Systematic Review

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Prenatal Predictors of Survival in Isolated Congenital Diaphragmatic Hernia

A Systematic Review and Meta-analysis

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OBJECTIVE: To evaluate prenatal fetal imaging findings associated with survival to hospital discharge, persistent pulmonary hypertension (PH), and need for extracorporeal membrane oxygenation (ECMO) in fetuses with isolated congenital diaphragmatic hernia (CDH) that are undergoing prenatal expectant management.

DATA SOURCES: A systematic search was conducted in MEDLINE through PubMed, EMBASE, Web of Science, and The Cochrane Central, and ClinicalTrials.gov from 2000 up to July 2023.

METHODS OF STUDY SELECTION: Studies that reported on prenatal imaging in fetuses with isolated CDH that were undergoing expectant management were included. Primary outcomes were survival to hospital discharge, persistent PH within 28 days of age, and need for ECMO. The quality of studies was assessed using the Newcastle-Ottawa Scale. Meta-analysis was performed when at least two studies reported on the same prenatal imaging evaluation. Subgroup analyses were performed according to the side (left or right) of CDH.

TABULATION, INTEGRATION, AND RESULTS: A total of 161 full-text articles were assessed for eligibility, with 48 studies meeting the inclusion criteria: 45 (N=3,977) assessed survival, eight (N=994) assessed persistent PH, and 12 (N=2,085) assessed need for ECMO. The pooled proportion was 2,833 of 3,977 (71.2%, 95% CI, 69.8–72.6%) for survival, 565 of 2,085 (27.1%, 95% CI, 25.2–29.1%) for need for ECMO, and 531 of 994 (53.4%, 95% CI, 50.3–56.6%) for need for persistent PH. Prenatal imaging findings that were significantly associated with survival included: total fetal lung volume (mean difference [MD] 13.42, 95% CI, 11.22–15.62), observed-to-expected (O-E) total fetal lung volume less than 30% (odds ratio [OR] 0.09, 95% CI, 0.05–0.17), O-E total fetal lung volume (MD 14.73, 95% CI, 11.62–17.84, I^2 46%), liver/intrathoracic ratio (MD −9.59, 95% CI, −15.73 to −3.46), O-E lung/head ratio (MD 14.03, 95% CI, 12.69–15.36), O-E lung/head ratio less than 25% (OR 0.07, 95% CI, 0.04–0.13), mediastinal shift angle (MD −6.17, 95% CI, −7.70 to −4.64), stomach position in mid-chest (OR 0.14, 95% CI, 0.06–0.36), and intrathoracic liver (OR 0.23, 95% CI, 0.15–0.35). In subgroup analyses, findings for left-sided CDH remained significant in all the aforementioned findings. The only prenatal imaging finding that was significantly associated with persistent PH was intrathoracic liver (OR 1.96, 95% CI, 1.14–3.37), but this association was no longer significant in subgroup analyses. Prenatal imaging findings that were significantly associated with need for ECMO included: O-E total fetal lung volume (MD −10.08, 95% CI, −13.54 to −6.62), O-E lung/head ratio (MD −9.88, 95% CI, 14.44 to −5.33, I^2 30%), subgroup analysis to the left-sided CDH remained significant, percentage of predicted lung volume (MD −9.81, 95% CI, −13.56 to −6.06, I^2 34%), and intrathoracic liver (OR 2.70, 95% CI, 1.60–4.57, I^2 0%), but this association was no longer significant in left-sided CDH subgroup analysis.

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CONCLUSION: Several prenatal imaging findings, including lung measurements, intrathoracic liver, and stomach position, were predictive of neonatal survival. Lung measurement was predictive of need for ECMO, and intrathoracic liver was significantly associated with persistent PH and need for ECMO.

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Congenital diaphragmatic hernia (CDH) is a severe developmental defect that affects 1 to 4 per 10,000 births,[1–3] characterized by a left-sided, right-sided, or mixed left-right defect with herniation of abdominal contents into the fetal thorax. The herniation results in lung hypoplasia and the risk of persistent pulmonary hypertension (PH).[4,5] Lung hypoplasia secondary to CDH is suspected to be due to extrinsic compression from abdominal contents and is possibly related to a disruption in organogenesis.[1] Persistent PH is attributed to an increase in precapillary resistance and changes in pulmonary vasculature, including arteriolar thickening and compromised vasoreactivity.[4,6] Persistent pulmonary hypertension leads to poor neonatal oxygenation and cardiac function and confers a worse prognosis and diminished survival.[4] When maximal medical therapy has failed, extracorporeal membrane oxygenation (ECMO) is an additional intervention that may be used in the neonatal period to support survival.[7,8]

Individual studies have evaluated the association between antenatal imaging findings and outcomes of mortality, persistent PH, and need for ECMO to individualize the prognosis for fetuses with isolated CDH. These efforts aim to allow for improved prognostication for expecting parents and appropriately prepare medical teams for anticipated neonatal resuscitation after delivery.[9–19] Both ultrasonography and magnetic resonance imaging (MRI) have been used antenatally to assess the degree of lung hypoplasia and lung vascularization.[20] Additional antenatal imaging findings considered include stomach position in the chest, liver herniation and percentage of herniation, and mediastinal shift angle, among others.[21–25]

Accurate prognostication of CDH disease severity (ie, pulmonary hypoplasia and risk for persistent PH) would aid in appropriate resource mobilization and preparations for advanced postnatal treatment options. In this study, we aimed to conduct a systematic review and meta-analysis evaluating antenatal imaging findings prognostic value in predicting survival, persistent PH, and need for ECMO in fetuses with isolated CDH.

