REVIEW

Prenatal detection of pulmonary hypoplasia in fetuses with congenital diaphragmatic hernia: A systematic review and meta-analysis of diagnostic studies

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Abstract

Background. Fetuses with congenital diaphragmatic hernia (CDH) are at risk of death from pulmonary hypoplasia at birth. *Objective.* To determine the value of prenatal imaging parameters for predicting lethal pulmonary hypoplasia in fetuses with CDH.

Search strategy. Relevant papers were identified by searching MEDLINE (1966–2008), EMBASE (1988–2008) and the Cochrane Library (2008 issue 3).

Selection criteria. Selected studies examined diagnostic tests for the prenatal prediction of lethal pulmonary hypoplasia in fetuses with CDH. The primary outcome measure was perinatal survival.

Results. Twenty-one studies fulfilled the entry criteria, of which six examined entirely unique heterogeneous parameters and the remaining 15 examined lung-head ratios (LHR) and/or the presence of liver in the fetal thorax. The strongest association was that of LHR \geq 0.6 compared to <0.6 (OR: 17.02; 95% CI: 2.10–137.89), although more clinically relevant was that of LHR > 1.0 (OR: 5.07; 95% CI: 2.94–8.74). The finding of liver in the fetal chest was a poor prognostic feature (survival OR: 0.32; 95% CI: 0.21–0.49).

Conclusion. In CDH, LHR and the presence of liver in the fetal thorax may be a useful predictive indicator of perinatal survival. Future usage of developing techniques needs careful evaluation prior to usage to guide therapy.

Keywords: Congenital diaphragmatic hernia, pulmonary hypoplasia, diagnostic test, ultrasound, lung-head ratio

Introduction

Congenital diaphragmatic hernia (CDH) has an incidence of approximately 2 per 1000 livebirths [1] and 3–5 per 10,000 total births [2,3]. Recent population-based studies quote an overall perinatal survival rate of 60% with the majority of deaths occurring secondary to pulmonary hypoplasia or associated pulmonary hypertension in the neonatal period [1,4]. The presence of associated congenital structural abnormalities, including karyotypic anomalies, worsens the overall prognosis [5]. However, the antenatal identification of those fetuses most likely to

develop lethal pulmonary hypoplasia remains a diagnostic challenge.

Many different imaging parameters have been investigated in the literature to predict the presence of pulmonary hypoplasia. These include measurements of the fetal thorax or lung, fetal breathing movements and acceleration and ejection time ratio within the pulmonary arteries. The lung-head ratio (LHR), most commonly measured by ultrasound, has been the most extensively studied [6,7]. The LHR, measured using ultrasound, is the ratio of the area of the contralateral lung (to the hernia defect) to the fetal head circumference. The fetal lung area is

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measured at the plane of the four chamber view of the fetal heart and the most commonly performed method uses the longer of two perpendicular transverse measurements, in millimeters [8]. The fetal head circumference is also in millimetres. This measurement has been used to guide prognosis and offer fetoscopically-directed fetal therapy to those fetuses in the worst prognostic groups by fetal surgical centres both in the USA and in Europe [9,10]. However, clinicians offering such therapy have used differing thresholds for intervention. This is because there is currently no definitive consensus as to which value of LHR that confers the optimal threshold for intervention, or indeed if this is the best test of adverse prognosis to use.

A recent systematic review examined the usefulness of the LHR for predicting outcome in fetuses with CDH [11]. They concluded that there was no statistically significant difference in LHR in survivors and non survivors with CDH. This, however, excluded fetuses that had LHR measurements performed > 32 weeks because of a study that reported favourable surgical outcomes up to 32 weeks and the principle that surgery beyond that time was less likely to be beneficial. However, after this gestation it would still be useful to have prognostic information to guide parents and professionals. Although LHR is universally regarded as a guide to prognosis, it has not been evaluated against alternative diagnostic tests for predicting neonatal outcome. In addition, the FETO group in Europe is advocating a randomised controlled trial (RCT) of 'Tracheal occlusion to accelerate lung growth' (TOTAL) where transient occlusion of the trachea by a 'balloon' is performed between 30 and 32+6 weeks in pregnancies with CDH is present. The balloon will then be removed at 34 + 6 weeks. They have used an additional parameter, the observed to expected LHR (value between 25 and 35%) to define those in a moderately poor prognostic group (survival rate: 30-60%) and therefore at possible benefit of intervention. The observed to expected ratio describes: the actual LHR as described by Metkus, divided by the observed mean LHR for gestational age from a group of normal fetuses. This parameter has also been shown to be a predictor of survival in some series [12].

