of Neonatology and Paediatric Critical Care Medicine, University Hospital Bonn, Bonn, Germany

[5]Department of Obstetrics and Prenatal Medicine, University Hospital Bonn, Bonn, Germany

[6]Department of Neonatology, University Hospital Mannheim, Mannheim, Germany

[7]Centre Reference Maladie Rare, Hernie de Coupole Diaphragmatique, Clamart, France

[8]Department of Obstetrics and Gynaecology, Hospital Antoine Béclère, University Paris-Saclay, Clamart, France

[9]Department of Obstetrics and Gynaecology, Mount Sinai Hospital, Toronto, Ontario, Canada

[10]Division of General and Thoracic Surgery, Department of Surgery, The Hospital for Sick Children, Toronto, Ontario, Canada

[11]Department of Surgery, University of Toronto, Toronto, Ontario, Canada

[12]Department of Neonatology, Radboud University Medical Centre, Radboud Institute for Health Sciences, Amalia Children's Hospital, Nijmegen, The Netherlands

[13]Department of Obstetrics and Gynaecology, Radboud University Medical Centre Nijmegen, Nijmegen, The Netherlands

[14]Division of Obstetrics and Fetal Medicine, Department of Obstetrics and Gynaecology, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

[15]Department of Epidemiology, Erasmus MC University Medical Centre, Rotterdam, the Netherlands

[16]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

[17]Toronto Centre for Liver Disease, University Health Network, Toronto, Ontario, Canada

Correspondence
Philip L. J. DeKoninck, Department of Obstetrics and Gynaecology, Division of Obstetrics and Fetal Medicine, Erasmus MC University Medical Centre – Sophia Children's Hospital, PO Box 2060, 3000 CB Rotterdam, The Netherlands.
Email: p.dekoninck@erasmusmc.nl

Funding information
Stichting Vrienden van het Sophia, Grant/Award Number: S19-12

Abstract

Objectives: To describe the outcomes of preterm born infants with congenital diaphragmatic hernia (CDH; ≤32.0 weeks of gestation) and the associations between prenatal imaging markers and survival.

Design: Retrospective cohort study.

Setting: Multicentre study in large referral centres.

Population: Infants with an isolated unilateral CDH, live born at 32.0 weeks or less of gestation, between January 2009 and January 2020.

Methods: Neonatal outcomes were evaluated for infants that were expectantly managed during pregnancy and infants that underwent fetoscopic endoluminal tracheal occlusion (FETO) therapy, separately. We evaluated the association between prenatal imaging markers and survival to discharge. Prenatal imaging markers included

observed to expected lung-to-head ratio (o/e LHR), side of the defect, liver position, stomach position grade, and observed to expected total fetal lung volume (o/e TFLV).
Main Outcome Measure: Survival to discharge.
Results: We included 53 infants born at 30^{+4} (interquartile range 29^{+1}–31^{+2}) weeks. Survival in fetuses expectantly managed during pregnancy was 48% (13/27) in left-sided CDH and 33% (2/6) in right-sided CDH. Survival in fetuses that underwent FETO therapy was 50% (6/12) in left-sided CDH and 25% (2/8) in right-sided CDH. The o/e LHR at baseline was positively associated with survival in cases expectantly managed during pregnancy (odds ratio [OR] 1.20, 95% CI 1.07–1.42, $p < 0.01$), but not in cases that received FETO therapy (OR 1.01, 95% CI 0.88–1.15, $p = 0.87$). Stomach position grade ($p = 0.03$) and o/e TFLV were associated with survival ($p = 0.02$); liver position was not ($p = 0.13$).
Conclusions: In infants with CDH born at or before 32 weeks of gestation, prenatal imaging markers of disease severity were associated with postnatal survival.

KEYWORDS
congenital diaphragmatic hernia, counselling, mortality, prediction, prematurity, prenatal imaging, pulmonary hypoplasia

1 | INTRODUCTION

The risk of preterm birth (<37 weeks of gestation) is higher in fetuses with a congenital diaphragmatic hernia (CDH) than in fetuses without any malformations (22–35% versus 9.7%).[1–7] One could expect an increase in the incidence of preterm birth as prenatal surgery in the form of fetoscopic endoluminal tracheal occlusion (FETO) is now a valid option in the severest cases.[6] Both CDH and prematurity are associated with postnatal problems, hence the CDH-related risk of mortality will probably increase if combined with prematurity-related morbidity.[4,8–10] This was clearly demonstrated by data from the CDH study group registry, showing a positive relationship between survival rate and gestational age at birth irrespective of other factors: 38% in very preterm infants (≤32 weeks), 57% in moderate and late preterm infants (32–37 weeks), and 73% in term infants.[4]

Survival in CDH is mainly determined by the severity of pulmonary hypoplasia, as it correlates with respiratory insufficiency and pulmonary hypertension after birth.[11] During pregnancy, the best validated method to assess the severity of pulmonary hypoplasia is the observed to expected lung-to-head ratio (o/e LHR) determined on a two-dimensional ultrasound image of the contralateral lung.[8] In left-sided CDH, this is often combined with evaluation of the liver position.[8,12,13] Alternative parameters are the observed to expected total fetal lung volume (o/e TFLV) by means of magnetic resonance imaging (MRI) volumetry or the grading of stomach position with ultrasound.[14–18] It could be hypothesised that prematurity-related morbidity attenuates the existing association between prenatal ultrasound markers and CDH-related mortality.[8] This study therefore aimed to describe the outcomes of infants with a CDH born at or before 32.0 weeks of gestation, and the associations between currently used prenatal imaging markers and FETO therapy against the outcome of survival.

