Prenatal predictors of mortality in fetuses with congenital diaphragmatic hernia: a systematic review and meta-analysis

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Abstract

Purpose

This study aimed to evaluate prenatal predictors of mortality in fetuses with congenital diaphragmatic hernia (CDH).

Methods

A systematic literature search was performed to identify relevant observational studies that evaluated the ability of lung-to-head ratio (LHR), observed-to-expected LHR (o/e-LHR), observed-to-expected total fetal lung volume (o/e-TFLV), lung-to-thorax transverse area ratio (L/T ratio), intrathoracic herniation of the liver and the stomach, and side of diaphragmatic hernia, using a threshold for the prediction of mortality in fetuses with CDH. Study quality was assessed using the QUADAS-2 tool. Hierarchical summary receiver operating characteristic curves were constructed.

Results

A total of 50 articles were included in this meta-analysis. The QUADAS-2 tool identified a high risk of bias in more than one domain scored in all parameters. Among those parameters, the diagnostic odds ratio of mortality with o/e-LHR < 25%, o/e-TFLV < 25%, and L/T ratio < 0.08 were 11.98 (95% confidence interval (CI), 4.65–30.89), 11.14 (95%CI, 5.19–23.89), and 10.28 (95%CI, 3.38–31.31), respectively. The predictive values for mortality were similar between the presence of liver herniation and retrocardiac fetal stomach position.

Conclusions

This systematic review suggests that o/e-LHR, o/e-TFLV, and L/T ratio are equally good predictors of neonatal mortality in fetuses with isolated CDH.

Introduction

Congenital diaphragmatic hernia (CDH) is a disease, that affects 1 in 4000 live births, in which the abdominal organs herniate into the thoracic cavity through a congenital defect in the diaphragm [1]. The severity of CDH varies widely from mild, which are completely asymptomatic at birth, to the most severe cases, in which death occurs immediately after birth. The severity of CDH depends on the presence of pulmonary hypoplasia and pulmonary hypertension [2–5]. Recently, prenatal imaging such as prenatal ultrasound or magnetic resonance imaging (MRI) has been used to assess the degree of lung hypoplasia in CDH, which is directed at improving its fidelity and prognostic ability. Advancements in prenatal diagnostic imaging and perioperative respiratory and circulatory management have recently improved the prognoses of patients. An accurate prenatal assessment of severity including pulmonary hypoplasia is essential for the standardization of perinatal care, and trials of prenatal therapy such as fetoscopic tracheal occlusion (FETO) [6, 7]. Furthermore, the prenatal prognostic classification of CDH would provide more precise information about the estimated prospective course of treatment, and allow the establishment of a standardized protocol based on the prenatal findings.

Several antenatal prognostic parameters of postnatal survival in fetuses with CDH have been reported [8–21]. Most of them were direct or indirect measurements of fetal lung size, either by ultrasound or MRI. It has been reported that the antenatal predictors, which include lung area-to-head circumference ratio (LHR) [10, 11], observed to expected LHR (o/e-LHR) [22, 23], observed-to-expected total fetal lung volume (o/e-TFLV) [15, 18, 24, 25], and lung-to-thorax transverse area ratio (L/T ratio) [8, 16, 26] are reliable predictors for postnatal mortality and morbidity. Other parameters are related to a worse prognosis such as the presence of herniated intrathoracic abdominal organs, among which the commonly evaluated was liver and stomach herniation, either classified as abdominal (entire visceria within the abdomen) or thoracic (any portion of the visceria into the thorax) [9, 13, 14, 27–33], and a right side of the diaphragmatic defect in patients with CDH [34–36]. However, the evidence supporting the use of specific antenatal parameters to predict postnatal outcome in prenatally diagnosed patients with CDH, which was the optimal threshold, is limited.
Therefore, this study conducted a systematic review and meta-analysis of currently available literature to evaluate the utility of antenatal predictors of postnatal mortality in fetuses with CDH.

**Materials And Methods**

**Search strategy**

An electronic and systematic literature search for prenatal diagnostic studies predicting the mortality in fetuses with CDH was performed on December 6, 2020 and December 7, 2020 using MEDLINE and the Cochrane Library to identify studies using relevant keywords, Medical Subject Headings, and subheadings (supplement 1).

**Definitions of prenatal predictors and thresholds**

The following parameters were included: (1) LHR was the ratio of the contralateral lung area, which was the product of the longest diameter of the lung and lung circumference via manual tracing, to the head circumference measured by ultrasound [10, 11]; (2) o/e-LHR was the ratio of the observed LHR measured by ultrasound to the expected LHR obtained from data of normal fetuses [22, 23, 37]; (3) o/e-TFLV was the ratio of total lung volume (both right and left lungs) measured by MRI, to the expected total lung volume for gestational age from the reference tables [15]; (4) L/T ratio was the ratio of the area of the contralateral lung via manual tracing, to the area of the thorax defined as the space surrounded by the inner border of the bilateral ribs, the sternum, and the vertebra [38] measured using ultrasonography of the transverse section containing the four-chamber view of the heart [8], (5) intrathoracic herniation of the liver (liver-up) was defined as any part of the liver observed in the thorax space using ultrasound or MRI; (6) stomach in chest was the presence of any portion of the stomach above the level of the diaphragm by prenatal imaging or stomach-down [30, 39-42]. Retrocardiac stomach herniation was defined as herniation of more than half of the stomach into the contralateral thoracic cavity or others; and (7) a side of diaphragmatic hernia (right or left). The continuous parameters related to fetal lung size, such as LHR, o/e-LHR, o/e-TFLV, and L/T ratio, were converted to binary variables using the threshold values. The threshold of LHR, o/e-LHR, o/e-TFLV, and L/T ratio were determined according to previous reports [22, 38, 43–45]. Accordingly, we defined the thresholds of <1 for LHR, <25% for o/e-LHR, <25% for o/e-TFLV, and <0.08 for L/T ratio.

**Inclusion and exclusion criteria**

Inclusion criteria were peer reviewed full papers published from 2000 onward (to ensure that the findings were retrieved in accordance with, and relevant to, current care protocols for patients with CDH). Each study had to fulfill the following criteria: (1) studies with prenatally diagnosed CDH patients, (2) observational studies (prospective or retrospective cohort studies, case-control studies, and case series) evaluating the ability of LHR, o/e-LHR, o/e-TFLV, and L/T ratio or prenatal imaging parameters, such as intrathoracic herniation of liver and stomach, right-sided CDH, using an ultrasound or MRI for the purpose of prognostication to predict survival, (3) studies which reported adequately on study population and definition of prenatal predictors, (4) studies with sufficient information on the outcome (survive or not) to construct 2 × 2 tables, (5) studies with the main outcome measures were mortality of prenatally diagnosed patients with CDH, and (6) studies with fetuses that underwent fetal therapy were included.

The studies with an article type of review, case report, or letter with no full text available, studies that included postnatally diagnosed as CDH but did not focus on the imaging parameters using the defined threshold, or studies that had insufficient reporting of data for analysis were excluded.