We therefore undertook a systematic review of the literature in order to establish the best and most predictive test of pulmonary hypoplasia secondary to isolated CDH. We wanted to evaluate all the available diagnostic tests (often described in the methodological literature as the index test) using the imaging modalities of ultrasound or MRI. We subdivided this into those fetuses where the predictive test was performed up to 32 weeks gestation, to assess the usefulness of the test to guide intervention and those predictive tests where there was no gestational age restriction, to guide counselling and prognosis irrespective of gestation.

Methods

Sources and study selection

Literature was identified by searching bibliographic data bases: MEDLINE (1966–May 2008), EM-BASE (1988–May 2008) and the Cochrane library (2008 issue 3). The search used the MESH headings 'fetal development', 'fetal diseases', 'fetus', 'fetal research', 'fetal therapies', 'magnetic resonance imaging', 'ultrasonography' and 'lung' with free text terms, the details of which are available from the authors. There were no language restrictions. Reference lists of all known reviews and primary studies were checked.

Study selection criteria.

- 1. *Population:* Human pregnancies with fetuses complicated by isolated CDH (left or right sided).
- 2. *Test:* Any diagnostic test using *in-utero* imaging (ultrasound or magnetic resonance imaging) for predicting pulmonary hypoplasia. This was initially reviewed at any gestation and then only those studies using imaging prior to 32 completed weeks were re-analysed.
- 3. Outcome: Gross perinatal survival.
- 4. *Study design:* Observational studies, evaluating the effect of a diagnostic test and pulmonary hypoplasia prediction. Case series where fetuses received prenatal intervention were not included as this could potentially affect the neonatal outcome. Case series >5 patients were included.

The title and abstracts of the electronic searches were examined, and the full manuscripts of all the potentially relevant citations were obtained. The final inclusion/exclusion decisions were made after evaluation of the full papers by two reviewers (EK and DL). Figure 1 represents a numerical flow diagram of included studies. Studies were rejected if they did not meet the inclusion criteria above and or 2×2 table of outcome could not be constructed. In cases of data duplication (i.e. the same data published in two or more reports), only the most recent report with the largest cohort size and the longest follow up was included.

Quality assessment and data abstraction

Two reviewers (EK and DL) extracted data from all papers meeting the selection criteria including



Figure 1. Flow diagram of included studies.

data on features of methodological quality. The studies were assessed for quality by the following criteria:

- 1. *Study design*: Observational studies were considered ideal.
- 2. *Data collection*: Prospective collection of data was considered ideal, retrospective collection was considered second best. Consecutive enrolment was considered preferable to random enrolment.
- 3. *Description of interventions*: Considered adequate if the description allowed replication by other researchers.
- 4. Blinding of assessors of imaging to outcome: This was considered ideal.
- Outcome ascertainment: Greater than 90% follow up of the original study population was considered ideal, less than 90% was considered second best.

Data extraction sought information regarding the underlying pathology, severity and diagnostic tests performed. Details of diagnostic test included the technique, timing and number of diagnostic tests performed. The primary outcome measure was overall perinatal survival. Data were abstracted to allow construction of 2×2 tables of treatment

versus control. Data extraction revealed many instances of inexact duplication (i.e. new data with some overlap with data in a previous report from the same centre.

We initially included all such reports in our systematic review to allow us to examine the development of the work. However, for metaanalysis, we only used the largest and the most complete data set, in the presence of partial duplication of results.

The results were expressed as odds ratios (95% CI). The advantage of this is that it combines sensitivity and specificity together into one index of diagnostic performance; the higher the odds ratio, the better the association between survival and the diagnostic test used [13]. This way the value of the test can be interpreted without the need for two indices. The Mantel–Haenszel method was used to generate odds ratios as this has been shown to be the preferred method with rare events with the event rate >1% [14].