2 | METHODS

2.1 | Study population

We performed a retrospective cohort study in seven large referral centres experienced with the assessment and management of CDH in the prenatal period. These centres adhere to standardised international consensus guidelines for postnatal management and participated in the Tracheal Occlusion to Accelerate Lung Growth (TOTAL) trials.[5,6,12,19] We included all consecutive infants with unilateral CDH who were live born at or before 32.0 weeks of gestation between January 2009 and January 2020, and had no associated major structural or genetic abnormalities diagnosed either before or after birth. Further exclusion criteria included infants planned for postnatal palliative care and infants without prenatal measurement of o/e LHR.

2.2 | Baseline characteristics

Maternal and neonatal baseline characteristics were collected from hospital records. Fetal growth restriction was defined as (1) fetal abdominal circumference (AC) or estimated fetal weight (EFW) below the third centile, or (2) absent end-diastolic flow in the umbilical artery, or (3) AC/EFW below the tenth centile combined with uterine artery pulsatility index greater than the 95th centile and/or umbilical artery pulsatility index greater than the 95th centile.[20] We recorded whether fetuses were expectantly managed during pregnancy or underwent FETO. FETO therapy was considered in fetuses in the following subgroups: (1) left-sided CDH, o/e LHR 25% or less, irrespective of liver position; (2) left-sided CDH, o/e LHR 26–35%, irrespective of liver position; (3) left-sided CDH, o/e LHR 36–45% with intrathoracic liver, and (4) right-sided CDH, o/e LHR 45% or less with intrathoracic

liver.[5,6] Probably as a result of the preliminary results of Russo et al.,[21] one fetus with right-sided CDH and o/e LHR of 49% received FETO therapy as well.

2.3 | Prenatal predictors

Prenatal ultrasound markers included the o/e LHR value, which was used for prenatal counselling, side of the defect, liver position and stomach position grade. Also, the o/e TFLV was measured on MRI. The o/e LHR was measured by experienced sonographers using either the tracing or the longest axis method, normalised to a gestational age reference value according to a standardised protocol.[22] Subgroups for left-sided CDH were: o/e LHR up to 25%, o/e LHR 26–35%, o/e LHR 36–45%, and o/e LHR greater than 45%.[8] Subgroups for right-sided CDH were o/e LHR up to 50% and o/e LHR greater than 50%.[21] Liver position and stomach position grade were only reported in left-sided CDH. Liver position was either intra-abdominal (down) or intrathoracic (up). The axial plane at the level of the four-chamber view of the heart was used to evaluate stomach position grade, which was graded according to Cordier et al.[14,22] Stomach position is graded as follows: Grade 1, stomach not visualised; Grade 2, stomach visualised anteriorly, next to the apex of the heart, with no structure between stomach and sternum; Grade 3, stomach visualised along from the apex of the heart and abdominal structures anteriorly; or Grade 4, Grade 3 with stomach posterior to the level of the atrioventricular heart valves.[14]

2.4 | Outcome measures

The primary outcome of interest was survival to discharge from the intensive care unit (ICU). Secondary outcomes were occurrence of pulmonary hypertension at any point during ICU admission (mild: right ventricular systolic pressure [RVSP]/systolic blood pressure [SBP] <2/3; moderate: RVSP/SBP 2/3–1; severe: RVSP/SBP >1),[23] pulmonary hypertension treatment with inhaled nitric oxide and/or sildenafil, use of extracorporeal membrane oxygenation (ECMO) therapy, number of days on mechanical ventilation, and presence of bronchopulmonary dysplasia (which was assessed at a postmenstrual age of 36 weeks using the criteria from Jobe et al.[24]).

2.5 | Statistical analysis

Continuous data are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) depending on the distribution. Categorical data are expressed as absolute number (*n*) and percentage (%). Odds ratios (OR) and corresponding 95% CI were calculated for risk factors for preterm birth that have an incidence of at least 10% in our data. Continuous data were analysed using the Mann–Whitney *U* test or one-way analysis of variance test and categorical variables were analysed using the Fisher exact test. The area under the receiver operating characteristic curve was used to evaluate the discriminative ability of o/e LHR for survival in infants with left-sided CDH expectantly managed during pregnancy. The optimal cut-off was calculated with the Youden index, which gives equal weight to sensitivity and specificity, by using the R package 'cutpointr'.