**Data extraction from included studies**

A predesigned form was used for data extraction, where titles and abstracts were independently screened by two individual authors. The following characteristics were collected for each eligible study: study design, authors’ names, year of the publication, study duration, country of the study, testing sample size, characteristics of the population (isolated or non-isolated CDH, side of the diaphragmatic hernia), gestational age of measurement, prenatal imaging (ultrasound or MRI), prenatal predictors with a threshold, mortality of each parameter, and the follow-up period. Two individual authors independently screened full text papers. After completing the data abstraction, a second reviewer resolved the disagreements between prior reviewers at full text stage.

**Assessment of risk of bias**
Quality assessment was done using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool consisting of four domains to assess the risk of bias [46], including patient selection, index test (i.e., the antenatal predictors), reference standard (the test considered as the gold standard against which index test results are compared), and flow and timing of patient. All domains are rated with regard to the risk of bias, and the first three items are also rated in terms of concerns regarding applicability to the research question. Studies were categorized as having low, high, or unclear risk, according to the judgment of the reviewers about each domain. Quality assessment was performed by two reviewers and checked by the second reviewer. Any disagreements were resolved through discussion and consensus.

**Statistical analysis**

For each study included in the meta-analysis, we examined the information to produce a 2 × 2 table of the number of true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN), for the calculation of sensitivity and specificity. Using Review Manager (RevMan) version 5.4 software, forest plots were constructed to show sensitivity and specificity for all included studies graphically. The bivariate random-effect model and the hierarchical summary receiver operating characteristic (HSROC) model were used to estimate summary points at 95% confidence intervals for sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR). Furthermore, the summary curve, including the 95% credibility regions, 95% prediction region, and the area under the HSROC curve (AUC) were estimated. Statistical analyses were performed using STATA SE software, version 16 (Stata Corp, College Station, TX, USA).

**Results**

**Study selection**

A total of 1260 studies were identified and screened in the systematic database search. The selection process is presented in the flow diagram (Fig. 1). Of the 1260 search results, 1070 studies were excluded on first screening based on titles and abstracts. The full texts of all the potentially relevant citations were obtained. After the second screening, the remaining 190 studies, based on their full texts, were narrowed down to 75 records from 50 articles published from 2000 to 2020. The characteristics of the studies are shown in Fig. 2. Among them, 19 studies (38.0%) were conducted in Europe, 15 studies (30.0%) in the United States, 12 studies (24.0%) in Asia, two studies (4.0%) in North America, and two studies (4.0%) in South America. Of these articles, five studies included data on LHR < 1 [14, 43, 47–49], six studies on o/e-LHR < 25% [22, 50–54], four studies on o/e-TFLV < 25% [44, 45, 55, 56], five studies on L/T ratio < 0.08 [26, 38, 51, 57, 58], 27 studies on liver-up [13, 14, 18, 19, 22, 25, 26, 44, 45, 48, 49, 59–74], seven studies on intrathoracic stomach herniation [19, 33, 44, 47, 54, 61, 75], six studies on retrocardiac stomach position [16, 19, 33, 54, 67, 76], and 15 studies on the right side of diaphragmatic hernia [18, 22, 25, 35, 60, 61, 63, 73, 76–82]. The parameters in relation to the fetal lung volume and intrathoracic fetal stomach position included all patients with isolated CDH, while other parameters of both intrathoracic herniation of the liver and the right side of diaphragmatic hernia included studies with non-isolated CDH patients. The total sample size of each parameter was 344 for LHR, 1,018 for o/e-LHR, 321 for o/e-TFLV, 355 for L/T ratio, 2756 for liver position, 713 for stomach in chest, 817 for retrocardiac stomach position, and 2649 for the side of diaphragmatic hernia (Table 1).
Table 1
The results of the summary of sensitivity, specificity, DOR, PLR, NLR, and AUC of antenatal parameter.

| Study                  | Number of patients | Combined mortality rate (%) | Sensitivity (95% CI) | Specificity (95% CI) | DOR (95% CI) | PLR (95% CI) | NLR (95% CI) | AUC (95% CI) |
|------------------------|--------------------|-----------------------------|----------------------|----------------------|--------------|--------------|--------------|--------------|
| LHR < 1 (ref, ≥ 1)     | 5                  | 344 (LHR < 1 88, ≥ 1 256)  | LHR < 1 61.3, ≥ 1 25.4 | 0.44 (0.33–0.56)     | 0.83 (0.71–0.91) | 3.9 (1.54–9.92) | 2.62 (1.31–5.25) | 0.67 (0.52–0.87) | 0.51 (0.47–0.55) |
| o/e-LHR < 25% (ref, ≥ 25%) | 6                | 1018 (o/e-LHR < 25% 172, ≥ 25% 846) | o/e-LHR < 25% 50.0, ≥ 25% 16.7 | 0.39 (0.20–0.62)     | 0.95 (0.77–0.99) | 11.98 (4.65–30.89) | 7.71 (2.48–24.02) | 0.64 (0.48–0.86) | 0.72 (0.68–0.76) |
| o/e-TFLV < 25% (ref, ≥ 25%) | 4                | 321 (o/e-TFLV < 25% 86, ≥ 25% 235) | o/e-TFLV < 25% 80.2, ≥ 25% 26.8 | 0.50 (0.38–0.63)     | 0.92 (0.81–0.97) | 11.14 (5.19–23.89) | 6.03 (2.87–12.67) | 0.54 (0.43–0.68) | 0.74 (0.70–0.77) |
| L/T ratio < 0.08 (ref, ≥ 0.08) | 5              | 355 (L/T < 0.08 81, ≥ 0.08 274) | L/T < 0.08 53.1, ≥ 0.08 8.4 | 0.65 (0.48–0.78)     | 0.85 (0.58–0.96) | 10.28 (3.38–31.31) | 4.29 (1.47–12.49) | 0.42 (0.30–0.59) | 0.75 (0.71–0.79) |
| Liver-up (ref, liver-down) | 27           | 2756 (liver-up 1364, liver-down 1392) | Liver-up 46.5, liver-down 16.6 | 0.77 (0.70–0.82)     | 0.62 (0.57–0.67) | 5.44 (4.01–7.38) | 2.03 (1.79–2.30) | 0.37 (0.30–0.47) | 0.74 (0.70–0.78) |
| Stomach in chest (ref, stomach-down) | 7      | 713 (stomach in chest 573, stomach-down 140) | Stomach in chest 23.9, stomach-down 1.4 | 0.99 (0.68–1.00)     | 0.19 (0.15–0.23) | 31.82 (0.49–2061.73) | 1.22 (1.15–1.29) | 0.04 (0.00–2.42) | 0.52 (0.47–0.56) |
| Retrocardiac stomach position (ref, others) | 6     | 817 (retrocardiac stomach 216, others 601) | Retrocardiac stomach 45.3, others 9.7 | 0.62 (0.42–0.78)     | 0.78 (0.61–0.89) | 5.67 (3.59–8.95) | 2.80 (1.85–4.23) | 0.49 (0.35–0.70) | 0.76 (0.72–0.79) |
| Right-sided CDH (ref, left-sided) | 15   | 2649 (right-sided 410, left-sided 2239) | Right-sided 40.2, left-sided 30.5 | 0.19 (0.16–0.23)     | 0.87 (0.84–0.89) | 1.63 (1.2–2.21) | 1.51 (1.17–1.94) | 0.93 (0.88–0.97) | 0.59 (0.55–0.63) |

CDH: congenital diaphragmatic hernia, LHR: lung-to-head ratio, o/e-LHR: observed-to-expected LHR, o/e-TFLV: observed-to-expected total fetal lung volume, L/T ratio; L/T ratio; lung-to-thorax transverse area ratio, CI: confidence interval, DOR; diagnostic odds ratio, PLR; positive likelihood ratio, NLR; negative likelihood ratio, AUC; area under the curve.

