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# How useful is the lung-to-head ratio in predicting outcome in the fetus with congenital diaphragmatic hernia? A systematic review and meta-analysis

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**KEYWORDS:** congenital diaphragmatic hernia; fetus; lung-to-head ratio; outcomes

## ABSTRACT

***Objective*** *Fetal surgery to improve lung growth comprises tracheal occlusion in selected 'high-risk' fetuses with congenital diaphragmatic hernia (CDH). Sonographically measured fetal lung-to-head ratio (LHR) is utilized to recruit candidates for fetal surgery. This study provides a meta-analysis of the evidence regarding the prognostic use of lung-to-head ratio measurements in fetal CDH.*

***Methods*** *MEDLINE, SCOPUS and ISI PROCEEDINGS databases were searched for MeSH terms: lung, head, hernia and ratio. References in retrieved studies were also searched. Studies were categorized as follows: Phase I studies measured normal fetal LHR; Phase II studies compared fetal LHR in CDH survivors and non-survivors (if LHR informed therapy decisions or LHR was not measured during the window for intervention (< 32 weeks' gestation), studies were excluded); Phase III studies used LHR to guide selection for fetal surgery (non-randomized trials were excluded); Phase IV studies measured CDH survival before and after LHR application in clinical practice.*

***Results*** *The one Phase I study showed that LHR varied substantially with gestation and technique. No complete studies met the selection criteria for Phase II: meta-analysis of subgroups revealed similar LHR in CDH survivors and non-survivors. A single Phase III study revealed no benefit for LHR-directed fetal surgery. No Phase IV studies were identified.*

***Conclusion*** *The prognostic use of LHR in fetal CDH entered clinical practice prior to publication of robust normal data and is not supported by current evidence. Application of a structured approach to any 'new' prognostic test could improve its validity and clinical application. Copyright © 2007 ISUOG. Published by John Wiley & Sons, Ltd.*

## INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a birth defect with an incidence of 1 : 3000 births. It is associated with high mortality (50–60%) due to lung hypoplasia and pulmonary hypertension[1]. Although better outcomes are now emerging from specialist centers, hidden mortality (*in-utero* deaths, terminations of pregnancy (TOP)) continues to obscure true survival rates, with recent population-based surveys still reporting a high level of mortality when all prenatal and perinatal cases of CDH are included[2]. Improved prenatal diagnosis has led to pioneering efforts over the last two decades to enhance survival by offering fetal surgery for CDH, with prenatal intervention to rescue abnormal lung growth being targeted at those fetuses considered least likely to survive with conventional postnatal medical therapy[1]. Selecting 'high-risk' CDH patients for fetal surgery requires accurate prognostic scoring; a number of anatomical prognostic indicators have been developed and proposed over the years by various investigators (Table 1).

The lung-to-head ratio (LHR) has been favored as a prognostic indicator for CDH by specialist fetal surgical centers. The LHR, measured by ultrasound, is the ratio of the area of the lung contralateral to the hernia defect to the fetal head circumference. The area of the lung is measured at the level of the four-chamber view of the fetal heart, and is defined as the product of the longest two perpendicular transverse diameters, in millimeters. Fetal head circumference is also measured in millimeters[3].

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**Table 1** Anatomical prenatal prognostic indicators in congenital diaphragmatic hernia (CDH)

| *Basis of indicator/Indicator* | *Reference* |
|---|---|
| Prenatal estimation of lung size | |
| Lung-to-head ratio | Metkus *et al.* (1996)[3] |
| Absolute lung volume values measured by: | |
| Ultrasound | Ruano *et al.* (2004)[25] |
| Magnetic resonance imaging | Paek *et al.* (2001)[26] |
| Lung diameter/thoracic circumference ratio | Bahlmann *et al.* (1999)[27] |
| Lung–thorax transverse area ratio | Hasegawa *et al.* (1990)[28] |
| Prenatal estimation of hernia size | |
| Thoracic stomach in left-sided CDH | Hatch *et al.* (1992)[29] |
| Abdominal circumference | Teixeira *et al.* (1997)[30] |
| Herniation of the liver | Albanese *et al.* (1998)[31] |
| Hernia/heart area ratio | Crawford *et al.* (1989)[32] |
| Early (< 25 weeks) gestational age at diagnosis | Metkus *et al.* (1996)[3], Adzick *et al.* (1989)[33] |
| Mediastinal shift | Dommergues *et al.* (1996)[34] |
| Visceral herniation | Stringer *et al.* (1995)[35] |
| Associated or resultant morbidities | |
| Associated anomalies | Witters *et al.* (2001)[36] |
| Polyhydramnios | Adzick *et al.* (1989)[33], (1985)[37] |
| Underdevelopment of the left heart region | Sharland *et al.* (1992)[38] |
| Fetal pulmonary vasculature | Mahieu-Caputo *et al.* (2004)[39] |