SOURCES

The study was conducted based on the 2020 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[26] The protocol for this study was submitted on PROSPERO with the registration code CRD42023428103 before initiation. A systematic literature search was performed by two independent authors (A.T. and F.A.) in MEDLINE through PubMed, EMBASE, Web of Science, Cochrane Central, and ClinicalTrials.gov from January 2000 to July 2023. The electronic search strategy included both MeSH terms and keywords (free text words) and is detailed in Appendix 1, available online at http://links.lww.com/AOG/D782. Reference lists and topic-related reviews also were manually reviewed to identify further relevant studies.

STUDY SELECTION

Studies generated from the search process were transferred into Rayyan, which is an automated software used for systematic reviews.[27] Duplicates were removed through Rayyan followed by a manual check for supplicates. The studies were selected in two phases. First, the titles and abstracts of the articles were screened independently by two reviewers (A.T. and F.A.). Full-text copies of the selected articles were assessed independently for their eligibility by the same two reviewers according to the inclusion and exclusion criteria. Disagreements between reviewers were resolved by discussion or by a third reviewer (H.M.) as needed. For studies that included overlapping data, only the largest and most complete data set was included.

Using the PICO (Patient-Intervention-Comparison-Outcome) framework, the following eligibility criteria were determined to include all relevant original articles: pregnant individuals with a prenatal diagnosis of CDH (Patient); pregnant individuals with CDH who had antenatal imaging by ultrasonography or MRI for prognostication (Intervention/Indicator); comparison of three groups– survivors vs nonsurvivors, persistent PH vs not, and the need for ECMO (Comparison); survival up to hospital discharge, persistent PH, and need for ECMO (Outcome).

Inclusion criteria included observational and interventional studies, studies published in English, adequate reports on population, definition of prenatal imaging studies, and postnatal outcomes. We only included studies on fetuses with isolated CDH (ie, without associated anatomical malformations or known genetic conditions), regardless of the side of the defect. Pregnant individuals with antepartum fetal therapy were excluded. Studies on all relevant ultrasound and

MRI imaging studies were eligible for inclusion, if an accurate description of the technique was provided. We excluded studies that were published as case reports, reviews, or articles with no full text available, and also excluded studies that only reported outcomes beyond 1 month of age. Individuals with pregnancies that ended in termination or lacked information on postnatal outcomes also were excluded.

Primary outcomes assessed were survival to hospital discharge, persistent PH within 28 days of age, and need for ECMO. *Persistent PH* was defined as the presence of tricuspid regurgitation, septal bowing, and continuous or dominant right-to-left shunting through a patent ductus arteriosus on cardiac ultrasonography or by a preductal–postductal saturation difference greater than 10%.[28–30] *Extracorporeal membrane oxygenation* was defined as the primary indication of failure of conventional therapy[31–33] applied according to consensus criteria.[34,35]

The antenatal imaging findings considered include:

1. Lung/head ratio. The ratio of the contralateral lung area (at the level of the four-chamber view of the heart) to the head circumference measured by ultrasonography. The contralateral lung area is measured by one of three methods: 1) longest diameter, the product of the longest diameter of the lung by its longest perpendicular diameter; 2) antero-posterior method, the product of the anterior-posterior diameter of the lung at the mid-clavicular line by the perpendicular diameter at the midpoint of the antero-posterior diameter; 3) the trace method, manual tracing of the lung circumference.
2. Observed-to-expected (O-E) lung/head ratio. Ratio of the O-E lung/head ratio measured by ultrasonography. The expected lung/head ratio is obtained by the data from normal fetuses by Peralta et al.[36]
3. Total fetal lung volume. The sum of both lung volumes measured by MRI.
4. Observed-to-expected total fetal lung volume. Ratio of the O-E total fetal lung volume measured by MRI. The expected lung volume for O-E total fetal lung volume was calculated by various formulas, most commonly the formula by Rypens et al.[37]
5. Percentage of predicted lung volume. The measured thoracic volume minus measured mediastinal volume as measured by MRI.
6. Liver herniation by ultrasonography. Presence of portion of the liver above the level of the diaphragm.
7. Magnetic resonance imaging quantification of liver herniation. Determination of the amount of herniated liver by MRI described in two ways: 1) liver/intrathoracic ratio, the ratio of herniated liver volume to total thoracic volume; and 2) percentage liver herniation, the ratio of the volume of herniated liver volume to total fetal liver volume.

The Newcastle-Ottawa Scale for cohorts was used for risk of bias assessment. It consists of three domains to evaluate the selection of the cohort population, matching and adjustment for confounders between exposed and nonexposed populations, and the accuracy of the cohort's outcome reporting process.[38] Assessment was performed by two reviewers independently (A.T. and F.A.).