Quality Assessment of studies
The summary of the analyzed quality assessment for each included study, according to the QUADAS-2 tool, is presented in Fig. 3. The detailed analysis of each study was captured in supplement 2. In all studies included in this review, the high risk of bias in each domain was 46.0% (23/50) for patient selection, 22.0% (11/50) for index test, 46.0% (23/50) for reference standard, and 6.0% (3/50) for flow and timing. The high risk of bias in more than one domain was observed in all parameters. Hence, there was a high risk of quality concerns in the domains of patient selection, index test, and reference standard. The risk of bias in patient selection was considered high in all parameters, mainly because majority of the studies were case-control or case-series which did not use random sampling. Additionally, some studies did not include all cases. The risk of bias in performance of the index test and the reference standard was also considered high in five and six parameters, respectively. Meanwhile, the risk of bias arising from patient flow and timing of procedures was considered low or unclear in the majority of the studies, owing to missing information in almost all studies, and it was not clear if a reference standard was performed in every patient. With regards to applicability, there was a high risk identified for patient selection and reference standard, but a low risk for index test application as most included studies reported detailed information with validated tests.
Quantitative analysis of antenatal predictors

The summary results of sensitivity, specificity, DOR, PLR, NLR, AUC, and the 95% CIs of each antenatal parameter are listed in Table 1. The constructed HSROC curves from the meta-analysis of the antenatal predictors are shown in Fig. 4. Among those parameters, the high predicting values of mortality included PLR and DOR observed in o/e-LHR, o/e-TFLV, and L/T ratio, respectively. On the contrary, the right side of the hemia had the lowest predicting values in sensitivity and DOR. With regards to the viscera herniated into the chest, the predicting values for mortality were similar between liver-up and retrocardiac stomach position. Among them, the stomach in chest had the lowest NLR which was 0.04 (95% confidence interval (CI), 0.0-2.42), and the highest DOR which was 31.82 (95%CI, 0.49-2061.73), with an AUC of 0.52 (95%CI, 0.47–0.56). The prediction contours of LHR, o/e-LHR, o/e-TFLV, L/T ratio, liver-up, stomach in chest, and retrocardiac stomach position are large, which indicates a high possibility of the presence of heterogeneity between the studies in the HSROC curve.

Discussion

The current systematic review evaluated the contribution of selected antenatal predictors on mortality in fetuses with prenatally diagnosed CDH. The main finding of the study was that the antenatal parameters related to fetal lung volume were found to be equally good predictors of mortality, including the o/e-LHR < 25%, o/e-TFLV < 25%, and L/T ratio < 0.08, in isolated CDH patients.

The predictive value of LHR in fetuses with CDH was first described in 1996 by Metkus et al. However, the use of LHR has been controversial, as it was shown to increase according to the gestational age [22, 37]. Thereafter, a ratio of the o/e-LHR by Jani et al. [22, 23], which is not influenced by gestational age, was more informative in fetuses with isolated CDH. In our review, we found that o/e-LHR had both the highest summary DOR and PLR among those parameters related to fetal lung size, and this was consistent with the previous review [21]. Furthermore, both o/e-LHR on ultrasound and o/e-TFLV on MRI were superior in predicting mortality compared to LHR, due to their ability to control chronological change in gestational age. It has been demonstrated that the lung ipsilateral to the side of the hemia is more hypoplastic than the contralateral lung, which suggests that evaluation of both lungs may better estimate the degree of pulmonary hypoplasia in isolated CDH patients [45, 83]. LHR is a simple measurement of the contralateral lung by ultrasound, but MRI is more advantageous in reliably visualizing and measuring both the ipsilateral and contralateral lungs compared to ultrasonography [25, 44, 83]. However, our review demonstrated that the predictive values for mortality were similar between o/e-TFLV and o/e-LHR. In severe CDH with o/e-TFLV < 25%, the contribution of the affected ipsilateral lung may be reasonably small, and it may have contributed to discordance.

Among the antenatal parameters related to the lung volume, LHR, o/e-LHR, and o/e-TFLV are the most commonly used worldwide. L/T ratio is an ultrasonographic indicator of the severity of fetal CDH which is widely used in Japan. It was first described in 1990 for the assessment of pulmonary hypoplasia in CDH [8] and has been applied in the evaluation of pulmonary hypoplasia in CDH neonates since then [16, 38]. Usui et al. reported that L/T ratio was linearly correlated with o/e-LHR; thus the two parameters can be interconverted [51]. Specifically, an L/T ratio of 0.08 is equivalent to an o/e-LHR of 25%. Calculating o/e-LHR is complex and requires a healthy reference value for the LHR, which may vary depending on nationality and ethnicity. In contrast, the L/T ratio appears to be a reliable predictive parameter as it is reportedly not influenced by gestational age in fetuses with CDH [51]. The combination of L/T ratio and liver-up is useful in prenatal risk stratification of patients with CDH [16, 84]. In our review, L/T ratio was also a good predictor for neonatal mortality in fetuses with isolated left-sided CDH.

The intrathoracic herniation of the liver has been associated with a poorer outcome [4, 13, 19, 85], and the amount of liver herniation into the thorax was also related to poor outcomes in fetuses with CDH [28, 86]. The presence of liver herniation led to a direct reduction in the sizes of the right and left lungs [87]. However, previous studies reported that the position of the liver did not provide a significant contribution to the prediction of survival [12, 49]. This systematic review demonstrated that liver-up has relatively low levels of summary in terms of specificity, DOR, and PLR in predicting mortality, compared to the other parameters related to fetal lung volume. One of the reasons was the heterogeneity of the definition of the liver position. Some of the included studies have prenatal assessment by ultrasound as well as fetal MRI, and revealed wide variations in the definition of liver herniation from authors in different studies. Another reason was the modality, in which some studies described the definition of liver herniation evaluated by the ultrasound, while others applied MRI, or both. The other reason was the degree of herniation, which is consistent with the size of the defect in the diaphragm. The percentage of herniated liver with respect to the total liver volume calculated by MRI
was found to have a strong correlation with survival, in comparison to the presence or absence of liver herniation [18, 44]. Further evaluation of the degree of intrathoracic herniated liver is warranted as it was not evaluated in this study.