Results

A total of 8581 citations were generated by the search of which 61 were considered relevant and the full

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discharge				expiratory ratio					unreported	et al. [23]
Posthospital	8/14	Not defined	34-41	Inspiratory:	Ultrasound	16	Other anomalies	CDH	Unreported,	Badalian
Ourchotica	liver down 9		60-07	taver up	DIM	60		CDH	unreported	W aish CL al. [24]
				ratio					-	
Unreported	19 survived total	Autopsy	28–37	Power Doppler, lung:thorax	Ultrasound	42	Other anomalies	Isolated R and L CDH	Prospective, unreported	Mahieu-caputo et al. [21]
		insufficiency		definition)				CDH	consecutive	
60 days	7/15 alive total	Clinical pulmonary	24–26	liver up LHR (Metkus	Ultrasound	31	Other anomalies	Isolated left	Prospective,	Lipshutz et al. [6]
Unreported		Inol delified	ОПКНОМП	definition),	Ultrasound	1/0	Outer anomatics	CDH	nerrospective, unreported	ivielkus el al. [o]
		-		definition)		l	:	CDH	arbitrary	et al. [20]
90 days	16/20	Not defined	Unknown	liver up LHR (Metkus	Ultrasound	20	Liver herniation	Isolated L	Retrospective,	Sbragia
220 days	8/11	Not defined	21–28	LHR (Metkus definition),	MRI	26	Other anomalies	Isolated left CDH	Prospective, unreported	Paek et al. [19]
									consecutive patient enrollment	
Hospital discharge	8 LHR < 1.4, 3 LHR < 1.4	Autopsy lung weight	Mean 34	LHR (Metkus definition)	Ultrasound	26	Other anomalies	Isolated left CDH	Retrospective collection,	Laudy et al. [18]
years) or death		analysis – not defined							arbitrary	
Surgery (within 3	13/22 alive total	Ventilation parameters not available for	16–38	LHR (Metkus definition)	Ultrasound	34	Other anomalies	Isolated CDH L and R	Prospective, patient enrolment	Heling et al. [17]
		body weight		definition)				CDH	collection, patient enrolment	et al. [7]
Unreported	126 9/12 total	Autopsy lung/	22–38	LHR (Metkus	Ultrasound	15	Other anomalies	Isolated left	Retrospective	Yoshimwa
3 months	Liver up 85, liver down	Not defined	22–28	Liver up, O/F LHR	Ultrasound	354	Other anomalies	Isolated left CDH	Retrospective, consecutive	Jani et al. [16]
	liver down 75		001-11	definition), liver up	CILLASOULU	FOT		CDH CDH	consecutive	Jam Ct al. [14]
home	2		0000	definition), liver up			-	CDH	- - -	et al. [15]
Discharge to	24/28	Not defined	27	LHR (Metkus	Ultrasound	43	Other anomalies	Isolated left	Unreported	Arkovitz
Follow up % length	Outcome (survival)	r'uimonary hypoplasia definition	Gestation of test (weeks)	Diagnostic test	Imaging	Population	Exclusions	Pulmonary pathology	Quality of study	Study identifier

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Table I. Table of included studies.

Study identifier	Quality of study	Pulmonary pathology	Exclusions	Population	Imaging	Diagnostic test	Gestation of test (weeks)	Pulmonary hypoplasia definition	Outcome (survival)	Follow up % length
Bahlmann et al. [24]	Prospective, unrenorted	Isolated L and R CDH	Other anomalies	19	Ultrasound	Lung diameter	19–38	Autopsy	3/10	Unreported
Fuke et al. [25]	Prospective, unreported	CDH L and R	Other anomalies	17	Ultrasound	Acceleration time: ejection time ratio fetal pulmonary arteries	20–39	Autopsy or persistent pulmonary hypertension	11/15	Unreported
Thebaud et al. [26]	Retrospective, unreported	CDH	Other anomalies /terminations	40	Ultrasound	Liver up	Unknown	Autopsy lung/body weight	8/29	Unreported
Broth et al. [27]	Retrospective, consecutive	CDH	Other anomalies	10	Ultrasound	Fetal pulmonary artery blood flow changes with maternal hyperoxygenation	30–36	Clinical pulmonary hypoplasia or persistent pulmonary hymertension	6/10	Unreported
Mahieu-Captu et al. [28]	Prospective	Isolated R and L CDH	Other anomalies	13	MRI	Liver up, lung volume	Unknown	Autopsy	4/13	4 months
Thorpe-Beeston et al. [29]	Unreported, consecutive	Isolated CDH	Termination	17	Ultrasound	Fetal breathing movements	Unknown	Not defined	9/15	Unreported
Usui et al. [30]	Retrospective, consecutive	Isolated CDH	Other anomalies, unclear views	68	Ultrasound	Early and late Lung thorax ratio and LHR (1.2 and 2 Methus definition)	Early < 33 weeks, late > 34 weeks	Not defined	43/55	2 months
Keller et al. [31]	Prospective, unreported	Left sided isolated, liver up	Treatment group, other anomalies	46	Ultrasound	LHR (Metkus definition)	21–33	Not defined	10/21	Hospital discharge

Table I. (Continued).