Data extraction was performed by two independent authors (A.T. and F.A.) using a standardized Excel spreadsheet. Disagreements were resolved after discussion with a third author (H.M.). The following data were abstracted: 1) study characteristics including author, publication year, study period, country, involved institutions, study design, inclusion and exclusion criteria, population size, CDH side as left-sided, right-sided, or mixed left-right sided; 2) antenatal imaging findings including type of imaging (ultrasonography or MRI), type of test, methodology, cut-off point (if applicable), gestational age at test, type of reference standard, and time and treatment between index test and reference standard; and 3) incidence of outcomes including survival to discharge, persistent PH, and need for ECMO.

Statistical analysis was performed with Review Manager 5.4 and Comprehensive Meta-Analysis 3. If data were presented as median (range) or median (interquartile range), data were converted to mean and standard deviation using the Wan formula.[39] Pooled effect sizes were presented using mean difference (MD) or odds ratio (OR), using the Mantel-Haenszel test, with 95% CI for continuous and categorical variables, respectively. Only variables that were reported in at least two studies were analyzed. Subgroup analyses for studies that reported on left-sided CDH only were conducted. I^2 tests were used to examine heterogeneity across the included studies; I^2 50% or greater and $P<.05$ indicate heterogeneity. I^2 more than 75% represents considerable heterogenicity. A random-effects model was used owing to the anticipated heterogeneity of included studies. A leave-one-out analysis was performed for variables that were statistically significantly different by outcome to evaluate the effect of each study on the pooled results by removing each of them one at a

time. Potential publication bias was assessed using Begg's correlation test. $P<.05$ was considered statistically significant.

RESULTS

A total of 161 full-text articles were assessed for eligibility, with 113 studies excluded (Fig. 1) and 48 studies included in analysis. Study characteristics are outlined in Table 1. Of the 48 included studies, 45 studies (N=3,977) assessed survival, eight studies assessed persistent PH (N=994), and 12 studies assessed need for ECMO (N=2,085). There were 39 retrospective cohort studies and nine prospective cohort studies. The inclusion and exclusion criteria for each study are outlined in Table 1. Twenty studies included both left-sided and right-sided CDH types, 23 studies included only left-sided CDH, and five studies only included right-sided CDH.

Across all included studies, the pooled proportion was 2,833 of 3,977 (71.2%, 95% CI, 69.8–72.6%) for survival, 531 of 994 (53.4%, 95% CI, 50.3–56.6%) for persistent PH, and 565 of 2,085 (27.1%, 95% CI, 25.2–29.1%) for need for ECMO.

Of the antenatal imaging findings evaluated that were significantly associated with survival (Table 2), the strongest predictors included total fetal lung volume (MD 13.42, 95% CI, 11.22–15.62), O-E total fetal lung volume (MD 14.73, 95% CI, 11.62–17.84, I^2 46%) and O-E lung/head ratio (MD 14.03, 95% CI, 12.69–15.36). In the subgroup analysis limited to left-sided CDH only, O-E lung/head ratio remained significantly associated with survival, with heterogeneity of 0% (OR 14.21, 95% CI, 12.09–16.32). Although percentage of predicted lung volume (OR 7.86, 95% CI, 3.71–12.02) was significantly associated with survival among all cases of CDH, this was no longer significant in the subgroup analysis of left-sided CDH only, with the heterogeneity of 73% (OR 6.30, 95% CI, 1.47–11.13). Forest plots can be seen in Appendix 2, available online at http://links.lww.com/AOG/D782.

The only antenatal imaging finding that was significantly associated with persistent PH was intrathoracic liver (OR 1.96, 95% CI, 1.14–3.37, I^2 0%; Table 3). In subgroup analysis of only left-sided CDH, this association was no longer observed (OR 1.41, 95% CI, 0.68–2.95, I^2 0%). Mean O-E lung/head ratio, mean lung/head ratio, and gestational age were not significantly associated with persistent PH. Forest plots can be seen in Appendix 3, available online at http://links.lww.com/AOG/D782.

Antenatal imaging findings that were significantly associated with need for ECMO included O-E total fetal lung volume (MD −10.08, 95% CI, −13.54