Fetuses with CDH and intrathoracic liver herniation (designated 'liver-up' cases) are deemed to have high mortality with standard postnatal care; LHR has been employed alongside designated liver-up cases to further stratify the risk of these candidates for fetal surgery[4–6]. Prenatal intervention involves occlusion of the fetal trachea (i.e. 'plugging', initially by open surgery[7,8] and now by endoscopic techniques[4–6]). Variable outcomes with plugging have been reported. LHR criteria employed by various investigators to target those best suited for fetal surgery may contribute to these results. Since it was first described in 1995[3], the value of LHR as a prognostic marker has been supported[8,9] and debated[10] by various researchers. In this study, we employed a new structured approach to evaluate systematically the evidence for the use of LHR as a prognostic indicator in fetal CDH.

## METHODS

### The four-phase approach to evaluation of diagnostic tests

In 2005, Gluud and Gluud[11] proposed that diagnostic tests should undergo systematic four-stage assessment to establish their value (Table 2). LHR is a prognostic test that is used to diagnose fetuses with high-risk of CDH. We modified Gluud's approach to critically evaluate LHR as a prognostic test in fetal surgery case selection. Applying Gluud's methodology, if diagnostic tests have two possible results ('normal' in the healthy, 'abnormal' in those with disease), an idealized prognostic test can be thought of as having three values: (a) 'healthy', (b) with 'disease' but good prognosis, (c) with 'disease' and poor prognosis. Adjusting Gluud and Gluud's system to accommodate these groups we emerged with a new system (Table 3). Additional details about every phase in the modified system are given below.

### Inclusion/exclusion criteria

Phase I included studies that measured LHR in the normal fetus. Studies were excluded if their population included abnormal fetuses and the data for normal fetuses could not be clearly identified, or if the LHR measurement method was different from that described by Metkus *et al.*[3].

Phase II included studies that compared LHR in surviving and non-surviving CDH patients. Studies in this category were included in the meta-analysis only if the following criteria were met. (1) Studies were conducted on a population of unilateral (right- or left-sided) CDH fetuses that received conventional postnatal care (i.e. no prenatal intervention). (2) LHR was not part of the antenatal decision-making process for these fetuses (to avoid potential bias introduced by subjecting the group with low LHR to higher rates of TOP and/or fetal surgery). (3) LHR was measured before 32 weeks' gestation (LHR is generally used to guide fetal intervention before 32 weeks).

Phase III included studies that compared prenatal intervention to standard postnatal care. Studies were included in the meta-analysis only if: (1) selection criteria were the same for the intervention and control groups; (2) the LHR value was used to select CDH cases for inclusion; (3) unborn patients were allocated randomly to either fetal surgery or conventional postnatal therapy. The theory for Phase III studies was that if LHR is a good prognostic test, intervention guided by it will select appropriate patients and therefore show treatment benefit.

Phase IV included studies that compared survival rates in CDH fetuses before and after adopting LHR measurements in clinical practice. Studies were included in the meta-analysis only if they used a control group (historical or contemporary) with similar population characteristics (including side of hernia defect, absence of other anomalies and timing of CDH diagnosis

**Table 2** The four phases in the architecture of diagnostic research according to Gluud and Gluud[11]

| *Phase* | *Characteristics* |
|---|---|
| I | Determining the normal range of values for a diagnostic test through observational studies in healthy people |
| II | Determining diagnostic accuracy through case–control studies, including healthy people as well as (a) people with known disease assessed by diagnostic standards and (b) people with suspected disease |
| III | Determining the clinical consequences of introducing a diagnostic test through randomized trials |
| IV | Determining the effects of introducing a new diagnostic test into clinical practice by surveillance in large cohort studies |