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manuscript reviewed but of these only 21 fulfilled the entry criteria (Figure 1). The most common reason for exclusion was lack of outcome data. Studies were also excluded if they failed to meet the entry criteria or 2×2 tables of outcome were not available. The details of the included studies are included in Table I. The quality of these studies is described in Figure 2.

Eighteen studies used prenatal ultrasound as the diagnostic test imaging modality while three other studies used *in-utero* magnetic resonance imaging (MRI) – these results will be considered separately.

Ultrasound findings

The most frequently used diagnostic test was LHR all performed using ultrasound. All studies using this test used the LHR technique described by Metkus [6]. Within this group, two studies considered the diagnostic threshold of a LHR >0.6 [9,17], eight considered LHR ≥ 1.0 [6,7,10–12,16,17,30], seven studies considered LHR ≥ 1.4 [6,11,12,16,17,18], three LHR ≥ 1.2 [11,17,29] and two LHR ≥ 1.6 [11,20] for the diagnosis of pulmonary hypoplasia. Although LHR is a continuous variable, the studies provided data about absolute 'cut offs' and outcome and therefore this is how our data is presented. All studies for which numerical data regarding LHR is available contained data for left sided isolated CDH only except one which combined left- and right-sided lesions [17]. This study is not included in the data < 33 weeks.

All gestations: LHR

The different diagnostic thresholds of LHR ≥ 0.6 , ≥ 1.0 , ≥ 1.2 , 1.4 or ≥ 1.6 had a significant association with perinatal survival. The odds ratio (OR) was greatest for LHR ≥ 0.6 compared to < 0.6 (OR:



Figure 2. Quality of included studies.

17.02, 95% CI: 2.10–137.89); however, there were only seven fetuses with LHR < 0.6 within the literature that met the criteria for inclusion within this review.

Fetuses with LHR \geq 1.0 had a survival OR of 5.07 (95% CI: 2.94–8.79), for those with LHR \geq 1.2 was 4.35 (95% CI: 2.44–7.74), LHR \geq 1.4, OR of 3.05 (95% CI: 1.79–5.21) and for LHR \geq 1.6, OR of 5.49 (95% CI: 2.19–13.79).

It was not possible to stratify the data further for additional LHR values given the data available as the data was reported with these specific limits only.

Conversely, fetuses with the liver present in the fetal thorax on ultrasound had less chance of perinatal survival compared to those fetuses with liver in the fetal abdomen (OR: 0.32; 95% CI: 0.21–0.49).

Only three studies provided data for the measured LHR in conjunction with the presence of liver in the fetal thorax [16,17,19]. Of theses two studies [15,17] included both left- and right-sided diaphragmatic hernia and from the data presented in this article, it was not possible to extract information for left-sided hernias only. The OR survival for the ultrasound finding of LHR \geq 1.0 compared to <1.0 was OR: 7.72 (95% CI: 2.70– 22.07). Data was also available for the ultrasound finding of liver up and LHR \geq 1.4 which had an OR of 2.15 (95% CI: 0.81–5.76).

Additional ultrasound tests

In addition, six further studies utilised prenatal diagnostic tests [23–25,27,29,30] and fulfilled the entry criteria, but the heterogeneous nature of the outcomes studied and small sample size of the reports evaluating these diagnostic tests mean they can not be subject to comparative or statistical analysis. The details of the tests examined are provided in Table I.

Data for imaging prior to 33 weeks

Association with LHR. Six studies had data available for imaging prior to 33 weeks [6,10,11,15, 17,18]. The data were graphically displayed in forest plots [Figures 3(a)-3(c)].

Statistical data were only available for the LHR > or <1.0, 1.2 and 1.4 when imaging prior at earlier gestations was considered. The odds ratio for survival was greater, the lower the comparison threshold used.