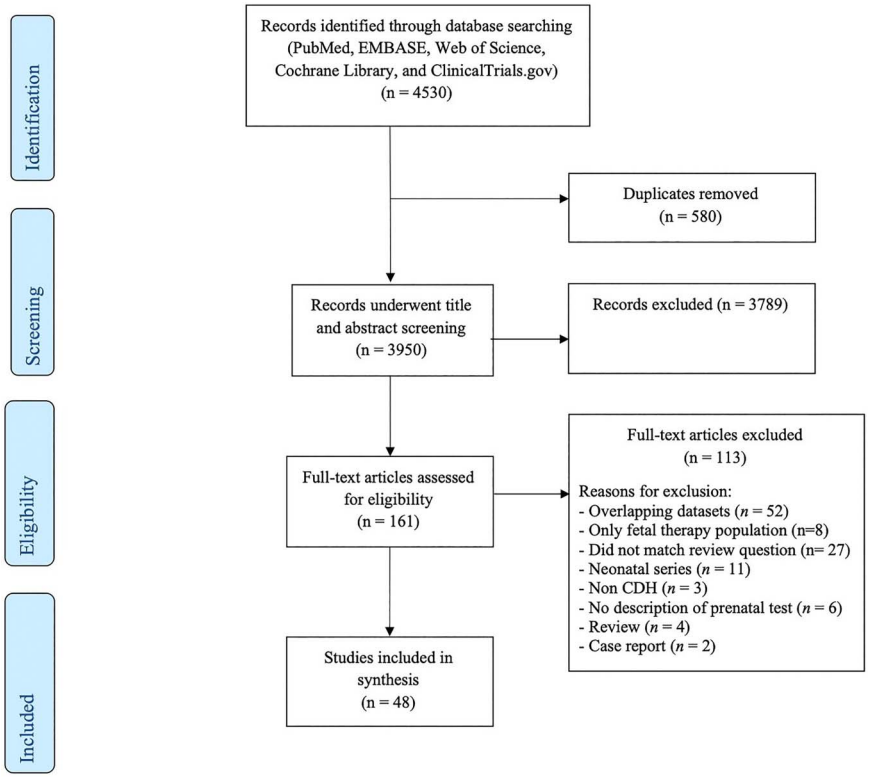

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of search and selection process. CDH, congenital diaphragmatic hernia.

Tofte. Prenatal Predictors of Outcomes in CDH. O&G Open 2024.

Table 1. Characteristics of the 48 Included Studies

First Author, Year	Study Period	Country	Institution	Study Design	Inclusion Criteria	Exclusion Criteria	CDH Type
Bonfils, 2006[40]	2000–2004	France	Grenoble Teaching Hospital	Prospective cohort	Prenatally diagnosed isolated CDH	TOP, no FLV measurement	Left and right
Arkovitz, 2007[41]	2002–2005	United States	Columbia	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Fetal anomalies including CHD	Left
Barnewolt, 2007[42]	2005–2005	United States	Children's Hospital Boston	Prospective cohort	Prenatally diagnosed isolated CDH	Fetal anomalies, CHD, genetic abnormalities, multiple gestation	Left and right
Büsing, 2008[43]	2000–2004	France	Grenoble Teaching Hospital	Retrospective cohort	Prenatally diagnosed isolated CDH	TOP, no FLV measurement	Left and right
Cannie, 2008[44]	2004–2008	Belgium	University Hospitals Leuven	Retrospective cohort	Prenatally diagnosed isolated CDH	Fetal anomalies, genetic abnormalities	Left and right
Datin-Dorriere, 2008[45]	2000–2005	France	Fetal Medicine Center, Necker Hospital	Retrospective cohort	Prenatally diagnosed isolated CDH	Fetal anomalies, genetic abnormalities, TOP	Left and right
Tsukimori, 2008[46]	2000–2005	Japan	Kyushu University Hospital	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Fetal anomalies, genetic abnormalities, maternal comorbidities	Left
Alfaraj, 2011[47]	2011	Canada	University of Toronto, Ontario	Retrospective cohort	Prenatally diagnosed isolated CDH	Fetal anomalies, bilateral CDH, less than 30 wk GA, TOP	Left and right
Aspelund, 2011[48]	2002–2009	United States	Morgan Stanley Children's Hospital	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Fetal anomalies, CHD, genetic abnormalities, missing data, transferred patients, no prenatal diagnosis	Left
Schaible, 2011[49]	2002–2008	Germany	University Medical Center Mannheim	Retrospective cohort	Prenatally diagnosed isolated CDH	Bilateral CDH, fetal anomalies, genetic abnormalities, FETO	Left and right
Ruano, 2012[50]	2004–2010	Brazil	University of São Paulo	Prospective cohort	Prenatally diagnosed isolated CDH	Fetal anomalies, genetic abnormalities, FETO	Left and right
O'Mahoney, 2012[51]	1996–2008	Australia	Royal Women's Hospital	Retrospective cohort	Prenatally diagnosed isolated CDH	Postnatal diagnosis, lethal fetal anomalies, genetic abnormalities	Left and right
Cannie, 2013[9]	2008–2012	Belgium	University Hospital Brugman	Retrospective cohort	Prenatally diagnosed isolated CDH	TOP, IUFD, MRI not available	Left and right
Garcia, 2013[52]	2001–2011	United States	Morgan Stanley Children's Hospital of NewYork-Presbyterian	Retrospective cohort	Prenatally diagnosed isolated CDH	Transferred patients, patients with insufficient LHR data	Left and right
Kehl, 2013[53]	2008–2011	Germany	Mannheim University Medical Center	Prospective cohort	Prenatally diagnosed isolated CDH	Not documented	Left and right
Bebbington, 2014[16]	2002–2010	United States	Center for Fetal Diagnosis and Treatment, Children's Hospital of Pennsylvania	Retrospective cohort	Prenatally diagnosed isolated CDH	Fetal anomalies, TOP, incomplete MRI, IUFD, twin gestation, incorrect referral, FETO	Left
Coleman, 2014[54]	2005–2013	United States	Cincinnati Fetal Center	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Fetal anomalies, genetic abnormalities, TOP, IUFD, preterm delivery before 32 wk	Left
DeKoninck, 2014[55]	2002–2012	Spain, Belgium	University Hospitals Leuven and Barcelona	Retrospective cohort	Right-sided prenatally diagnosed isolated CDH	Fetal anomalies, genetic abnormalities	Right
Kehl, 2014[56]	2008–2012	Germany	Mannheim University Medical Center	Prospective cohort	Prenatally diagnosed isolated CDH	Prior FETO	Left
Weidner, 2014[57]	2001–2011	Germany	University Medical Center Mannheim	Retrospective cohort	Prenatally diagnosed isolated CDH	Fetal anomalies, genetic abnormalities, FETO, preterm birth before 34 wk	Left and right
Coughlin, 2015[58]	2005–2013	United States	C.S. Mott Children's and VonVoightlander Women's Hospital	Retrospective cohort	Prenatally diagnosed isolated CDH	Significant fetal anomalies, CHD, genetic abnormalities	Left and right