**Table 3** The four phases in the architecture of diagnostic research according to Gluud's modified system used in this meta-analysis investigating the prognostic use of fetal lung-to-head ratio (LHR) in congenital diaphragmatic hernia (CDH)

| *Phase* | *Characteristics* |
|---|---|
| I | To establish LHR values in normal fetuses. Trends of LHR during pregnancy and inter- and intraobserver variability are essential parts of Phase I assessment |
| II | To establish LHR values in surviving and non-surviving CDH patients |
| III | To define CDH survival with and without antenatal interventions that select patients using LHR value |
| IV | To define CDH outcome following wide application of LHR in practice. (Does LHR application improve CDH overall prognosis?) |

(prenatal/postnatal)). Two types of survival rates could be considered for Phase IV studies, and they should be considered separately: (1) survival of all CDH patients (includes those having prenatal diagnosis); LHR could in theory improve the survival of this group by selecting high-risk fetuses for prenatal intervention; (2) survival in 'liveborn' CDH cases; LHR could improve the survival of this group by selecting high-risk fetuses for either prenatal intervention or for TOP.

### Search strategy

The MEDLINE, SCOPUS and ISI PROCEEDINGS (Web of Knowledge) databases were searched for the following MeSH terms: hernia, lung, head and ratio, up to and including 24th July 2007, to retrieve both published papers and conference proceedings. No language or time limits were applied to the search. Retrieved studies were assessed by reading the abstracts; full papers were retrieved for relevant human studies only. Reference lists in retrieved studies were searched manually for any additional relevant articles. Single case reports were excluded. Authors of included studies were contacted for additional relevant data.

### Assessment of retrieved studies

Retrieved studies were analyzed independently by two of the authors (M.E.B. and E.C.J.). The studies were first grouped by our modified Gluud phase system and then assessed according to the inclusion/exclusion criteria for the meta-analysis. Studies from the same center were assessed for potential overlap of cases; this was identified: (a) when the authors described this; or (b) in studies from the same center when cases were drawn from a shared time-period. When such overlap was noted, the largest study was included and the rest were excluded.

### Statistics

When raw data were given in the study, these were used to calculate parameters of interest with SPSS 12 for windows (SPSS Inc, Chicago, IL, USA). Meta-analysis was carried out using RevMan 4.2.8 software (Review Manager for Windows; The Nordic Cochrane Centre, The Cochrane Collaboration, 2003, Copenhagen, Denmark). The results are presented as follows: (1) for Phase I studies, descriptive analysis; the main points of interest were normal LHR values between 22 and 32 weeks' gestation; (2) for Phase II studies, weighted mean difference (WMD) and 95% CI for LHR in CDH survivors compared with non-survivors; (3) for Phase III studies, pooled survival odds ratio (OR) and 95% CI of fetal surgery compared with conventional postnatal care; (4) for Phase IV studies, pooled survival OR and 95% CI of CDH fetuses before and after LHR application in clinical practice.

## RESULTS

### Phase I

Only one Phase I study was retrieved (Table 4). Notably, the study was published 10 years after the initial description and application of LHR in practice. It was conducted on 650 normal fetuses and the main conclusions were that normal LHR differed between right and left lungs, and that LHR increased exponentially during pregnancy.

### Phase II

There were 18 Phase II studies retrieved initially (Table 5) and exclusion of duplicate reports left seven[3,8,10,12–15]. One study[14] had a population of CDH fetuses that had prenatal intervention and was excluded. Two further

 

**Table 4** Phase I study retreived from the literature

| *Reference* | *GA (weeks, range)* | *n* | *Remarks* |
|---|---|---|---|
| Peralta *et al.* (2005)[19] | 12–32 | 650 | The latest study to be published<br>LHR differed between right and left sides<br>LHR increased exponentially during pregnancy<br>Normal LHR measured using right lung was 2.12 (1.45, 2.79) at 22 weeks, 2.76 (1.88, 3.64) at 28 weeks and 3.05 (2.03, 4.07) at 32 weeks' gestation<br>The lung area calculation method in LHR overestimated the lung area by 45% |

GA, gestational age at time of lung-to-head ratio (LHR) measurement.

studies were excluded because LHR was part of the counseling process[8,13]. The remaining four studies were excluded because their population included fetuses with gestational ages over 32 weeks. Thus, no complete Phase II studies matched the predefined selection criteria.