Logistic regression analyses evaluated the association between selected covariates and the outcome of interest; survival to discharge. We selected the following covariates based on clinical relevance and literature: o/e LHR, side of the defect and FETO therapy. As a result of the limited sample size, we were not able to include additional covariates. Univariate logistic regression was used to test the main effects of the selected covariates in specified subgroups: all infants, infants with left-sided CDH, infants with right-sided CDH, infants expectantly managed during pregnancy, and infants that underwent FETO therapy. Multivariable logistic regression was used to test the linearity of o/e LHR and interactions between covariates, because we expected o/e LHR and FETO therapy to have an interaction. The choice of model is based on clinical insight along with the Akaike information criterion (AIC), which selects the model with the lowest AIC as the best fitting model. The effect estimates are reported as OR with 95% CI. For interaction terms that include the o/e LHR, a continuous variable, effect estimates are reported at clinically relevant o/e LHR cutoffs.

The statistical analyses were designed and performed in collaboration with the Department of Epidemiology & Biostatistics of the Erasmus MC University Medical Centre. We analysed the data using the statistical software of R (R Core Team [2020], v4.1.1). A value of p less than 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

In total, 53 infants were included with a median gestational age at birth of 30^{+4} (IQR 29^{+1}–31^{+2}) weeks. Mean maternal age at time of delivery was 31 ± 5 years and 27 women were nulliparous. Three fetuses were diagnosed with minor genetic or anatomical abnormalities, which were deemed unlikely to influence outcomes (one with mega-ureter, one with low-grade mosaicism of chromosome 4 without any other phenotypic anomalies than CDH, and one with bilateral clubfeet). Baseline characteristics for expectantly managed fetuses are depicted in Table 1. In infants expectantly managed before birth, we did not find differences in odds of mortality between infants with and without known risk factors concerning preterm birth (i.e. amniocentesis, pre-existing maternal disease, intrauterine infection, polyhydramnios and preterm premature rupture of the membranes; Table S1). The ORs of mortality associated with smoking during pregnancy, history of preterm birth, maternal sepsis and oligohydramnios

TABLE 1 Baseline characteristics of preterm born infants with congenital diaphragmatic hernia that were expectantly managed during pregnancy.

	Left-sided CDH		Right-sided CDH	
	n	(*n* = 27)	*n*	(*n* = 6)
o/e LHR (%)	27	33 (29–42)	6	35 (29–41)
Gestational age at measurement o/e LHR (weeks^{+days})	27	25^{+4} (23^{+0}–27^{+4})	6	26^{+2} (24^{+2}–27^{+5})
o/e TFLV (%)	17	30 (24–34)	3	25 (20–27)
Gestational age at measurement o/e TFLV (weeks^{+days})	11	25^{+5} (24^{+4}–27^{+0})	5	27^{+4} (26^{+0}–28^{+3})
Intra-thoracic liver position	27	15 (56%)	6	6 (100%)
Stomach position				
Grade 1	18	3 (12%)	6	6 (100%)
Grade 2		8 (31%)		0
Grade 3		6 (23%)		0
Grade 4		9 (35%)		0
Fetal growth restriction	27	3 (11%)	6	0
Prenatal corticosteroids	27	27 (100%)	6	5 (83%)
Vaginal birth	27	14 (52%)	6	1 (17%)
Gestational age at birth (weeks)	27	29^{+4} (27^{+6}–30^{+6})	6	29^{+5} (29^{+2}–30^{+5})
Male	27	16 (59%)	6	4 (67%)
Birth weight (g)	27	1250 (955–1470)	6	1385 (1195–1579)
Apgar score at 5 minutes	23	6 (5–8)	6	7 (5–8)
Umbilical cord pH	15	7.30 (7.26–7.37)	5	7.41 (7.23–7.42)

Note: Data are expressed as median (interquartile range) or number (%).

Abbreviations: CDH, congenital diaphragmatic hernia; FETO, fetoscopic endoluminal tracheal occlusion; o/e LHR, observed to expected lung-to-head ratio; o/e TFLV, observed to expected total fetal lung volume.

are not reported because of low incidences (<10%) in this study population.

3.2 | Left-sided CDH expectantly managed during pregnancy

In left-sided CDH ($n = 27$), median o/e LHR was 33% (IQR 29–42%). The survival rate was 48% (13/27) and non-surviving infants died at a median of day 2 (IQR 1–9). All surviving infants and two non-surviving infants underwent surgical correction of the defect at day 6 (IQR 3–7), and 87% (13/15) required patch repair. Pulmonary hypertension was diagnosed in 24 (89%) infants on day 1 (IQR 1–1). In two survivors, no signs of pulmonary hypertension were present, whereas the presence of pulmonary hypertension was not evaluated in one non-survivor because death occurred before evaluation. Treatment of pulmonary hypertension consisted of inhaled nitric oxide in 21 infants, of whom nine infants were also treated with sildenafil. One infant born at a gestational age of 31^{+6} weeks received ECMO therapy; the cannulas were placed at 46 hours of life and the ECMO run lasted until death at 23 days. Surfactant was administered in 21 infants. Mechanical ventilation was provided for 21 (IQR 9–23) days in surviving infants. The prevalence of prematurity-related morbidity was as follows: necrotising enterocolitis in one infant, retinopathy of prematurity Stage ≥3 in two infants, intraventricular haemorrhage in eight infants, sepsis confirmed with blood culture in nine infants and bronchopulmonary dysplasia in 12 infants. Survivors were admitted to the ICU for 69 (IQR 43–101) days. Four infants required supplemental oxygen after discharge.