(*continued*)

Table 1. Characteristics of the 48 Included Studies (*continued*)

First Author, Year	Study Period	Country	Institution	Study Design	Inclusion Criteria	Exclusion Criteria	CDH Type
Lusk, 2015[59]	2002–2012	United States	University of California San Francisco	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Fetal anomalies, genetic abnormalities	Left
Stranák, 2015[60]	2003–2015	Czech Republic	Charles University	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Right or bilateral CDH, lethal fetal anomalies	Left
Barrière, 2017[61]	2011	France	France National Registry	Prospective cohort	Prenatally diagnosed isolated CDH	Fetal anomalies	Left and right
Madenci, 2017[62]	2004–2015	United States	Brigham and Women's Hospital	Retrospective cohort	Prenatally diagnosed isolated CDH	Severe chromosomal abnormalities, no echo between day of life 3 and 30, postnatal diagnosis	Left and right
Snoek, 2017[13]	2008–2014	The Netherlands	Erasmus University Medical Centre	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Right-sided CDH, TOP, premature birth (before 30 wk), FETO, fetal anomalies, genetic abnormalities	Left
Tsuda, 2017[63]	2008–2016	Japan	Nagoya University Graduate School of Medicine	Prospective cohort	Prenatally diagnosed isolated CDH	Underwent follow-up for less than 1 y	Left and right
Senat, 2018[64]	2008–2013	France	Center for Rare Disease	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Right CDH, FETO, TOP, IUFD	Left
Victoria, 2018[14]	2002–2014	United States	Children's Hospital of Philadelphia	Retrospective cohort	Right-sided prenatally diagnosed isolated CDH	Technically limited imaging, not at study institution, incorrect diagnosis, other lung lesions	Right
Weis, 2018[65]	2001–2015	Germany	University Medical Center Mannheim	Retrospective cohort	Prenatally diagnosed isolated CDH	Additional severe fetal anomalies, genetic abnormalities	Left and right
Cruz-Martinez, 2019[66]	2012–2018	Mexico	Fetal Medicine and Surgery Center	Prospective cohort	Left-sided prenatally diagnosed isolated CDH	Bilateral CDH, fetal anomalies, genetic abnormalities, FETO, missing or absent data	Left
Kim, 2019[67]	2010–2019	United States	University of Michigan	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Right or bilateral CDH, fetal anomalies, genetic abnormalities, FETO, multiple gestation	Left
Romiti, 2020[68]	2013–2016	Italy	Bambino Gesù Children's Hospital	Prospective cohort	Left-sided prenatally diagnosed isolated CDH	Right or bilateral CDH, TOP	Left
Savelli, 2020[12]	2013–2018	Italy	Bambino Gesù Children's Hospital and Research Institute	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Right or bilateral CDH, TOP, missing data, multiple gestation, premature delivery before 30 wk	Left
Style, 2020[69]	2004–2017	United States	Baylor College of Medicine	Retrospective cohort	Prenatally diagnosed isolated CDH	FETO	Left and right
Amodeo, 2021[70]	2012–2018	Italy	Fondazione IRCCS	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Bilateral or right-sided CDH	Left
Basurto, 2021[71]	2008–2020	Spain	BCNatal and Lewen, University of Barcelona	Retrospective cohort	Prenatally diagnosed isolated CDH	Fetal anomalies, genetic abnormalities	Left
Cruz-Martinez, 2021[19]	2012–2021	Mexico	Fetal Medicine and Surgery Center	Retrospective cohort	Right-sided prenatally diagnosed isolated CDH	Bilateral or left CDH, fetal anomalies, genetic abnormalities, missing data, FETO	Right
Jeong, 2021[72]	2006–2020	Korea	Asan Medical Center	Retrospective cohort	Right-sided prenatally diagnosed isolated CDH	Fetal anomalies, genetic abnormalities	Right
Khan, 2021[22]	2000–2018	United States	UT Southwestern	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Right or bilateral CDH, fetal anomalies, genetic abnormalities	Left

(*continued*)

Table 1. Characteristics of the 48 Included Studies (*continued*)