Although the intrathoracic fetal stomach position was an accurate predictor of neonatal prognosis and has been associated with poorer outcome in isolated left-sided CDH [19, 30, 32, 33], it has not been broadly applied as a predictor of postnatal outcome. In patients with isolated CDH, the intra-abdominal fetal stomach position has been associated with a favorable prognosis with a survival rate of more than 90% [9, 32, 61]. Our review also found that the intrathoracic fetal stomach herniation demonstrated the lowest summary of NLR for mortality, with a mortality rate of fetuses with an intra-abdominal stomach of 1.4% (2/140) [19, 33, 44, 47, 54, 61, 75]. Meanwhile, it has already been established that for isolated CDH, more abnormal fetal stomach herniation was associated with adverse outcomes [30, 33]. As per previous reports, our review demonstrated that retrocardiac fetal stomach position was predictive of postnatal mortality in isolated CDH, compared to fetuses with other positions. It provides evidence that fetal stomach position alone was associated with a postnatal outcome in isolated CDH.

In our review, we have demonstrated that the predictive values for mortality in patients with right-sided CDH were low. It has been reported that the patients with right-sided CDH have been found to have a greater mortality rate [34–36], larger lesions of diaphragmatic defect, and more type C and D defects as described by the CDHSG classification system [82, 88]. Meanwhile, although the high incidence of the predictors for adverse outcomes was observed in right-sided CDH compared with left-sided cases, postnatal mortality remained similar with regard to laterality [53, 81]. These findings suggest that right- and left-sided CDH may have a different pathophysiology. Currently, Terui et al. have reported a simple scoring system based on widely available prenatal ultrasound findings that included the right side of the hernia [89], and it is thought to be useful for predicting the prognosis of fetuses with CDH.

We acknowledge that the present study has some limitations. Most studies selected for our analysis were retrospective observation studies, including case-control and case-series studies, which had very different size populations. Also, selection bias could have occurred because only data from patients who underwent both prenatal MRI and ultrasound were used. The other limitations of the included studies are the high risk of bias in many studies, due to mainly patient selection and reference standard. Some studies were excluded due to the lack of outcome data or impossibility of calculating 2 × 2 tables using the difference thresholds of antenatal parameters. The reported difference between the sample size for the true positives and true negatives in the article may have affected the results. Furthermore, the review revealed wide variations in the definition of liver and stomach herniation by various investigators in different countries, and the lack of consistency in the timing of the performance of prenatal assessment. Hence, we recognized the need to standardize the definition. The postnatal mortality with different timings of follow-up in the included studies may have contributed to the postnatal outcome as well. This review included some studies with neonates with CDH who were treated with ECMO. The use of ECMO in CDH patients has been reported as predictive to lower hospital survival [90], and the variability in the use of ECMO might have affected the outcome. Regarding CDH laterality, right-sided CDH was not associated with increased mortality, but was associated with an increased requirement for pulmonary vasodilator therapy, supplemental oxygen at discharge, and a need for tracheostomy [80]. Lastly, it is important to realize that many factors contribute to mortality, such as perinatal management and therapeutic strategies, where practices at each institution have changed over the study period.

Conclusion

In summary, our systematic review and meta-analysis suggest that an o/e-LHR of < 25%, o/e-TFLV of < 25%, and L/T ratio of < 0.08 are equally good predictors of the mortality in fetuses with isolated CDH. Furthermore, liver-up and retrocardiac fetal stomach position were also good predictors of mortality, and an intra-abdominal fetal stomach position is a favorable antenatal prognostic parameter.

Declarations

Acknowledgments: This work was supported by a grant from the Ministry of Health, Labour and Welfare of Japan (Health and Labour Sciences Research Grants for Research on Intractable Diseases).

Conflict of interest: All authors declare that they have no conflict of interest.
Author Contributions Statement: KM carried out the statistical analysis, interpreted the data, drafted the initial manuscript, and reviewed and revised the manuscript. MY, SU, KN, KT, MS, MH, SA, KM, TO, NI, KT, YK, TF, YY, AY, ME, YT, and HO made substantial contributions to the acquisition and interpretation of the data, and critically reviewed and revised the manuscript. MF carried out the statistical analysis, interpreted the data, and reviewed and revised the manuscript. NU contributed to the conception and design of the work, interpreted the data, and critically reviewed and revised the manuscript. These authors contributed equally to this work: KM, MY, and SU. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

References

1. Yang W, Carmichael SL, Harris JA, Shaw GM (2006) Epidemiologic characteristics of congenital diaphragmatic hernia among 2.5 million California births, 1989–1997. Birth Defects Res A Clin Mol Teratol 76:170–174. https://doi.org/10.1002/bdra.20230

2. Dommergues M, Louis-Sylvestre C, Mandelbrot L, et al (1996) Congenital diaphragmatic hernia: Can prenatal ultrasonography predict outcome? Am J Obstet Gynecol 174:1377–1381. https://doi.org/10.1016/S0002-9378(96)70688-9

3. Buss M, Williams G, Dilley A, Jones O (2006) Prevention of heart failure in the management of congenital diaphragmatic hernia by maintaining ductal patency. A case report. J Pediatr Surg 41:e9-11. https://doi.org/10.1016/j.jpedsurg.2006.01.003

4. Knox E, Lissauer D, Khan K, Kilby M (2010) Prenatal detection of pulmonary hypoplasia in fetuses with congenital diaphragmatic hernia: A systematic review and meta-analysis of diagnostic studies. J Matern Neonatal Med. 23:579–588

5. Russo FM, Eastwood MP, Keijzer R, et al (2017) Lung size and liver herniation predict need for extracorporeal membrane oxygenation but not pulmonary hypertension in isolated congenital diaphragmatic hernia: systematic review and meta-analysis. Ultrasound Obstet Gynecol 49:704–713

6. DeKoninck P, Gratacos E, Van Mieghem T, et al (2011) Results of Fetal Endoscopic Tracheal Occlusion for congenital diaphragmatic hernia and the set up of the randomized controlled TOTAL trial. Early Hum Dev 87:619–624. https://doi.org/10.1016/j.earlhumdev.2011.08.001

7. Deprest JA, Nicolaides KH, Benachi A, et al (2021) Randomized Trial of Fetal Surgery for Severe Left Diaphragmatic Hernia. N Engl J Med 385:107–118. https://doi.org/10.1056/nejmoa2027030

8. Hasegawa T, Kamata S, Imura K, Ishikawa S, Okuyama H, Okada A CY (1990) Use of lung-thorax transverse area ratio in the antenatal evaluation of lung hypoplasia in congenital diaphragmatic hernia. J Clin Ultrasound 18:705–709

9. Hatch EI, Kendall J, Blumhagen J (1992) Stomach position as an in utero predictor of neonatal outcome in left-sided diaphragmatic hernia. J Pediatr Surg 27:778–779. https://doi.org/10.1016/S0022-3468(05)80116-2

10. Metkus AP, Filly RA, Stringer MD, et al (1996) Sonographic predictors of survival in fetal diaphragmatic hernia. J Pediatr Surg 31:148–151; discussion 151–152.