Stomach position grade was significantly associated with survival (grade 1: 3/3 [100%], grade 2: 5/8 [63%], grade 3: 3/6 [50%], and grade 4: 1/9 [11%], stomach grade missing $n = 1$; $p = 0.03$). Also, a higher stomach position grade was associated with a lower o/e LHR ($p < 0.001$). In contrast, dichotomously measured liver position was not significantly associated with survival (intra-abdominal liver 8/12 [67%] and intrathoracic liver 5/15 [33%], $p = 0.13$). The o/e TFLV was significantly higher in survivors than in non-survivors (36% [IQR 31–40%] versus 28% [IQR 23–31%], $p = 0.02$). The association between o/e LHR and survival is depicted in Figure 1. The area under the receiver operating characteristic curve for prediction of survival to discharge from the o/e LHR was 0.87. The optimal cutoff, defined by highest sensitivity and specificity, for the o/e LHR to predict survival was 42%, with a sensitivity of 62% and specificity of 100%.

3.3 | Right-sided CDH expectantly managed during pregnancy

In right-sided CDH ($n = 6$), median o/e LHR was 35% (IQR 29%–41%). The survival rate was 33% (2/6) and non-surviving infants died at a median of day 16 (IQR 1–85). Four infants underwent surgical correction of the defect at day 5 (IQR 4–6), and 75% required patch repair. Pulmonary hypertension was diagnosed in 5 (83%) infants on day 1 (IQR 1–1). Treatment consisted of inhaled nitric oxide in four infants, of whom three infants were also treated with sildenafil. Surfactant was administered in four infants. Mechanical ventilation was provided for 19 (IQR 3–39) days. The prevalence of prematurity-related morbidity was as follows: necrotising enterocolitis and retinopathy of prematurity Stage ≥3 in zero infants, intraventricular haemorrhage in one infant, sepsis confirmed with blood culture in three infants and bronchopulmonary dysplasia in four infants. Infants were admitted to the ICU for 42 (IQR 9–92) days. The association between o/e LHR and survival is depicted in Figure 1. Due to the limited number of right-sided CDH cases, we did not evaluate the association between additional prenatal markers and survival in this group.

BJOG An International Journal of Obstetrics and Gynaecology

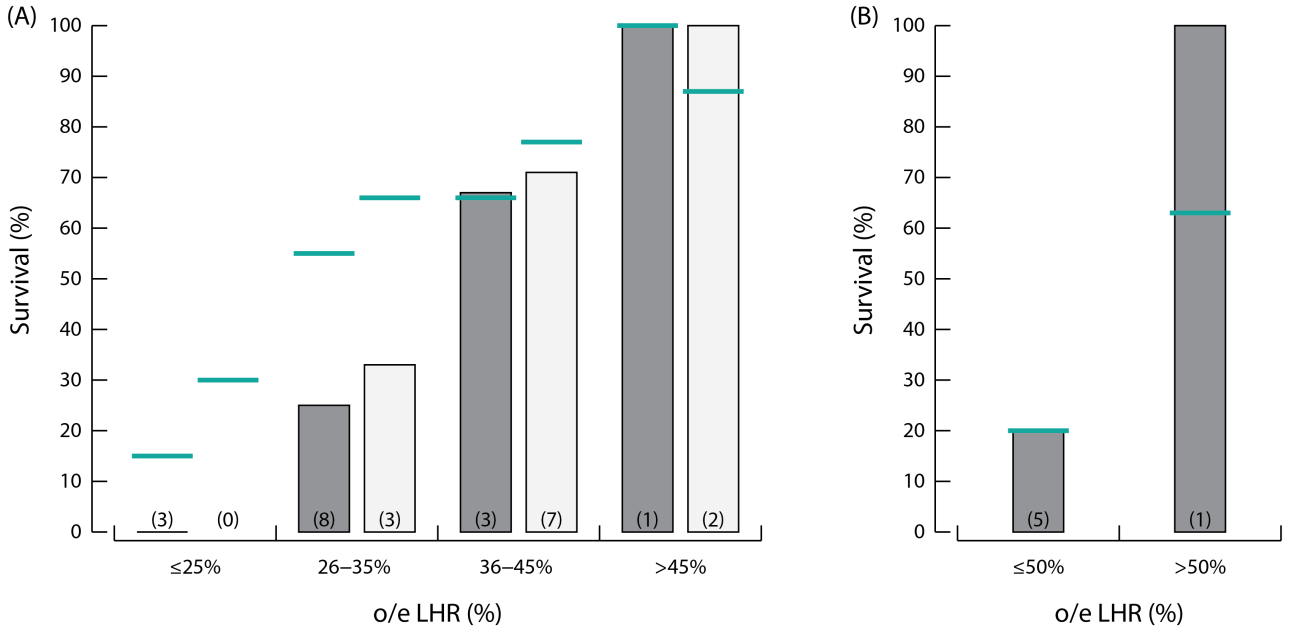

FIGURE 1 Survival rates for each severity group in infants that received expectant prenatal management with left-sided (A) and right-sided (B) congenital diaphragmatic hernia and were born at or before 32.0 weeks of gestation. The filled bars represent fetuses with intrathoracic liver position and the open bars represent fetuses with intra-abdominal liver position. Numbers per group are depicted between brackets. The solid lines represent historical data from Jani et al.[8] (A) and from Russo et al.[21] (B). Abbreviation: o/e LHR, observed to expected lung-to-head ratio.