We then searched the retrieved studies for subgroups of fetuses that met our inclusion criteria. The study of Metkus *et al.*[3] reported a subgroup of CDH fetuses that had conventional postnatal therapy, for which LHR was not part of prenatal counseling, and for which the gestational age was $< 25$ weeks at the time of LHR measurement; we were able to extract a similar group from the study of Heling *et al.*[10] (Table 6). Meta-analysis of these two subgroups used a random effects model because of the heterogeneity of the studies ($I^2 = 77.2\%$): there was no significant difference in LHR between CDH survivors and non-survivors (WMD, 0.12 (95% CI, −0.15 to 0.38), $P > 0.05$; Figure 1).

### Phase III

Nine Phase III studies were retrieved initially (Table 7) and exclusion of duplicate reports left four[4,8,16,17]. Only one study[16] met all inclusion criteria. Enrollment into the study was stopped early because of the unexpectedly high survival rate with standard care. Eight of 11 fetuses (73%) in the tracheal-occlusion group and 10 of 13 (77%) in the group that received standard care survived ($P = 1.00$).

The other three studies[4,8,17] were controlled non-randomized studies. They differed in many important aspects, including type of fetal surgery (open *vs.* minimal access tracheal plug), LHR cut-off values used for recruitment (1.4 *vs.* 1.0), and conventional treatment policies for the control groups (e.g. availability of extracorporeal membrane oxygenation for entire control group not clearly stated in one study).

### Phase IV

No studies were retrieved under this category.

## DISCUSSION

CDH is associated with a considerable mortality rate[1], and prenatal diagnosis led to the development of fetal surgery in an effort to improve outcomes. LHR has emerged as the favorite prognostic tool with which to select fetuses with isolated, 'liver-up' CDH for tracheal occlusion. We have performed a comprehensive literature review and meta-analysis of the available evidence to assess the utility of LHR in this role. We found that the use of LHR needs further careful study before it can be considered evidence-based. Any future studies should report absolute LHR values (rather than cut-off values such as $< 1.0$, $< 1.4$) in a manner that is agreed prospectively, perhaps through international consensus.

Methodology chosen to assess prognostic tests remains a subject of debate and, as a consequence, reviewers of prognostic studies have tended to devise their own criteria[18]. In what we believe is the first such application to prognostic tests, we have adapted Gluud and Gluud's[11] four-phase approach to diagnostic tests. We believe that for a specialized area such as LHR, this four-phase system provides concise and comprehensive assessment. It also offers an invaluable framework with which to identify gaps in knowledge. Only one Phase I study to define normal LHR was retrieved[19]; use of the Gluud approach has proved invaluable in making the paucity of information on normal LHR values abundantly clear. The fact that the single Phase I study was one of the most recent publications of all those retrieved (citation 2005), despite LHR having become embedded in clinical practice over a decade ago, indicates that this knowledge gap had been overlooked. It is instructive to note that the normal LHR range recently described for the right lung at 22 weeks' gestation was 1.45–2.79. Yet, a value of $< 1.4$ has been used as a criterion for recruiting CDH fetuses for prenatal intervention by at least one center[16]. In that study, prenatal surgery did not show any benefit over conventional postnatal treatment.