11. Lipshutz GS, Albanese CT, Feldstein VA, et al (1997) Prospective analysis of lung-to-head ratio predicts survival for patients with prenatally diagnosed congenital diaphragmatic hernia. J Pediatr Surg 32:1634–1636.

12. Albanese CT, Lopoo J, Goldstein RB, et al (1998) Fetal liver position and perinatal outcome for congenital diaphragmatic hernia. Prenat Diagn 18:1138–1142. https://doi.org/10.1002/(SICI)1097-0223(199811)18:11<1138::AID-PD416>3.0.CO;2-A

13. Kitano Y, Nakagawa S, Kuroda T, et al (2005) Liver position in fetal congenital diaphragmatic hernia retains a prognostic value in the era of lung-protective strategy. J Pediatr Surg 40:1827–1832. https://doi.org/10.1016/j.jpedsurg.2005.08.020

14. Hedrick HL, Danzer E, Merchant A, et al (2007) Liver position and lung-to-head ratio for prediction of extracorporeal membrane oxygenation and survival in isolated left congenital diaphragmatic hernia. Am J Obstet Gynecol 197:422.e1-4. https://doi.org/10.1016/j.ajog.2007.07.001

15. Cannie M, Jani J, Meersschaert J, et al (2008) 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 32:633–639. https://doi.org/10.1002/uog.6139

16. Usui N, Kitano Y, Okuyama H, et al (2011) Prenatal risk stratification for isolated congenital diaphragmatic hernia: Results of a Japanese multicenter study. J Pediatr Surg 46:1873–1880. https://doi.org/10.1016/j.jpedsurg.2011.06.007

17. Terui K, Omoto A, Osada H, et al (2011) Prediction of postnatal outcomes in congenital diaphragmatic hernia using MRI signal intensity of the fetal lung. J Perinatol 31:269–273. https://doi.org/10.1038/jp.2010.119
18. Ruano R, Lazar DA, Cass DL, et al (2014) Fetal lung volume and quantification of liver herniation by magnetic resonance imaging in isolated congenital diaphragmatic hernia. Ultrasound Obstet Gynecol 43:662–669. https://doi.org/10.1002/uog.13223
19. Lusk LA, Wai KC, Moon-Grady AJ, et al (2015) Fetal ultrasound markers of severity predict resolution of pulmonary hypertension in congenital diaphragmatic hernia. Am J Obstet Gynecol 213:216.e1-8. https://doi.org/10.1016/j.ajog.2015.03.036
20. Yamoto M, Inamura N, Terui K, et al (2016) Echocardiographic predictors of poor prognosis in congenital diaphragmatic hernia. J Pediatr Surg 51:1926–1930. https://doi.org/10.1016/j.jpedsurg.2016.09.014
21. Oluyomi-Obi T, Kuret V, Puligandla P, et al (2017) Antenatal predictors of outcome in prenatally diagnosed congenital diaphragmatic hernia (CDH). J Pediatr Surg. 52:881–888
22. Jani J, Nicolaides KH, Keller RL, et al (2007) Observed to expected lung area to head circumference ratio in the prediction of survival in fetuses with isolated diaphragmatic hernia. Ultrasound Obstet Gynecol 30:67–71. https://doi.org/10.1002/uog.4052
23. Jani JC, Benachi A, Nicolaides KH, et al (2009) Prenatal prediction of neonatal morbidity in survivors with congenital diaphragmatic hernia: A multicenter study. Ultrasound Obstet Gynecol 33:64–69. https://doi.org/10.1002/uog.6141
24. Mayer S, Klaritsch P, Petersen S, et al (2011) The correlation between lung volume and liver herniation measurements by fetal MRI in isolated congenital diaphragmatic hernia: A systematic review and meta-analysis of observational studies. Prenat Diagn 31:1086–1096. https://doi.org/10.1002/pd.2839
25. Ruano R, Takashi E, Da Silva MM, et al (2012) Prediction and probability of neonatal outcome in isolated congenital diaphragmatic hernia using multiple ultrasound parameters. Ultrasound Obstet Gynecol 39:42–49. https://doi.org/10.1002/uog.10095
26. Tsukimori K, Masumoto K, Morokuma S, et al (2008) The lung-to-thorax transverse area ratio at term and near term correlates with survival in isolated congenital diaphragmatic hernia. J Ultrasound Med. 27:707–713
27. Kunisaki SM, Barnewolt CE, Estroff JA, et al (2008) Liver position is a prenatal predictive factor of prosthetic repair in congenital diaphragmatic hernia. Fetal Diagn Ther 23:258–262. https://doi.org/10.1159/000123611
28. Worley KC, Dashe JS, Barber RG, et al (2009) Fetal magnetic resonance imaging in isolated diaphragmatic hernia: volume of herniated liver and neonatal outcome. Am J Obstet Gynecol 200:318.e1-6. https://doi.org/10.1016/j.ajog.2008.10.008
29. Stressig R, Fimmers R, Eising K, et al (2011) Intrathoracic herniation of the liver ('liver-up') is associated with predominant left heart hypoplasia in human fetuses with left diaphragmatic hernia. Ultrasound Obstet Gynecol 37:272–276. https://doi.org/10.1002/uog.7747
30. Kitano Y, Okuyama H, Saito M, et al (2011) Re-evaluation of stomach position as a simple prognostic factor in fetal left congenital diaphragmatic hernia: A multicenter survey in Japan. Ultrasound Obstet Gynecol 37:277–282. https://doi.org/10.1002/uog.8892
31. Lazar DA, Ruano R, Cass DL, et al (2012) Defining "liver-up": Does the volume of liver herniation predict outcome for fetuses with isolated left-sided congenital diaphragmatic hernia? J Pediatr Surg 47:1058–1062.
32. Cordier AG, Jani JC, Cannie MM, et al (2015) Stomach position in prediction of survival in left-sided congenital diaphragmatic hernia with or without fetoscopic endoluminal tracheal occlusion. Ultrasound Obstet Gynecol 46:155–161. https://doi.org/10.1002/uog.14759
33. Basta AM, Lusk LA, Keller RL, Filly RA (2016) Fetal Stomach Position Predicts Neonatal Outcomes in Isolated Left-Sided Congenital Diaphragmatic Hernia. Fetal Diagn Ther 39:248–255. https://doi.org/10.1159/000440649
34. Skari H, Bjornland K, Haugen G, et al (2000) Congenital diaphragmatic hernia: A meta-analysis of mortality factors. J Pediatr Surg 35:1187–1197. https://doi.org/10.1053/jpsu.2000.8725
35. Fisher JC, Jefferson RA, Arkovitz MS, Stolar CJH (2008) Redefining outcomes in right congenital diaphragmatic hernia. J Pediatr Surg 43:373–379. https://doi.org/10.1016/j.jpedsurg.2007.10.049
36. Duess JW, Zani-Ruttenstock EM, Garriboli M, et al (2015) Outcome of right-sided diaphragmatic hernia repair: a multicentre study. Pediatr Surg Int 31:465–471. https://doi.org/10.1007/s00383-015-3695-y
37. Peralta CFA, Cavoretto P, Csapo B, et al (2005) Assessment of lung area in normal fetuses at 12–32 weeks. Ultrasound Obstet Gynecol 26:718–724. https://doi.org/10.1002/uog.2651
38. Usui N, Kitano Y, Okuyama H, et al (2011) Reliability of the lung to thorax transverse area ratio as a predictive parameter in fetuses with congenital diaphragmatic hernia. Pediatr Surg Int 27:39–45. https://doi.org/10.1007/s00383-010-2725-z
39. Russo FM, Cordier AG, De Catte L, Saada J, Benachi A, Deprest J (2018) Workstream Prenatal Management, ERNICA European reference network. 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 38:629–637. doi: 10.1002/pd.5297
40. Ibirogba ER, Novoa Y Novoa VA, Sutton LF, et al (2019) Standardization and reproducibility of sonographic stomach position grades in fetuses with congenital diaphragmatic hernia. J Clin Ultrasound 47:513–517. doi: 10.1002/jcu.22759
41. Perrone EE, Abbasi N, Cortes MS, et al (2021) Prenatal assessment of congenital diaphragmatic hernia at north american fetal therapy network centers: A continued plea for standardization. Prenat Diagn 41:200–206. doi: 10.1002/pd.5859
42. Cordier AG, Laup L, Letourneau A, et al (2021) Prenatal stomach position predicts gastrointestinal morbidity at 2 years in fetuses with left-sided congenital diaphragmatic hernia. Ultrasound Obstet Gynecol 57:959–967. doi: 10.1002/uog.22086
43. Jani J, Keller RL, Benachi A, et al (2006) Prenatal prediction of survival in isolated left-sided diaphragmatic hernia. Ultrasound Obstet Gynecol 27:18–22. https://doi.org/10.1002/uog.2688
44. Heling KS, Wauer RR, Hammer H, et al (2005) Reliability of the lung-to-head ratio in predicting outcome and neonatal ventilation parameters in fetuses with congenital diaphragmatic hernia. Ultrasound Obstet Gynecol 25:112–118. https://doi.org/10.1002/uog.1837
45. Arkovitz MS, Russo M, Devine P, et al (2007) Fetal lung-head ratio is not related to outcome for antenatal diagnosed congenital diaphragmatic hernia. J Pediatr Surg 42:107–111. https://doi.org/10.1016/j.jpedsurg.2006.09.010
46. Kehl S, Siemer J, Brunnemer S, et al (2014) Prediction of postnatal outcomes in fetuses with isolated congenital diaphragmatic hernias using different lung-to-head ratio measurements. J. Ultrasound Med. 33:759–767
47. Usui N, Okuyama H, Kanamori Y, et al (2014) The lung to thorax transverse area ratio has a linear correlation with the observed to expected lung area to head circumference ratio in fetuses with congenital diaphragmatic hernias. J Pediatr Surg 49:1191–1196. https://doi.org/10.1016/j.jpedsurg.2013.10.021
48. Snoek KG, Peters NCJ, van Rosmalen J, et al (2017) The validity of the observed-to-expected lung-to-head ratio in congenital diaphragmatic hernia in an era of standardized neonatal treatment; a multicenter study. Prenat Diagn 37:658–665. https://doi.org/10.1002/pd.5062
49. Victoria T, Danzer E, Oliver ER, et al (2018) Right congenital diaphragmatic hernias: Is there a correlation between prenatal lung volume and postnatal survival, as in isolated left diaphragmatic hernias? Fetal Diagn Ther 43:12–18. https://doi.org/10.1159/000464246
50. Yamoto M, Ohfuji S, Urushihara N, et al (2021) Optimal timing of surgery in infants with prenatally diagnosed isolated left-sided congenital diaphragmatic hernia: a multicenter, cohort study in Japan. Surg Today 51:880–890. https://doi.org/10.1007/s00595-020-02156-7
51. Paek BW, Coakley F V., Lu Y, et al (2001) Congenital diaphragmatic hernia: Prenatal evaluation with MR lung volumetry - Preliminary experience. Radiology 220:63–67. https://doi.org/10.1148/radiology.220.1.r01j4163
52. Gorincour G, Bouvenot J, Mourot MG, et al (2005) Prenatal prognosis of congenital diaphragmatic hernia using magnetic resonance imaging measurement of fetal lung volume. Ultrasound Obstet Gynecol 26:738–744. https://doi.org/10.1002/uog.2618
57. Nakata M, Sase M, Anno K, et al (2003) Prenatal sonographic chest and lung measurements for predicting severe pulmonary hypoplasia in left-sided congenital diaphragmatic hernia. Early Hum Dev 72:75–81. https://doi.org/10.1016/S0378-3782(03)00026-4