The odds ratio for survival for LHR \geq 1.0 was 7.74 (95% CI: 3.96–15.13). The odds ratio for survival for LHR \geq 1.2 was 3.44 (95% CI: 1.86–6.36). The odds ratio for survival for LHR \geq 1.4 was 2.43 (95%

Study or sub-category	Survival LHR>thresho n/N	old Survival LHR <threshold n/N</threshold 	d OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
01 survival LHR 1.0 paek lipshultz Arkovitz	8/8 7/12 16/17	0/3 0/3 8/11		0.17 1.45 2.57	119.00 [1.95, 7273.18] 9.55 [0.40, 225.19] 6.00 [0.54, 67.28]
jani Subtotal (95% CI) Total events: 135 (Treatment), Test for heterogeneity: Chi ² = 1 Test for overall effect: Z = 5.98	104/138 175 22 (Control) .83, df = 3 (P = 0.61), l ² = 0% (P < 0.00001)	14/46 63	•	23.26 27.46	6.99 [3.34, 14.62] 7.74 [3.96, 15.13]
02 survival LHR 1.2	4/4	4/7		1.56	7 00 [0 27, 178 47]
jani Subtotal (95% CI) Total events: 83 (Treatment), 4 Test for heterogeneity: Chi ² = 0 Test for overall effect: Z = 3.94	79/104 108 3 (Control) .20, df = 1 (P = 0.66), I ² = 0% (P < 0.0001)	39/80 87	*	47.65 49.20	3.32 [1.77, 6.23] 3.44 [1.86, 6.36]
03 survival LHR 1.4	0.44	0./1			
раек sbragia	8/11	8/9		10.79	Not estimable 0.33 [0.03, 3.93]
jani Subtotal (95% CI) Total events: 21 (Treatment) 38 Test for heterogeneity: Chi ² = 3 Test for overall effect: Z = 1.75	13/17 29 3 (Control) .29, df = 1 (P = 0.07), l ² = 69.6 (P = 0.08)	30/69 79 %	•	12.55 23.34	4.23 [1.25, 14.28] 2.43 [0.90, 6.56]
(a)		0.001 Favours LHR< thresh	0.01 0.1 1 10 10 hold Favours LH	00 1000 IR > threshold	
Study Survival or sub-category	liver up and LHR> threshold n/N	Survival liver up and LHR < n/N	threshold OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
01 liver up and LHR >1.0 paek	5/5	0/3		1.08	77.00 [1.22, 4848.82]
jani Subtotal (95% CI) Total events: 45 (Treatment), 3 Test for heterogeneity: Chi ² = 0 Test for overall effect: Z = 4.61	40/59 64 (Control) .47, df = 1 (P = 0.49), I ² = 0% (P < 0.00001)	3/27 30	*	28.72 29.80	16.84 [4.51, 62.96] 19.03 [5.43, 66.66]
02 survival liver up and LHR >1 paek jani Subtotal (95% CI) Total events: 14 (Treatment), 3 Test for heterogeneity: Chi ² = 0	.4 1/1 13/17 18 4 (Control) .10, df = 1 (P = 0.75), I ² = 0%	4/7 30/69 76		9.75 60.45 70.20	2.33 [0.07, 76.67] 4.23 [1.25, 14.28] 3.96 [1.26, 12.50]
Test for overall effect: Z = 2.35	(* = 0.02)				
		0.001		00 1000	
(b)		and LHR < thresho	old and LHR > tl	nreshold	
Study or sub-category	survival: liver up n/N	survival: liver down n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% Cl
paek Arkovitz Jani 2007	5/8 9/12 85/161	3/3 15/16 126/168		2.98 5.08 91.95	0.22 [0.01, 5.80] 0.20 [0.02, 2.23] 0.37 [0.23, 0.59]
Total (95% CI) Total events: 99 (survival: liver Test for heterogeneity: Chi ² = 0 Test for overall effect: Z = 4.43	181 up), 144 (survival: liver down) .33, df = 2 (P = 0.85), l ² = 0% (P < 0.00001)	187	•	100.00	0.36 [0.23, 0.57]
(c)		0.001 Eavoi	0.01 0.1 1 10 10 urs liver down Favours live	00 1000 rup	

Figure 3. Survival according to (a) LHR ultrasound < 33 weeks, (b) liver in fetal thorax and LHR ultrasound < 33 weeks and (c) liver in fetal thorax: ultrasound < 33 weeks.