Normal LHR is now known to: rise with advancing gestation, overestimate lung area by 45% on average and have significant interobserver error[19]. A recent study showed that the original concept of using LHR to standardize measurements for gestational age did not work, and that additional standardization in the form of the observed-to-expected LHR was needed[20]. Simple mathematics may contribute to these observations: LHR is a ratio between square and linear measurements. As a result, even if the linear dimensions of lung and head increase proportionately the LHR numerator will rise faster than the denominator. Moreover, this

 

**Table 5** Phase II studies retreived from the literature

| *Reference* | *Center/recruitment period* | *Prosp./Retro.* | *Treatment (Conv./Pre.)* | *GA of study group (weeks)* | *Sidedness of CDH (L/R)* | *LHR part of counseling process* | *LHR (n, mean LHR ± SD)* | | *Incl./ Excl./ Subgrp* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *Survivors* | *Non-survivors* | |
| Metkus *et al.* (1996)[3] (D) | San Francisco, USA Sept. 1990–1994 | Retro. | Conv. only | < 25–38 | L | No | 36 1.33 ± 0.50 | 19 0.87 ± 0.32 | Excl./Subgrp |
| Lipshutz *et al.* (1997)[40] (C) § | San Francisco, USA March 1995–Aug. 1996 | Prosp. | Conv. only | 24–26 | L | Yes | 7 1.46 ± 0.33 | 8 1.05 ± 0.30 | Excl. |
| Sbragia *et al.* (2000)[41] (A), (C), (D) * | San Francisco, USA Sept. 1993–Nov. 1999 | Retro. | Conv. only | 16–26 | L | Yes | 16 1.49 ± 0.25 | 4 1.48 ± 0.15 | Excl. |
| Flake *et al.* (2000)[8] | Philadelphia, USA Sept. 1995–Jan. 1999 | Prosp. | Conv. only | 23–25 | L | Yes | 29 N/A | 18 N/A | Excl. |
| Paek *et al.* (2001)[42] (A) | San Francisco, USA Sept. 1997–Feb. 2000 | Prosp. | Conv. only | 21–28 | L | Yes (Ref. 5) | 8 1.2 ± 0.16 | 3 0.73 ± 0.15 | Excl. |
| Keller *et al.* (2003)[43] (A), (C) (D) †# | San Francisco, USA Sept. 1993–1999 | Retro.; LHR measured prosp. | Conv. and Pre. | 21–33 | L | Yes | 28 Median, 1.10 (IQR, 0.98–1.25) | 28 Median, 0.90 (IQR, 0.67–1.23) | Excl. |
| Laudy *et al.* (2003)[9] (B) | Rotterdam, The Netherlands Jan. 1991–Dec. 2002 | Retro. | Conv. only | 28–37 | L | No | 11 1.78 ± 0.58 | 10 1.02 ± 0.14 | Excl. |
| Hedrick *et al.* (2004)[23] ¶# | Philadelphia, USA Sept. 1995–Sept. 2002 | Retro. | Conv. and Pre. | 19–36 | R | No | 19 N/A | 8 N/A | Excl. |
| Jani *et al.* (2004)[44] (A), (C) | (1) University Hospital Gasthuisberg, Belgium; (2) King's College Hospital, UK; (3) Valld'Hebron Hospital, Spain; (4) University of California, San Francisco, USA; (5) Hopital Necker-Enfants Malades, France; (6) Hopitaux Universitaires De Strasbourg, France 1995–2004 | Retro. | Conv. only | < 28 | L | Yes | 58 N/A | 65 N/A | Excl. |
| Jani *et al.* (2005)[45] (A), (C) | Same as Jani (2004)[44] 1995–2005 | Retro. | Conv. only | < 28 | L | Yes (Ref. 16) | 58 N/A | 65 N/A | Excl. |

(*continued overleaf*)