58. Kido S, Hidaka N, Sato Y, et al (2017) Re-evaluation of lung to thorax transverse area ratio immediately before birth in predicting postnatal short-term outcomes of fetuses with isolated left-sided congenital diaphragmatic hernia: A single center analysis. Congenit Anom (Kyoto) 58:87–92. https://doi.org/10.1111/cga.12243

59. Walsh DS, Hubbard AM, Olutoye OO, et al (2000) Assessment of fetal lung volumes and liver herniation with magnetic resonance imaging in congenital diaphragmatic hernia. Am J Obstet Gynecol 183:1067–1069. https://doi.org/10.1067/mob.2000.108895

60. Casaccia G, Ravà L, Bagolan P, Di Ciummo VM (2008) Predictors and statistical models in congenital diaphragmatic hernia. Pediatr Surg Int 24:411–414. https://doi.org/10.1007/s00383-008-2108-x

61. Datin-Dorriere V, Rouzies S, Taupin P, et al (2008) Prenatal prognosis in isolated congenital diaphragmatic hernia. Am J Obstet Gynecol 198:80.e1-5. https://doi.org/10.1016/j.ajog.2007.06.069

62. Jani J, Nicolaides KH, Benachi A, et al (2008) Timing of lung size assessment in the prediction of survival in fetuses with diaphragmatic hernia. Ultrasound Obstet Gynecol 31:37–40. https://doi.org/10.1002/uog.5198

63. Alfaraj MA, Shah PS, Bohn D, et al (2011) Congenital diaphragmatic hernia: Lung-to-head ratio and lung volume for prediction of outcome. Am J Obstet Gynecol 205:43.e1-8. https://doi.org/10.1016/j.ajog.2011.02.050

64. Aspelund G, Fisher JC, Simpson LL, Stolar CJH (2012) Prenatal lung-head ratio: Threshold to predict outcome for congenital diaphragmatic hernia. J Matern Neonatal Med. 25:1011–1016