CI: 0.9–6.56). Overall, the odds ratio values were greater than imaging performed without gestation restrictions although the values were similar. The

studies considering LHR > 1.4 showed considerable heterogeneity ($I^2 = 70.9\%$) and should be interpreted with caution.

Association with liver in the fetal thorax. Three studies examined this association in imaging prior to 33 weeks [10,15,17]. The OR with survival for liver in the thorax was 0.36 (95% CI: 0.23-0.56).

LHR and liver in the fetal thorax. Only two studies had data to available examine the effect of LHR on survival with the liver in the fetal thorax when the imaging was performed prior to 33 weeks [11,17]. The results are displayed in Figure 3(b). The improved survival for those fetuses with LHR \geq threshold compared to those <the threshold value being studied was more marked for those fetuses with LHR \geq 1.0 (OR: 19.03; 95% CI: 5.43–66.66) compared to those \geq 1.4 (OR: 3.96; 95% CI: 1.26–12.50).

MRI imaging – All gestations

Three studies used MRI as the imaging modality [17,21,27]. However, one of those studies used ultrasound to determine the LHR and liver position. This was therefore analysed within the ultrasound section. Thus, only two studies had extractable data and this was for liver position only [21,27]. This revealed a poorer chance of survival with liver in the fetal thorax (survival OR: 0.14; 95% CI: 0.039–0.48).

Both studies performed MRI imaging after 33 weeks and it was therefore not possible to provide comparative data for imaging prior to 33 weeks gestation.

Discussion

CDH is a potentially surgically correctable fetal malformation but significantly it carries a significant mortality rate prior to surgery [4]. It is the 'hidden mortality' of pulmonary hypoplasia that is associated with at least 20-30% of mortality observed with this congenital anomaly [3]. Because of the associated high perinatal loss rates, prenatal diagnosis within fetal surgical centres has lead to triage and the potential for fetal therapy in the most severe cases, principally by fetal 'transient tracheal occlusion', initially as open fetal surgery [32] and more contemporaneously using endoscopic techniques [10,33]. Such therapy has been focussed on those pregnancies where the fetus has the greatest risk of developing pulmonary hypoplasia. However, various predictive diagnostic tests have been used such as sonographic estimation of LHR, with varying different thresholds suggested to denote poor prognostic groups. The tests and parameters used prospectively to ascertain the risk of pulmonary hypoplasia are therefore important and have engendered much debate and controversy [17,34,35].

The LHR is often quoted in the literature as prognostic for outcome in terms of perinatal mortality secondary to pulmonary hypoplasia. This metaanalysis concurs with that view and gives cumulative information as to the threshold of sensitivity of such a diagnostic test. LHR of ≥ 1.6 , ≥ 1.4 , ≥ 1.2 , ≥ 1.0 and ≥ 0.6 were all associated with favourable survival compared to LHR < 1.6, < 1.4, < 1.0 and < 0.6, respectively. The LHR ≥ 0.6 had the greatest odds ratio for perinatal survival suggesting that the survival difference of LHR > and < 0.6 is greater than that between \geq and <1.0, 1.4 or 1.6. However, the confidence intervals reported are wide and only in seven fetuses was the LHR < 0.6. This level of LHR is also so small and rarely encountered that it is of limited clinical usefulness, but the results have been included for completeness. At a threshold of LHR >1.0, there was also a strong survival advantage compared to LHR < 1.0. From our data, a total of 82 fetuses had an ultrasound measured LHR < 1.0 of which 31 survived (37.8%). The available literature did not allow further stratification of the LHR values because these were the only reported outcomes studied within each paper.

This information has important implications for counselling of patients. In addition, the difference in survival for fetuses with LHR ≥ 1.4 compared to < 1.4, although significant, is less marked than the difference in survival for fetuses with LHR ≥ 1.0 compared to < 1.0. This is also important given the current introduction of fetoscopic tracheal occlusion, which is being offered to fetuses with the worst perinatal outlook. Interestingly, the two groups that have published data and provided comparative data on this subject have used LHR 1.4 and 1.0 as entry criteria. Harrison's group in the USA used an LHR (assessed using ultrasound) below 1.4 as threshold for intervention, and their randomised controlled trial was stopped prematurely because of the unexpectedly high survival rate in the standard care group [32]. There was international debate that this perceived similarity of outcome in the therapy and conservative group was because the inclusion of fetuses with good prognosis of survival in both arms of the study. In contrast, the Eurofetus consortium, led by Deprest et al. [33] used LHR < 1.0 as a threshold for fetoscopic 'plug' therapy and demonstrated an improved survival in their comparative, non-randomised cohort of treated compared to conservatively managed pregnancies with CDH. Our results would help to explain that in that there was a greater difference in survival for fetuses with LHR > 1.0 compared to < 1.0 than between fetuses with LHR >1.4 compared to <1.4.