3.4 | Fetuses that underwent FETO therapy

A total of 20 fetuses underwent FETO therapy in our cohort, of which 12 had left-sided CDH and 8 had right-sided CDH. The median duration of tracheal occlusion was 14 (IQR 10–23) days. The o/e LHR measurements before fetal surgery were 23% (IQR 20–28%) in left-sided CDH and 28% (IQR 26–37%) in right-sided CDH. Pulmonary hypertension was diagnosed in 15 (75%) infants and the remaining 5 infants died before evaluation. The survival rate was 50% (6/12) in left-sided CDH and 25% (2/8) in right-sided CDH.

3.5 | Prenatal imaging markers and survival

We performed logistic regression analyses to evaluate the associations between o/e LHR, side of the defect and FETO therapy against the outcome of survival including our complete cohort. Table 2 depicts the outcomes of the univariate logistic regression models, which showed that o/e LHR only had a significant association with survival in infants that received expectant prenatal management and in infants with left-sided CDH. The outcomes of the best fitting multivariable logistic regression model are depicted in Table 3. This final model includes the interaction term between o/e LHR and FETO (Table 3) to account for the interaction between these variables. According to this model, o/e LHR at baseline was positively associated with the odds of survival to discharge in cases that were expectantly managed during pregnancy. Conversely, this association was not present in infants who underwent FETO therapy (OR 1.01, 95% CI 0.88–1.15, $p = 0.87$; Table 3). A positive association between FETO and the odds of survival was observed in infants with o/e LHR up to 25% (Table 3). Although not significant, infants with right-sided CDH had lower odds of survival throughout all analyses (Tables 2 and 3).

4 | DISCUSSION

4.1 | Main findings

Our data from over 50 infants with CDH born at or before 32 weeks of gestation suggest that prematurity-related morbidity mainly influences mortality in infants with left-sided CDH and o/e LHR below 35%. Adding to the clinical use of prenatal ultrasound markers, the o/e LHR and stomach position are also associated with the probability of survival to discharge in very preterm born infants with left-sided CDH that are expectantly managed during pregnancy.[8,21]

4.2 | Interpretation

We observed a slightly higher overall survival rate in CDH infants born at or before 32.0 weeks of gestation than earlier reported: 43% versus 35–38%.[4,25] An explanation for this might be that we, in contrast to earlier series, excluded infants with major chromosomal and structural anomalies. Also, improvements in clinical care over the last 20 years, including the introduction of FETO for severe cases, and the high volume in the participating centres, may have contributed to the higher survival rates.[4]

TABLE 2 Results for univariate logistic regression for the odds of survival.

	All data			Left-sided CDH			Right-sided CDH			No FETO			FETO		
	n = 53			*n* = 39			*n* = 14			*n* = 33			*n* = 20		
	Survival = 23			Survival = 19			Survival = 4			Survival = 15			Survival = 8		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
o/e LHR (%)	1.07	1.01–1.15	0.314	1.11	1.03–1.23	0.017	1.04	0.96–1.15	0.343	1.20	1.07–1.41	0.008	0.98	0.85–1.09	0.675
CDH side															
Left (ref.)	—	—	—	NA			NA			—	—	—	—	—	—
Right	0.42	0.10–1.50	0.199							0.54	0.07–3.26	0.514	0.33	0.04–2.17	0.272
FETO															
No (ref.)	—	—	—	—	—	—	—	—	—	NA			NA		
Yes	0.80	0.25–2.46	0.698	1.08	0.27–4.28	0.915	0.67	0.06–7.55	0.733						

Abbreviations: CDH, congenital diaphragmatic hernia; CI, confidence interval; FETO, fetoscopic endoluminal tracheal occlusion; observed to expected LHR, lung-to-head ratio; OR, odds ratio.

TABLE 3 Results for multivariable logistic regression for the odds of survival.

	All data		
	n = 53		
	Survival = 23		
	OR	95% CI	*p*
o/e LHR (%)			
Without FETO	1.20	1.07–1.42	0.009
With FETO	1.01	0.88–1.15	0.865
CDH side			
Left (ref.)	—	—	—
Right	0.29	0.04–1.44	0.154
FETO			
No (ref.)	—	—	—
At o/e LHR = 25%	7.29	1.25–60.09	0.040
At o/e LHR = 35%	1.28	0.19–7.99	0.791
At o/e LHR = 45%	0.22	0.007–5.03	0.354
At o/e LHR = 50%	0.09	0.001–4.64	0.246

Note: This model includes the interaction term between o/e LHR and FETO therapy.

Abbreviations: CDH, congenital diaphragmatic hernia; CI, confidence interval; FETO, fetoscopic endoluminal tracheal occlusion; o/e LHR, observed to expected lung-to-head ratio; OR, odds ratio.