65. Sebastià C, Gomez O, Salvador R, et al (2015) Prognostic usefulness of derived T2-weighted fetal magnetic resonance imaging measurements in congenital diaphragmatic hernia. Radiologia 57:239–247. https://doi.org/10.1016/J.RX.2014.02.001

66. Kastenholz KE, Weis M, Hagelstein C, et al (2016) Correlation of observed-to-expected MRI fetal lung volume and ultrasound lung-to-head ratio at different gestational times in fetuses with congenital diaphragmatic hernia. Am J Roentgenol 206:856–866. https://doi.org/10.2214/AJR.15.15018

67. Hattori T, Hayakawa M, Ito M, et al (2017) The relationship between three signs of fetal magnetic resonance imaging and severity of congenital diaphragmatic hernia. J Perinatol 37:265–269. https://doi.org/10.1038/jp.2016.208

68. Straňák Z, Krofta L, Haak LA, et al (2017) Antenatal assessment of liver position, rather than lung-to-head ratio (LHR) or observed/expected LHR, is predictive of outcome in fetuses with isolated left-sided congenital diaphragmatic hernia. J Matern Neonatal Med 30:74–78. https://doi.org/10.3109/14767058.2016.1163539

69. Tsuda H, Kotani T, Miura M, et al (2017) Observed-to-expected MRI fetal lung volume can predict long-term lung morbidity in infants with congenital diaphragmatic hernia. J Matern Neonatal Med 30:1509–1513. https://doi.org/10.1080/14767058.2017.1299126

70. Weis M, Hoffmann S, Henzler C, et al (2018) Isolated impact of liver herniation on outcome in fetuses with congenital diaphragmatic hernia – A matched-pair analysis based on fetal MRI relative lung volume. Eur J Radiol 105:148–152. https://doi.org/10.1016/j.ejrad.2018.05.024

71. Aydin E, Lim FY, Kingma P, et al (2019) Congenital diaphragmatic hernia: the good, the bad, and the tough. Pediatr Surg Int 35:303–313. https://doi.org/10.1007/s00383-019-04442-z

72. Cruz-Martínez R, Etchegaray A, Molina-Giraldo S, et al (2019) A multicentre study to predict neonatal survival according to lung-to-head ratio and liver herniation in fetuses with left congenital diaphragmatic hernia (CDH): Hidden mortality from the Latin American CDH Study Group Registry. Prenat Diagn 39:519–526. https://doi.org/10.1002/pd.5458

73. Petroze RT, Caminsky NG, Trebichavsky J, et al (2019) Prenatal prediction of survival in congenital diaphragmatic hernia: An audit of postnatal outcomes. J Pediatr Surg 54:925–931. https://doi.org/10.1016/J.JPEDSURG.2019.01.021

74. Wang W, Pan W, Chen J, et al (2019) Outcomes of Congenital Diaphragmatic Hernia in One of the Twins. Am J Perinatol 36:1304–1309. https://doi.org/10.1055/s-0038-1676830

75. Schaible T, Büsing KA, Felix JF, et al (2012) Prediction of chronic lung disease, survival and need for ECMO therapy in infants with congenital diaphragmatic hernia: Additional value of fetal MRI measurements? Eur J Radiol 81:1076–1082. https://doi.org/10.1016/j.ejrad.2011.02.060
76. Hsieh YY, Chang FCC, Tsai HD, et al (2000) Accuracy of sonography in predicting the outcome of fetal congenital diaphragmatic hernia. Chinese Med J 63:751–757

77. Skari H, Bjornland K, Frenckner B, et al (2002) Congenital diaphragmatic hernia in Scandinavia from 1995 to 1998: Predictors of mortality. J Pediatr Surg 37:1269–1275. https://doi.org/10.1053/jpsu.2002.34980

78. Büsing KA, Kilian AK, Schaible T, et al (2008) MR lung volume in fetal congenital diaphragmatic hernia: Logistic regression analysis - Mortality and extracorporeal membrane oxygenation. Radiology 248:233–239. https://doi.org/10.1148/radiol.2481070934

79. Schaible T, Kohl T, Reinshagen K, et al (2012) Right-versus left-sided congenital diaphragmatic hernia: Postnatal outcome at a specialized tertiary care center. Pediatr Crit Care Med 13:66–71. https://doi.org/10.1097/PCC.0b013e3182192aa9

80. Partridge EA, Peranteau WH, Herkert L, et al (2016) Right- versus left-sided congenital diaphragmatic hernia: A comparative outcomes analysis. J Pediatr Surg 51:900–902. https://doi.org/10.1016/j.jpedsurg.2016.02.049

81. Sperling JD, Sparks TN, Berger VK, et al (2018) Prenatal Diagnosis of Congenital Diaphragmatic Hernia: Does Laterality Predict Perinatal Outcomes? Am J Perinatol 35:919–924. https://doi.org/10.1055/s-0037-1617754

82. Abramov A, Fan W, Hernan R, et al (2020) Comparative outcomes of right versus left congenital diaphragmatic hernia: A multicenter analysis. J Pediatr Surg 55:33–38. https://doi.org/10.1016/j.jpedsurg.2019.09.046

83. Jani JC, Cannie M, Peralta CFA, et al (2007) Lung volumes in fetuses with congenital diaphragmatic hernia: Comparison of 3D US and MR imaging assessments. Radiology 244:575–582. https://doi.org/10.1148/radiol.2442061158

84. Masahata K, Usui N, Shimizu Y, et al (2020) Clinical outcomes and protocol for the management of isolated congenital diaphragmatic hernia based on our prenatal risk stratification system. J Pediatr Surg 55:1528–1534. https://doi.org/10.1016/j.jpedsurg.2019.10.020

85. Mullassery D, Ba'ath ME, Jesudason EC, Losty PD (2010) Value of liver herniation in prediction of outcome in fetal congenital diaphragmatic hernia: A systematic review and meta-analysis. Ultrasound Obstet Gynecol 35:609–614. https://doi.org/10.1002/uog.7586

86. Cannie M, Jani J, Chaffiotte C, et al (2008) Quantification of intrathoracic liver herniation by magnetic resonance imaging and prediction of postnatal survival in fetuses with congenital diaphragmatic hernia. Ultrasound Obstet Gynecol 32:627–632. https://doi.org/10.1002/uog.6146

87. Langwieler T, Fiegel HC, Alaamian M, et al (2004) The relationship of diaphragmatic defect, liver growth, and lung hypoplasia in nitrofen-induced congenital diaphragmatic hernia in the rat. Pediatr Surg Int 20:509–514. https://doi.org/10.1007/s00383-004-1226-3

88. Lally KP, Lasky RE, Lally PA, et al (2013) Standardized reporting for congenital diaphragmatic hernia - An international consensus. In: Journal of Pediatric Surgery. J Pediatr Surg 48:2408–2415.