First Author, Year	Study Period	Country	Institution	Study Design	Inclusion Criteria	Exclusion Criteria	CDH Type
Russo, 2021[73]	2008–2018	Spain, Belgium, United Kingdom, France	BCNatal, Hopitaux Paris, King's College Hospital, University Hospitals Leuven	Retrospective cohort	Right-sided prenatally diagnosed isolated CDH	Fetal anomalies, genetic abnormalities	Right
Wang, 2021[74]	2008–2018	China	Xinhua Hospital, Shanghai Jiao Tong University School of Medicine	Retrospective cohort	Prenatally diagnosed isolated CDH	Cases due to Morgagni hernia, hiatal hernia, diaphragm eventration, TOP, IUFD	Left and right
Weller, 2021[15]	2007–2018	The Netherlands	Erasmus University Medical Center Rotterdam	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Right-sided or bilateral CDH, no postnatal confirmation of CDH	Left
Basurto, 2022[17]	2008–2019	Belgium	My FetUZ Fetal Research Center	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Fetal anomalies, genetic abnormalities, diaphragmatic eventration	Left
Ding, 2022[18]	2016–2021	China	Guangzhou Medical University	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Right or bilateral CDH, TOP, incomplete medical records	Left
Niemiec, 2022[23]	2011–2020	United States	Children's Hospital Colorado	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Fetal anomalies, genetic abnormalities, FETO	Left
Wang, 2022[75]	2012–2020	China	Shanghai Jiao Tong University School of Medicine	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Other severe congenital abnormalities, unclear outcome on discharge	Left
Yoneda, 2022[76]	2011–2016	Japan	Center for Child Health and Development	Retrospective cohort	Left-sided prenatally diagnosed isolated CDH	Fetal anomalies, genetic abnormalities,	Left

First Author, Year	FETO	Population	Survival	ECMO	PH	Investigated Outcome(s) and Variables	NOS Total Score
Bonfils, 2006[40]	No	22	10/22 (45.5)	NA	NA	Survival	6
Arkovitz, 2007[41]	No	28	24/28 (85.7)	4/28 (14.2)	NA	Survival, ECMO	6
Barnewolt, 2007[42]	No	14	11/14 (78.6)	7/14 (50)	NA	Survival, ECMO	7
Büsing, 2008[43]	No	85	79/85 (83)	33/85 (35)	NA	Survival	9
Cannie, 2008[44]	Mixed	53	34/53 (64.2)	NA	NA	Survival	8
Datin-Dorriere, 2008[45]	No	79	50/79 (63)	NA	NA	Survival	9
Tsukimori, 2008[46]	No	25	16/25 (64)	10/25 (40)	NA	Survival, ECMO	7
Alfaraj, 2011[47]	No	72	47/72 (65.3)	1/72 (1.3)	NA	Survival	8
Aspelund, 2011[48]	No	70	59/70 (84.3)	14/70 (20)	NA	Survival, ECMO	9
Schaible, 2011[49]	No	90	77/90 (85.5)	30/89 (33.7)	NA	Survival, ECMO	9
Ruano, 2012[50]	No	108	70/108 (64.8)	NA	68/108 (63.0)	Survival, PH	9
O'Mahoney, 2012[51]	No	85	45/85 (52.3)	NA	NA	Survival	7
Cannie, 2013[9]	Mixed	30	24/30 (80)	NA	NA	Survival	9
Garcia, 2013[52]	No	106	76/106 (71.7)	28/106 (26.4)	40/106 (38)	Survival, PH	9
Kehl, 2013[53]	No	118	92/118 (77.9)	36/102 (35.3)	NA	Survival	9
Bebbington, 2014[16]	No	85	55/85 (64.7)	NA	NA	Survival	9
Coleman, 2014[54]	Mixed	47	27/47 (57.4)	23/47 (48.9)	NA	Survival	9
DeKoninck, 2014[55]	Mixed	19	10/19 (52.6)	NA	NA	Survival	8
Kehl, 2014[56]	No	118	92/118 (77.9)	36/102 (35.3)	NA	Survival	9
Weidner, 2014[57]	No	96	78/96 (81.3)	35/96 (36.5)	NA	Survival, ECMO	9
Coughlin, 2015[58]	No	29	11/29 (37.9)	26/29 (92)	15/29 (51.7)	PH	8
Lusk, 2015[59]	Mixed	118	95/118 (80.5)	15/118 (12.7)	32/118 (27.1)	Survival, PH	9
Stranák, 2015[60]	No	59	43/59 (72.9)	18/59 (3)	NA	Survival	9
Barrière, 2017[61]	Yes	158	70/112 (62.5)	7/112 (6.3)	63/112 (56)	Survival	9
Madenci, 2017[62]	No	62	42/62 (67.7)	25/62 (78)	32/62 (52)	ECMO, PH	7
Snoek, 2017[13]	No	122	95/122 (77.8)	38/59 (64.4)	NA	Survival	9
Tsuda, 2017[63]	No	48	41/48 (85.4)	7/48 (14.6)	NA	Survival	9
Senat, 2018[64]	No	223	221/305 (72.5)	NA	NA	Survival	9
Victoria, 2018[14]	No	24	15/24 (62.5)	12/24 (50)	NA	Survival	8
Weis, 2018[65]	No	122 (61 matched pairs)	106/122 (86.9)	35/122 (28.7)	NA	Survival, ECMO	8