In our cohort, the survival rates for preterm born infants with left-sided CDH and a lesser degree of lung hypoplasia (o/e LHR ≥36%) seemed not to differ from what was observed in the algorithm of Jani et al.[8] Therefore, we speculate that prematurity-related morbidity might be a less important contributor to mortality in this selected group than the underlying pulmonary hypoplasia. It should be emphasised that the algorithm of Jani et al.[8] consists of historical data potentially underestimating current survival rates, but as similar survival rates were found in more recent studies, we do not expect a significant underestimation of differences between our cohort and this historical cohort. Furthermore, the survival rate in the group with left-sided CDH and o/e LHR of 35% or less was comparable to what is reported for infants with severe hypoplasia (o/e LHR <25%) that are born at a later gestational age. The effect of very preterm birth on survival therefore seems to be most pronounced in the group with severe left-sided CDH. We speculate that one of the explanations for this could be the fact that ECMO therapy is less likely to be offered to infants born preterm or with a birthweight below 1.8 kg.[26] Yet, the benefit of ECMO therapy in CDH is still controversial and, in fact, a considerable variability in its use in term CDH infants is present between the centres included in the current study.[27]

Prenatal grading of stomach position has been shown to correlate with respiratory outcomes and survival in term left-sided CDH infants.[14,15,28] Our results indicate that, also in very preterm born infants with left-sided CDH, the survival rates are different based on stomach position grade,

with lower survival rates for higher grades. This is consistent with the predicted outcome by o/e LHR, as a higher stomach grade was associated with a lower o/e LHR. On the other hand, stomach position grade is generally considered a proxy of liver position, but we could not confirm a statistically significant survival advantage in infants with intra-abdominal liver position.[29] This might be a consequence of our limited sample size and the fact that a standardised definition for the assessment of liver herniation is lacking. For this reason, and because of the limited number of cases with MRI investigations, we documented liver position as a dichotomous ultrasound-based variable (yes/no) rather than a continuous MRI-based variable, which potentially allows for better evaluation of the extent of liver herniation.[30–33]

The association between side of the diaphragmatic defect and survival to discharge has been the subject of debate with some studies indicating higher survival rates in left-sided CDH and others in right-sided CDH.[34,35] In our series, we observed that in this group of very preterm born infants, a right-sided defect resulted in a lower odds of survival than a left-sided defect. Although this effect was consistent in all analyses, it did not reach statistical significance, probably because of the limited number of right-sided CDH cases in our cohort.

Fetoscopic endoluminal tracheal occlusion therapy has recently been shown to be beneficial in terms of survival to discharge in infants with severe CDH, but the main limitation of fetal surgery remains the increased rate of preterm birth.[6,21,36] In our study, albeit a small observational retrospective cohort study, we observed apparent higher survival rates in infants that had been treated with FETO therapy, despite very preterm birth and only for left-sided cases.[6] Although these results are in line with recent studies, our observations should be interpreted with caution as our groups are very small.

As FETO therapy increases the chance of survival, the association between baseline o/e LHR (i.e. before fetal surgery) and survival to discharge is expected to be less strong in infants that underwent FETO.[37] In our data, we indeed only observed an association between baseline o/e LHR and survival in infants that had expectant management during pregnancy. Whether the o/e LHR after FETO therapy is associated with survival in very preterm born infants, requires further research.

4.3 | Strengths and limitations

To the best of our knowledge, this is the first study evaluating the association between various prenatal predictive imaging markers and survival in very preterm born infants with CDH. Albeit data were collected in seven large international referral centres, the rareness of the combination of very preterm birth and CDH inherently results in a limited sample size. We were therefore not able to include additional factors in our predictive models or to evaluate other neonatal outcomes because we wanted to avoid type-I-errors. Also, the number of patients was not sufficient to determine whether alternative cutoffs for severe, moderate or mild lung hypoplasia would be more accurate for this early gestational age. We do believe that our population is a valid reflection of the overall population of very preterm born CDH infants. Ideally, our results should be evaluated in a larger sample size but reaching a sufficiently large sample size in a population managed in a standardised manner will be challenging.

4.4 | Conclusion

The detrimental effects of prematurity-related morbidity are most pronounced in infants with left-sided CDH and expected severe pulmonary hypoplasia. Other than that, currently used prenatal imaging parameters are associated with postnatal survival in very preterm born infants with CDH, although solely in infants that did not receive FETO therapy. Our data provide relevant insights for counselling of parents that face imminent preterm delivery.

AUTHOR CONTRIBUTIONS

EJJHO, FMR, JAD, FK, AG, TS, NR, AGC, AB, NA, PPLC, WPdB, ES, NCJP, BEH, IKMR and PLJD were all involved in the conception of this paper. EJJHO, BEH and PLJD conceptualised and designed the statistical plan, and contributed to the analysis and the interpretation of the results. EJJHO wrote the first draft, which was critically reviewed by all authors. All authors have approved the final version of the manuscript.

ACKNOWLEDGEMENTS

None.

FUNDING INFORMATION

EJJHO and PLJD are supported by a grant from the Sophia Children's Hospital Foundation (SSWO, grant S19-12).