89. Terui K, Nagata K, Hayakawa M, et al (2020) Novel Risk Score for Fetuses with Congenital Diaphragmatic Hernia Based on Ultrasound Findings. Eur J Pediatr Surg 30:51–58. doi: 10.1055/s-0039-1698768

90. Nagata K, Usui N, Kanamori Y, et al (2013) The current profile and outcome of congenital diaphragmatic hernia: A nationwide survey in Japan. J Pediatr Surg 48:738–744. https://doi.org/10.1016/j.jpedsurg.2012.12.017

Figures
Total records identified through database search (n= 1269)
  - Medline (OvidSP) (n= 1216)
  - Cochrane Libray (n= 53)

Total records removed duplicate records before screening (n= 1257)

Additional records identified through other sources (n= 3)

Records screened (1st Screening) (n= 1260)

Records excluded (n= 1070)

Full-text articles assessed for eligibility (2nd Screening) (n= 190)

Full-text articles excluded, with reasons (n= 140):
  - Did not match outcome (n= 59)
  - Did not use comparative study design (n= 9)
  - Review (n= 11)
  - Others reasons (n= 61)

Studies included in qualitative synthesis (n= 50)

Studies included in quantitative synthesis (meta-analysis) (n= 50)

**Figure 1**

Flow diagram of the study selection process and inclusion of studies in meta-analysis.
### Figure 2

**Accuracy of individual studies of antenatal parameters for mortality prediction.**

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|----------------------|----------------------|
| Aboal 2011 | 8 | 14 | 17 | 33 | 0.32 (0.15, 0.54) | 0.70 (0.55, 0.85) |                      |                      |
| Arkov 2012 | 3 | 9 | 1 | 15 | 0.75 (0.10, 0.96) | 0.90 (0.81, 0.97) |                      |                      |
| Aydin 2011 | 28 | 8 | 23 | 66 | 0.86 (0.70, 0.94) | 0.92 (0.80, 0.96) |                      |                      |
| Cacace 2008 | 32 | 20 | 17 | 46 | 0.64 (0.42, 0.77) | 0.71 (0.57, 0.81) |                      |                      |
| Cetin 2015 | 16 | 30 | 9 | 39 | 0.61 (0.43, 0.75) | 0.61 (0.43, 0.75) |                      |                      |
| Dark 2016 | 36 | 39 | 10 | 99 | 0.81 (0.60, 0.92) | 0.88 (0.66, 0.98) |                      |                      |
| Davati 2014 | 11 | 10 | 2 | 43 | 0.60 (0.35, 0.80) | 0.81 (0.64, 0.92) |                      |                      |
| Eken 2012 | 17 | 28 | 14 | 75 | 0.65 (0.49, 0.77) | 0.72 (0.55, 0.83) |                      |                      |
| Hame 2012 | 10 | 9 | 8 | 23 | 0.66 (0.42, 0.81) | 0.72 (0.55, 0.83) |                      |                      |
| Hame 2011 | 19 | 21 | 6 | 58 | 0.69 (0.46, 0.83) | 0.76 (0.54, 0.90) |                      |                      |
| Hame 2010 | 22 | 18 | 7 | 64 | 0.72 (0.49, 0.87) | 0.76 (0.54, 0.90) |                      |                      |
| Hokma 2014 | 23 | 2 | 3 | 1 | 0.71 (0.56, 0.85) | 0.90 (0.81, 0.97) |                      |                      |
| Ince 2013 | 11 | 7 | 6 | 21 | 0.68 (0.48, 0.83) | 0.72 (0.55, 0.83) |                      |                      |
| Ince 2012 | 11 | 2 | 4 | 1 | 0.81 (0.60, 0.93) | 0.88 (0.66, 0.98) |                      |                      |
| Ince 2011 | 18 | 25 | 5 | 63 | 0.72 (0.49, 0.87) | 0.76 (0.54, 0.90) |                      |                      |
| Ince 2010 | 15 | 16 | 4 | 58 | 0.78 (0.56, 0.91) | 0.88 (0.66, 0.98) |                      |                      |
| Ince 2009 | 20 | 14 | 4 | 58 | 0.78 (0.56, 0.91) | 0.88 (0.66, 0.98) |                      |                      |
| Ince 2008 | 16 | 25 | 5 | 63 | 0.72 (0.49, 0.87) | 0.76 (0.54, 0.90) |                      |                      |
| Ince 2007 | 18 | 25 | 5 | 63 | 0.72 (0.49, 0.87) | 0.76 (0.54, 0.90) |                      |                      |
| Ince 2006 | 15 | 16 | 4 | 58 | 0.78 (0.56, 0.91) | 0.88 (0.66, 0.98) |                      |                      |
| Ince 2005 | 20 | 14 | 4 | 58 | 0.78 (0.56, 0.91) | 0.88 (0.66, 0.98) |                      |                      |
| Ince 2004 | 16 | 25 | 5 | 63 | 0.72 (0.49, 0.87) | 0.76 (0.54, 0.90) |                      |                      |
| Ince 2003 | 18 | 25 | 5 | 63 | 0.72 (0.49, 0.87) | 0.76 (0.54, 0.90) |                      |                      |
| Ince 2002 | 15 | 16 | 4 | 58 | 0.78 (0.56, 0.91) | 0.88 (0.66, 0.98) |                      |                      |
| Ince 2001 | 20 | 14 | 4 | 58 | 0.78 (0.56, 0.91) | 0.88 (0.66, 0.98) |                      |                      |
Figure 3

Summary of bias assessment using the QUADAS-2 tool of the studies included in the meta-analysis: (a) LHR<1; (b) o/e-LHR <25%; (c) o/e-TFLV <25%; (d) L/T ratio <0.08; (e) liver-up; (f) stomach in chest; (g) retrocardiac stomach position; (h) right side of diaphragmatic hernia. For the antenatal parameters (a-h), in green was highlighted a low risk of bias or low applicability concern and in red the studies with a high risk of bias or high applicability concerns. The bar with blue indicates the studies were where these risks of bias or applicability concerns could not be assessed properly (unclear).

QUADAS-2; Quality Assessment of Diagnostic Accuracy Studies, LHR; lung-to-head ratio, o/e-LHR; observed-to-expected LHR, o/e-TFLV; observed-to-expected total fetal lung volume, L/T ratio; lung-to-thorax transverse area ratio.
Figure 4

Constructed hierarchical summary receiver operating characteristics (HSROC) curves of antenatal parameters for the prediction of mortality in patients with prenatally diagnosed CDH: (a) LHR <1; (b) o/e-LHR <25%; (c) o/e-TFLV <25%; (d) L/T ratio <0.08; (e) liver-up; (f) stomach in chest; (g) retrocardiac stomach position; (h) right side of diaphragmatic hernia.

Each circle on the plot represents the pair of sensitivity and specificity from a study, and the size of the circle is scaled according to the sample size. The solid red block represents the summary of sensitivity and specificity, and this summary point is surrounded by a 95% confidence region (yellow dashed line) and 95% prediction region (blue dotted line).

CDH; congenital diaphragmatic hernia, LHR; lung-to-head ratio, o/e-LHR; observed-to-expected LHR, o/e-TFLV; observed-to-expected total fetal lung volume, L/T ratio; lung-to-thorax transverse area ratio.

Supplementary Files

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