**Table 5** (*Continued*)

| *Reference* | *Center/recruitment period* | *Prosp./Retro.* | *Treatment (Conv./Pre.)* | *GA of study group (weeks)* | *Sidedness of CDH (L/R)* | *LHR part of counseling process* | *LHR (n, mean LHR ± SD)* | | *Incl./ Excl./ Subgrp* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *Survivors* | *Non-survivors* | |
| Deprest *et al.* (2005)[46] (A), (C) | Same as Jani (2004)[44]<br>1995–2003 | Retro. | Conv. only | < 28 | L | Yes | 58<br>N/A | 65<br>N/A | Excl. |
| Jani *et al.* (2005)[47] (A), (C) | Same as Jani (2004)[44]<br>1995–2003 | Retro. | Conv. only | < 28 | L | Yes | 58<br>N/A | 65<br>N/A | Excl. |
| Heling *et al.* (2005)[10]‡ | Berlin, Germany<br>2000–2003 | Prosp. | Conv. only | 16–38 | R and L | No | 13<br>1.20 ± 0.38 | 9<br>1.22 ± 0.38 | Excl./Subgrp |
| Yoshimura *et al.* (2005)[12] | Nagasaki, Japan<br>Jan. 1989–Dec. 2003 | Retro. | Conv. only | 36–40 | L | No | 9<br>1.81 ± 0.63 | 3<br>0.43 ± 0.07 | Excl. |
| Jani *et al.* (2006)[13] (A), (B), (C) | Same as Jani (2004)[44] and: (1) Erasmus Medical Center, Rotterdam, The Netherlands; (2) Sheba Medical Center, Tel-Hashomer, Israel; (3) UMC Sint Radboud, Nijmegen, The Netherlands; (4) Hopital Jeanne de Flandre, Lille, France<br>1995–2004 | Retro./Prosp. | N/spec. (likely conv. only) | 22–28 | L | Yes | 118<br>N/A | 66<br>N/A | Excl. |
| Jani *et al.* (2006)[14] | (1) Fetal Medicine Units of the University Hospital Gasthuisberg, Leuven, Belgium; (2) King's College Hospital, London, UK; (3) Vall d'Hebron Hospital, Barcelona, Spain<br>Recruitment period N/spec. | Prosp. | Pre. | 23–29 | R and L | Yes | 16<br>0.75 ± 0.13∧ | 12<br>0.61 ± 0.11∧ | Excl. |
| Yang *et al.* (2007)[48] (A), (C) | San Francisco, USA<br>March 1995–June 2004 | Retro. | Conv. and Pre. | 20–34 | L | Yes | 64<br>Median, 1.13 (range, 0.60–2.60) | 43<br>Median, 0.95 (range, 0.50–1.50) | Excl. |
| Arkovitz *et al.* (2007)[15] | New York, USA<br>Jan. 2002–June 2005 | Retro. | Conv. only | 17–36 | L | Yes | 24<br>N/A | 4<br>N/A | Excl. |

*'Liver down' patients only. †'Liver up' patients only. ‡SD extrapolated from mean and range. §Reasons for exclusion of two patients not clarified. ¶Included cases diagnosed postnatally. #Included cases with congenital anomalies. ∧Values calculated from raw data given in the paper. (A), (B), (C), (D), Population overlap between studies with the same letter. Conv., conventional; Excl., excluded; Incl., included; N/A, not available; N/spec., not specified; Pre., prenatal surgery; Prosp., prospective; Ref, reference; Retro., retrospective; Subgrp, subgroup.

**Table 6** Phase II studies reporting subgroups meeting inclusion criteria

| *Reference* | *Center/ recruitment period* | *Prosp./ Retro.* | *Treat -ment (Conv./ Pre.)* | *GA of study group (weeks)* | *Sidedness of CDH (L/R)* | *LHR part of counseling process* | *LHR (n, mean LHR ± SD)* | | *Incl./ Excl.* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *Survivors* | *Non-survivors* | |
| Metkus *et al.* (1996)[3] | San Francisco, USA Sept. 1990–1994 | Retro. | Conv. | < 25 | L | No | 21 1.13 ± 0.37 | 17 0.86 ± 0.34 | Incl. |
| Heling *et al.* (2005)[10*] | Berlin, Germany 2000–2003 | Prosp. | Conv. | 22 to < 25 | R and L | No | 4 0.91 ± 0.10 | 2 0.91 ± 0.04 | Incl. |

*Numbers extracted from graphs in the original study. CDH, congenital diaphragmatic hernia; Conv., conventional; Excl., excluded; GA, gestational age; Incl., included; LHR, lung-to-head ratio; Pre., prenatal surgery; Prosp., prospective; Retro., retrospective.

mathematical relationship will magnify errors in lung-area estimation relative to those in head-circumference measurement. Together, these empirical and *a priori* considerations indicate that the actual utility of LHR may be limited. Variations in LHR measurement methods may exist in different institutions[19]. However, such specialist centers usually refer to the original technique of LHR determination described by Metkus *et al.*[3]. Interestingly, a recent multicenter study combining patients from North America and Europe notably did not take these variations in LHR methodology into consideration when reporting outcomes[13].