CONFLICT OF INTEREST STATEMENT

None declared. Completed disclosure of interests form available to view online as supporting information.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from PLJ DeKoninck upon reasonable request.

ETHICS APPROVAL

This study protocol was reviewed and approved by the Medical Ethics Review Committee of the Erasmus MC University Medical Centre, approval number MEC-2020-0134. Informed consent was waived.

ORCID

Emily J. J. Horn-Oudshoorn https://orcid.org/0000-0002-0582-1129
Jan A. Deprest https://orcid.org/0000-0002-4920-945X

REFERENCES

1. Levison J, Halliday R, Holland AJ, Walker K, Williams G, Shi E, et al. A population-based study of congenital diaphragmatic hernia outcome in New South Wales and the Australian Capital Territory, Australia, 1992–2001. J Pediatr Surg. 2006;41:1049–53.
2. McGivern MR, Best KE, Rankin J, Wellesley D, Greenlees R, Addor MC, et al. Epidemiology of congenital diaphragmatic hernia in Europe: a register-based study. Arch Dis Child Fetal Neonatal Ed. 2015;100:F137–44.
3. Purisch SE, DeFranco EA, Muglia LJ, Odibo AO, Stamilio DM. Preterm birth in pregnancies complicated by major congenital malformations: a population-based study. Am J Obstet Gynecol. 2008;199(287):e281–8.
4. Tsao K, Allison ND, Harting MT, Lally PA, Lally KP. Congenital diaphragmatic hernia in the preterm infant. Surgery. 2010;148:404–10.
5. Deprest JA, Benachi A, Gratacos E, Nicolaides KH, Berg C, Persico N, et al. Randomized trial of fetal surgery for moderate left diaphragmatic hernia. N Engl J Med. 2021;385:119–29.
6. Deprest JA, Nicolaides KH, Benachi A, Gratacos E, Ryan G, Persico N, et al. Randomized trial of fetal surgery for severe left diaphragmatic hernia. N Engl J Med. 2021;385(2):107–118.
7. Balayla J, Abenhaim HA. Incidence, predictors and outcomes of congenital diaphragmatic hernia: a population-based study of 32 million births in the United States. J Matern Fetal Neonatal Med. 2014;27:1438–44.
8. Jani J, Nicolaides KH, Keller RL, Benachi A, Peralta CF, Favre R, et al. Observed to expected lung area to head circumference ratio in the prediction of survival in fetuses with isolated diaphragmatic hernia. Ultrasound Obstet Gynecol. 2007;30:67–71.
9. Ali K, Grigoratos D, Cornelius V, Davenport M, Nicolaides K, Greenough A. Outcome of CDH infants following fetoscopic tracheal occlusion – influence of premature delivery. J Pediatr Surg. 2013;48:1831–6.
10. Bouchghoul H, Dumery G, Russo FM, Cordier AG, Le Sache N, Debeer A, et al. Optimal gestational age at delivery in isolated left-sided congenital diaphragmatic hernia. Ultrasound Obstet Gynecol. 2021;57:968–73.
11. Jani JC, Benachi A, Nicolaides KH, Allegaert K, Gratacós E, Mazkereth R, et al. Prenatal prediction of neonatal morbidity in survivors with congenital diaphragmatic hernia: a multicenter study. Ultrasound Obstet Gynecol. 2009;33:64–9.
12. Snoek KG, Reiss IK, Greenough A, Capolupo I, Urlesberger B, Wessel L, et al. Standardized postnatal management of Infants with congenital diaphragmatic hernia in Europe: the CDH EURO Consortium consensus – 2015 update. Neonatology. 2016;110:66–74.
13. Peralta CF, Cavoretto P, Csapo B, Vandecruys H, Nicolaides KH. Assessment of lung area in normal fetuses at 12–32 weeks. Ultrasound Obstet Gynecol. 2005;26:718–24.
14. Cordier AG, Jani JC, Cannie MM, Rodo C, Fabietti I, Persico N, et al. Stomach position in prediction of survival in left-sided congenital diaphragmatic hernia with or without fetoscopic endoluminal tracheal occlusion. Ultrasound Obstet Gynecol. 2015;46:155–61.
15. Weller K, Peters NCJ, van Rosmalen J, Cochius-Den Otter SCM, DeKoninck PLJ, Wijnen RMH, et al. Prenatal stomach position and volume in relation to postnatal outcomes in left-sided congenital diaphragmatic hernia. Prenat Diagn. 2021;42:338–47.
16. Kitano Y, Okuyama H, Saito M, Usui N, Morikawa N, Masumoto K, et al. Re-evaluation of stomach position as a simple prognostic factor in fetal left congenital diaphragmatic hernia: a multicenter survey in Japan. Ultrasound Obstet Gynecol. 2011;37:277–82.
17. Cannie M, Jani J, Meersschaert J, Allegaert K, Done E, Marchal G, et al. Prenatal prediction of survival in isolated diaphragmatic hernia using observed to expected total fetal lung volume determined by magnetic resonance imaging based on either gestational age or fetal body volume. Ultrasound Obstet Gynecol. 2008;32:633–9.