(*continued*)

Table 1. Characteristics of the 48 Included Studies (*continued*)

First Author, Year	FETO	Population	Survival	ECMO	PH	Investigated Outcome(s) and Variables	NOS Total Score
Cruz-Martinez, 2019[66]	No	144	46/144 (31.9)	NA (not available at center)	NA	Survival	9
Kim, 2019[67]	No	42	24/42 (57.1)	NA	NA	Survival	9
Romiti, 2020[68]	Mixed	24	16/24 (66.7)	NA	NA	Survival	8
Savelli, 2020[12]	No	34	24/34 (70.6)	NA	NA	Survival	9
Style, 2020[69]	No	57	45/57 (78.9)	23/57 (40.3)	38/57 (68)	Survival, ECMO, PH	9
Amodeo, 2021[70]	No	31	25/31 (80.6)	NA	NA	Survival	8
Basurto, 2021[71]	No	70	54/70 (77.1)	19/70 (27.1)	39/70 (55.7)	Survival, ECMO, PH	9
Cruz-Martinez, 2021[19]	No	58	16/58 (27.56)	NA	NA	Survival	8
Jeong, 2021[72]	No	39	26/39 (66.7)	5/39 (12.8)	NA	Survival	9
Khan, 2021[22]	No	40	21/40 (52.5)	11/40 (27.5)	NA	Survival	8
Russo, 2021[73]	Mixed	85	40/85 (47)	1/37 (2.7)	NA	Survival	8
Wang, 2021[74]	No	158	108/158 (68.4)	NA	NA	Survival	9
Weller, 2021[15]	Mixed	101	82/101 (81.2)	23/101 (22.8)	45/101 (44.6)	PH	9
Basurto, 2022[17]	Mixed	197	141/197 (71.6)	16/197 (8.1)	137/197 (69.5)	Survival, ECMO	9
Ding, 2022[18]	No	87	65/87 (74.7)	6/12 (50)	22/34 (64.7)	Survival	9
Niemiec, 2022[23]	No	63	53/63 (84)	21/63 (33.3)	NA	Survival, ECMO	8
Wang, 2022[75]	No	94	74/94 (78.7)	NA	NA	Survival	9
Yoneda, 2022[76]	Mixed	302	258/302 (85.4)	NA	NA	Survival	8

CHD, congenital heart disease; FETO, fetoscopic endotracheal balloon occlusion; ECMO, extracorporeal membrane oxygenation; PH, pulmonary hypertension; NOS, Newcastle-Ottawa Scale; TOP, termination of pregnancy; FLV, fetal lung volume; NA, not available; GA, gestational age; IUFD, intrauterine fetal death; MRI, magnetic resonance imaging; LHR, lung/head ratio; echo, echocardiogram.
Data are n/N (%) unless otherwise specified.

to −6.62), I^2 0%) and O-E lung/head ratio (MD −9.88, 95% CI, 14.44 to −5.33, I^2 30%; Table 4). Although liver up was significantly associated with need for ECMO (OR 2.70, 95% CI, 1.60–4.57, I^2 0% this was not identified in subgroup analysis limited to left-sided CDH only. Forest plots can be seen in Appendix 4, available online at http://links.lww.com/AOG/D782.

The Newcastle-Ottawa Scale was used to assess the risk of bias in included studies. Two studies had scores of 6, and the rest had scores of 7 or higher (Appendix 5, available online at http://links.lww.com/AOG/D782). No change in results was identified with the leave-one-out analysis. No publication bias was identified by observing the funnel plots nor by Begg's correlation test.

DISCUSSION

In this systematic review and meta-analysis in the population of pregnancies complicated by fetal isolated CDH, lung measurements, liver position, and stomach position were predictive of survival to hospital discharge. Liver position was associated with persistent PH and need for ECMO, and lung measurements were also associated with the postnatal need for ECMO.

Accurate prediction of neonatal severity of CDH is important to both counsel patients on neonatal outcomes at the time of diagnosis and adequately plan for resuscitation and intensive care after delivery.[4,7,31,77,78] Determining evidence-based antenatal predictors of outcomes for CDH has historically posed a challenge.[9,13,22,79,80] This is likely due to the low incidence of CDH, wide variation in institutional protocols and antenatal and postnatal management protocols, and a dearth of prospective and randomized studies that investigate survival and morbidity outcomes. Need for ECMO and the presence of persistent PH in the newborn have been associated with negative long-term outcomes.[3,6,81] The odds of survival has been historically estimated with several measurements of fetal lung volume, but these have yielded inconsistent results.[9,15,44,45,64,72,76,82,83]