For Phase II, because of the potential for bias, we excluded those studies in which LHR informed prenatal decision-making to terminate the pregnancy or deploy fetal surgery (considering both as forms of prenatal intervention). Stratifying prenatal cases as 'poor outcome' could have influenced postnatal treatment. Using these criteria, our meta-analysis of subgroups from identified studies showed no significant difference in LHR between CDH survivors and non-survivors. We accept that, whilst these eligibility criteria reduced bias, important studies could have been excluded. For example, on these grounds, we excluded a recent large retrospective study (Table 5) suggesting that LHR was a good prognostic test. Nevertheless, this approach appears justified when one observes that this study had higher termination rates in low-LHR compared with high-LHR cohorts[46]. In fact, we did not retrieve a single complete Phase II study that examined LHR and prognosis under conditions comparable to those used when LHR was used to select cases for fetal surgery. Although most reports about prenatal intervention put the upper gestational age limit for potential candidates at 28 weeks' gestation[16,21], one recent study reported favorable results with CDH fetuses which underwent surgery at 32 weeks[22]. We therefore included Phase II studies that measured LHR at < 32 weeks. Conducting the same analysis while including only studies that measured LHR at < 28 weeks did not yield different results.

From Phase III studies, the best available evidence shows no benefit from tracheal occlusion for fetuses with severe left-sided CDH. Although non-randomized studies suggest that fetal surgery can be beneficial when LHR < 1.0, this, albeit inconclusive, evidence applies to left-sided CDH only. LHR differs for right and left lungs[19] and there are currently insufficient data to evaluate the use of LHR as a prognostic guide in right-sided CDH. Using liver herniation as a prognostic indicator seems unlikely to help either, since it is ubiquitous in right-sided CDH[23], and terms such as 'significant liver herniation' may be poorly defined.

Potential weaknesses of the present study merit consideration at this point. Firstly, we used strict inclusion criteria; hence, the number of CDH cases recruited for analysis may be substantially smaller than the collective published experience. We believe, however, that our rigorous approach is justified, not least by the 'high stakes' decisions that are being made based upon LHR measures. Secondly, we investigated LHR over a period of time rather than at time-specific points, and we combined data for right- and left-sided CDH. As LHR is known to increase with advancing gestation, and to differ between right and left sides[19], this pooling of cases could be

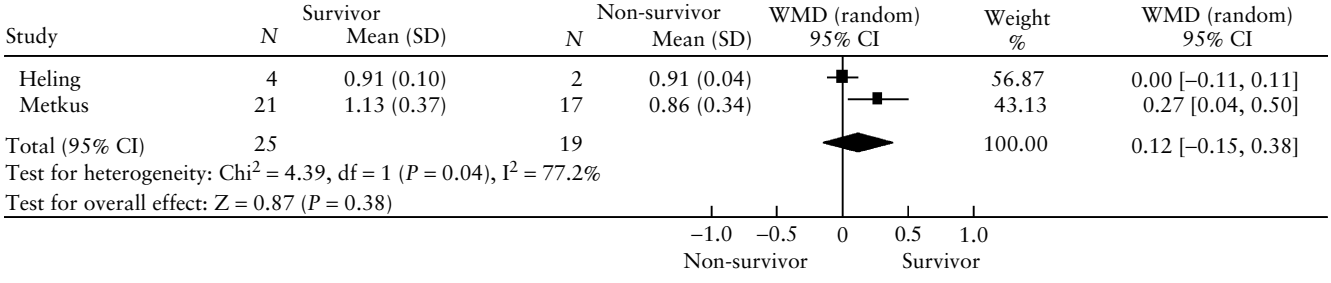


**Figure 1** Meta-analysis for subgroups in Phase II studies. There was no statistically significant difference in lung-to-head ratio value between surviving and non-surviving fetuses with congenital diaphragmatic hernia. WMD, weighted mean difference.