18. Debus A, Hagelstein C, Kilian AK, Weiss C, Schonberg SO, Schaible T, et al. Fetal lung volume in congenital diaphragmatic hernia: association of prenatal MR imaging findings with postnatal chronic lung disease. Radiology. 2013;266:887–95.
19. Reiss I, Schaible T, van den Hout L, Capolupo I, Allegaert K, van Heijst A, et al. Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH EURO Consortium consensus. Neonatology. 2010;98:354–64.
20. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016;48:333–9.
21. Russo FM, Cordier AG, Basurto D, Salazar L, Litwinska E, Gomez O, et al. Fetal endoscopic tracheal occlusion reverses the natural history of right-sided congenital diaphragmatic hernia: European multicenter experience. Ultrasound Obstet Gynecol. 2021;57:378–85.
22. Russo FM, Cordier AG, De Catte L, Saada J, Benachi A, Deprest J, et al. Proposal for standardized prenatal ultrasound assessment of the fetus with congenital diaphragmatic hernia by the European reference network on rare inherited and congenital anomalies (ERNICA). Prenat Diagn. 2018;38:629–37.
23. Gupta VS, Harting MT. Congenital diaphragmatic hernia-associated pulmonary hypertension. Semin Perinatol. 2019;44:151167.
24. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163:1723–9.
25. Peluso AM, Othman HF, Elsamny EM, Sammour I, Yeaney NK, Aly H. Survival trends and outcomes among preterm infants with congenital diaphragmatic hernia. J Perinatol. 2020;40:263–8.
26. Jancelewicz T, Brindle ME, Harting MT, Tolley EA, Langham MR Jr, Lally PA, et al. Extracorporeal membrane oxygenation (ECMO) risk stratification in newborns with congenital diaphragmatic hernia (CDH). J Pediatr Surg. 2018;53:1890–5.
27. Grover TR, Rintoul NE, Hedrick HL. Extracorporeal membrane oxygenation in infants with congenital diaphragmatic hernia. Semin Perinatol. 2018;42:96–103.
28. Abbasi N, Ryan G, Ruano R, Cortes MS, Ye XY, Shah PS, et al. Inter-rater agreement for sonographic stomach position classification in fetal diaphragmatic hernia across the north American fetal therapy network (NAFTNet). Prenat Diagn. 2021;42:348–56.
29. Cordier AG, Cannie MM, Guilbaud L, De Laveaucoupet J, Martinovic J, Nowakowska D, et al. Stomach position versus liver-to-thoracic volume ratio in left-sided congenital diaphragmatic hernia. J Matern Fetal Neonatal Med. 2015;28:190–5.
30. Cannie MM, Cordier AG, De Laveaucoupet J, Franchi-Abella S, Cagneaux M, Prodhomme O, et al. Liver-to-thoracic volume ratio: use at MR imaging to predict postnatal survival in fetuses with isolated congenital diaphragmatic hernia with or without prenatal tracheal occlusion. Eur Radiol. 2013;23:1299–305.
31. Lazar DA, Ruano R, Cass DL, Moise KJ Jr, Johnson A, Lee TC, et al. Defining "liver-up": does the volume of liver herniation predict outcome for fetuses with isolated left-sided congenital diaphragmatic hernia? J Pediatr Surg. 2012;47:1058–62.
32. Zamora IJ, Olutoye OO, Cass DL, Fallon SC, Lazar DA, Cassady CI, et al. Prenatal MRI fetal lung volumes and percent liver herniation predict pulmonary morbidity in congenital diaphragmatic hernia (CDH). J Pediatr Surg. 2014;49:688–93.
33. Niemiec SM, Louiselle AE, Phillips R, Gien J, Zaretsky MV, Derderian SC, et al. Third-trimester percentage predicted lung volume and percentage liver herniation as prognostic indicators in congenital diaphragmatic hernia. Pediatr Radiol. 2022;53:479–86.
34. Pinton A, Boubnova J, Becmeur F, Kuhn P, Senat MV, Stirnemann J, et al. Is laterality of congenital diaphragmatic hernia a reliable prognostic factor? French national cohort study. Prenat Diagn. 2020;40:949–57.
35. Skari H, Bjornland K, Haugen G, Egeland T, Emblem R. Congenital diaphragmatic hernia: a meta-analysis of mortality factors. J Pediatr Surg. 2000;35:1187–97.
36. Stolar CJH, Flake AW, Losty PD. Fetal surgery for severe left diaphragmatic hernia. N Engl J Med. 2021;385:2111–2.

37. Trad ATA, Czeresnia R, Ibirogba E, Narang K, Ruano R. Sonographic pulmonary response after tracheal occlusion in fetuses with severe isolated congenital diaphragmatic hernia. J Clin Ultrasound. 2022;50:185–90.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Horn-Oudshoorn EJJ, Russo FM, Deprest JA, Kipfmueller F, Geipel A, Schaible T, et al. Survival in very preterm infants with congenital diaphragmatic hernia and association with prenatal imaging markers: A retrospective cohort study. BJOG. 2023;00:1–9. https://doi.org/10.1111/1471-0528.17497