The diagnostic finding of fetal liver in the thorax, using both ultrasound and MRI, has also been associated with adverse perinatal outcome and this systematic review supports supposition. This finding was constant throughout the studies although the degree of association was variable. In addition, diagnostic information as to the extent of fetal liver herniation into the thorax was not quantified and it is possible that the amount of liver in the chest may be of significance. Comparative MRI data was only available for evaluating liver in the fetal thorax. However, as MRI is becoming used with increasing frequency, this may need future re-evaluation.

The primary outcome measure in this systematic review was perinatal mortality. Although this is largely due to the presence of severe pulmonary hypoplasia/ hypertension in the neonatal period, it was not always clarified within the studies. Even at autopsy the definition of pulmonary hypoplasia is under debate, and autopsy data was not available for all fetuses that did not survive. The details of the assessment of pulmonary hypoplasia are documented in Table I. Data regarding respiratory function and support needed after birth was also incompletely reported in these studies. In addition, some babies received ECMO support, which may have influenced overall survival.

A further limitation in our study is the timing of follow up of included studies (as documented in Table I). This was often unreported or stated as 'until discharge home'. This again reflects the differences in included studies and adds the additional potential bias of postnatal surgery into the outcome measure. It was not possible to standardise outcome time as the data was not available to do so.

The gestational age at which the diagnostic tests were performed, and the measurements made were also variable. There is evidence that LHR increases with gestation and this therefore may have an impact on perinatal mortality and the association with outcome [15]. There appears to be disagreement in the literature regarding the optimal timing of LHR measurement and this also needs to be further addressed in prospective studies [15]. However, with the launch of the TOTAL RCT study of transient occlusion between 30 and 32 + 6 weeks in pregnancies with CDH and the observed to estimated LHR is between 30 and 60%, inclusion of data in systematic reviews in the third trimester would appear more pertinent.

However, within these limitations, it would seem that LHR as measured by ultrasound may be a useful prognostic indicator for perinatal survival. Our results also reveal that LHR is the most extensively studied parameter for providing prognostic information in this area. Although many other investigations and diagnostic tests have been used in an attempt to stratify risk of pulmonary hypoplasia, such as fetal breathing movements [29] and acceleration time: ejection time ratio in the fetal pulmonary arteries [25], there is insufficient data in the literature to quantify their usefulness. Thus, given the evidence available, it would seem reasonable to utilise this when providing prognostic information.

The strength of association with survival is strongest for those fetuses with LHR ≥ 1.0 compared to < 1.0. This is further strengthened for those fetuses with LHR >1.0 who also have liver herniation into the fetal thorax, compared to those with liver herniation and LHR < 1.0. This is contrary to the findings of a recent systematic review, which found insufficient data to recommend LHR as a prognostic test [11]. However, they included cohort studies measuring LHR up to 32 weeks of gestation, as a recent study reported favourable outcomes for in-utero surgery up to this gestation. The definitive timing of *in-utero* fetoscopic surgery has yet to be determined; however, we therefore included studies that measured LHR after this gestation. Indeed, one recent study reports observed/expected LHR measurements at 32-33 weeks provided useful prognosis guidance [32]. Although this is distinct from LHR as an absolute value, the observed/expected ratio appears to be useful for prognosis independent of gestation. This method was not included in our results as the studies using this method did not meet our entry criteria as they did not provide data suitable to extract 2×2 data. We would suggest that until further information is available relating to optimal gestation, gestation of test should not be limited.

Our findings should be interpreted with caution because of the differences within the available literature relating to timing of diagnostic test and length of follow up and the quality of the included studies (Figure 2). However, they offer some guidance regarding prognostic indicators for isolated CDH. Further results on the use of the observed to expected LHR, which is gestation independent, may add to this in the future, as may the use of other imaging modalities such as MRI.

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