 

**Table 7** Phase III studies retreived from the literature

| Reference | Center/recruitment period | Patient recruitment criteria | Randomization | Survivors/Total (n) | | Incl./ Excl. |
|---|---|---|---|---|---|---|
| | | | | Prenatal intervention | Conventional postnatal treatment | |
| Harrison *et al.* (1998)[4] (B) | San Francisco, USA Nov. 1994–Aug. 1997 | Left-sided CDH; no other anomalies; diagnosed < 25 weeks; liver herniation LHR < 1.4 | None | 6/8 | 5/13 | Excl. |
| Flake *et al.* (2000)[8*] | Philadelphia, USA Sept. 1995–Jan. 1999 | Left-sided CDH; diagnosis < 25 weeks; liver herniation LHR < 1.0; no other anomalies | None | 3/13 | 0/7 | Excl. |
| Harrison *et al.* (2003)[5] (B) | San Francisco, USA Jan. 1996–Apr. 1999 | Left- and right-sided CDH; diagnosis < 25 weeks; liver herniation; LHR < 1.4 for left CDH; no other anomalies | None; control group results not reported | 13/19 | N/A | Excl. |
| Harrison *et al.* (2003)[16] | San Francisco, USA Apr. 1999–July 2001 | Left-sided CDH; no other anomalies; diagnosed between 22 and 28 weeks; liver herniation LHR < 1.4 | Random in permuted blocks stratified according to LHR value | 8/11 | 10/13 | Incl. |
| Deprest *et al.*[6] (2004) (A) | (1) Fetal Medicine Units of the University Hospital Gasthuisberg, Leuven, Belgium; (2) King's College Hospital, London, UK; (3) Vall d'Hebron Hospital, Barcelona, Spain Apr. 2002–Oct. 2003 | Left- and right-sided CDH in intervention group and left-sided only in control group; no other anomalies; diagnosed < 28 weeks; liver herniation LHR < 1.0 | None | 10/21 | 1/12 | Excl. |
| Jani *et al.* (2005)[17] (A) | Same as Deprest *et al.*[6] (2004) Recruitment period unclear but was done over 2 years | Left-sided CDH; no other anomalies; diagnosed < 28 weeks; liver herniation LHR < 1.0 | None | 12/20 | 1/12 | Excl. |
| Deprest *et al.* (2005)[46] (A) | Same as Deprest *et al.*[6] (2004) Recruitment period N/spec. | Same as[6] | None | 10/20 | 1/12 | Excl. |
| Jani *et al.* (2005)[47] (A) | Same as Deprest *et al.*[6] (2004) Over 28 months | Same as[17] | None | 12/24 | 3/32 | Excl. |
| Deprest *et al.* (2006)[21] (A) | Recruitment period unclear but was done over 28 months | Same as[17] | None | 12/24 | 3/32 | Excl. |

*Operated on right and left. Only left are shown in this table for comparability with the control group. (A, B) Population overlap between studies with the same letter. CDH, congenital diaphragmatic hernia; Excl., excluded; Incl., included; LHR, lung-to-head ratio; N/spec., not specified.

controversial. However, we believe this approach is justified as we elected to test LHR prognostic validity under application-matching conditions (i.e. similar to those used to select fetuses for prenatal intervention, with the same LHR cut-offs applied for right- and left-sided CDH, and for fetuses of < 32 weeks' gestation). Another issue from the current study is that it reflects data capture over a significant time period when it may be argued that CDH survival with improving postnatal care has itself changed over this period. This 'shifting baseline' (with apparent improving survival) may have already hampered a well-conducted randomized trial of fetal intervention for CDH[16]. Indeed, a recent survival analysis suggests significant improvement in CDH survival with optimal postnatal care in the last decade[24], which may invalidate all LHR measurements obtained from a cohort of patients recruited over a relatively long period of time. Our study could have yielded much better results if more data in the form of individual patient records had been available for analysis. We therefore recommend an internationally agreed, registry-based approach for future reporting of raw LHR values in each case and, in particular, a larger Phase II study, in which decisions are not based on LHR.

In conclusion, the current use of LHR as a prognostic tool in fetal CDH lacks a sufficient evidence base and is impaired by overlapping, methodologically heterogenous reporting. Further evaluation of LHR, or indeed newer alternatives, to predict outcome for the fetus with CDH could usefully employ the Gluud phasic approach to place such tests on a firmer scientific basis.

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