There are two prior systematic reviews and meta-analyses that have worked to identify valuable predictors for neonatal outcomes in CDH.[21,84] Russo et al found fetal lung size and liver herniation predicted need for ECMO but did not identify predictors for PH. A limitation was the single-institution origin of many of the predictors available for meta-analysis.[21] Additionally, the study included participants who had undergone fetoscopic endotracheal balloon occlusion, which may artificially improve the pooled predictive value of preintervention fetal ultrasound and MRI measurements given the therapeutic benefit of fetoscopic endotracheal balloon occlusion, whereas we excluded all fetoscopic endotracheal balloon occlusion–only studies.[21] In Oluyomi-Obi et al[84],

Table 2. Proposed Predictors of Survival Until Hospital Discharge in Fetuses With Congenital Diaphragmatic Hernia

Variable	CDH Type	No. of Studies	Survival	Nonsurvival	OR or MD (95% CI)	I^2 (%)	*P*
Mean TFLV	All cases	8[12,19,40,42,43,45,57,63]	358	117	13.42 (11.22–15.62)	50	<.001
	Left	2[12,19]	89	32	13.53 (9.58–17.48)	0	<.001
O-E TFLV less than 30%	All cases	12[9,14,16,19,23,40,45,47,49,61,67,69]	82/502	146/267	0.09 (0.05–0.17)	46	<.001
	Left	4[16,19,23,67]	16/197	55/80	0.03 (0.01–0.07)	0	<.001
Mean O-E TFLV	All cases	13[9,14,19,22,23,47,49,53–55,61,69,70]	571	219	14.73 (11.62–17.84)	49	<.001
	Left	4[22,23,54,70]	126	55	11.50 (7.88–15.11)	0	<.001
Mean LiTR	All cases	3[9,55,69]	79	27	−9.59 (−15.73 to −3.46)	0	.002
Mean O-E LHR	All cases	20[12,14,17,19,23,47,49,51,55,56,60,64,66,69–72,74,76]	1,369	560	14.03 (12.69–15.36)	99	<.001
	Left	6[17,23,68,70,71,76]	547	140	14.21 (12.09–16.32)	0	<.001
O-E LHR less than 25%	All cases	12[13,14,16,18,47,49,55,61,66,67,72,73]	13/539	129/439	0.07 (0.04–0.13)	0	<.001
	Left	4[18,66,67,72]	4/160	67/143	0.04 (0.01–0.11)	0	<.001
Mean LHR	All cases	7[18,45,51,56,60,63,69]	381	146	0.57 (0.44–0.69)	0	<.001
	Left	2[18,60]	108	28	0.74 (−0.46 to 1.94)	62	.22
LHR less than 1	All cases	5[41,46,52,59,61]	49/192	120/179	0.29 (0.09–0.76)	68	.01
	Left	2[44,50]	11/17	19/25	0.55 (0.14–2.20)	0	.40
Mean % herniated liver	All cases	2[44,50]	72	89	−2.12 (−13.95 to 9.70)	0	.72
Mean MSA	Left	5[12,18,68,70,74]	204	57	−6.17 (−7.70 to −4.64)	0	<.001
Stomach in midchest	All cases	3[72,75,76]	212/371	61/103	0.14 (0.06–0.36)	0	<.001
	Left	2[75,76]	211/332	60/64	0.12 (0.04–0.33)	0	<.001
Mean PPLV	All cases	3[23,42,54]	91	33	7.86 (3.71–12.02)	67	<.001
	Left	2[23,54]	80	30	6.30 (1.47–11.13)	73	.01
Liver up	All cases	20[17,40–42,46–48,50,59–61,63,65,66,69,72,74,75]	463/1,242	470/634	0.23 (0.15–0.35)	61	<.001
	Left	8[17,41,46,48,59,60,66,75]	214/492	187/237	0.21 (0.14–0.32)	0	<.001
GA at delivery	All cases	23[9,17,19,23,40,44,47,50,52,54,55,59–61,63,64,66,69,70,72,75,76]	1,516	696	0.66 (0.19–1.12)	87	.006

CHD, congenital heart disease; OR, odds ratio; MD, mean difference; TFLV, total fetal lung volume; O-E, observed-to-expected; LiTR, liver/thoracic volume ratio; LHR, lung/head ratio; MSA, mediastinal shift angle; PPLV, percentage of predicted lung volume; GA, gestational age.
Data are n or n/N unless otherwise specified.

meta-analysis found that O-E lung/head ratio by ultrasonography and O-E total fetal lung volume by MRI were superior in their ability to predict survival. Our study expanded on this prior work by also completing subanalyses by laterality of herniation, as well as considering a wider range of prenatal imaging predictors.

It is important to mention the variation in ECMO practices across countries and institutions within the United States, which may contribute to varying results in individual studies and this meta-analysis. In the recently completed Tracheal Occlusion to Accelerate Lung Growth trial (TOTAL) that included severe

Table 3. Proposed Predictors or Persistent Pulmonary Hypertension in Fetuses With Congenital Diaphragmatic Hernia

Variable	CDH Type	No. of Studies	PH	No PH	OR or MD (95% CI)	I^2 (%)	*P*
Mean O-E LHR	All cases	2[69,71]	89	28	−5.48 (−10.97 to 0.00)	0	.05
Mean LHR	All cases	2[50,58]	49	77	−0.48 (−1.35 to 0.40)	89	.28
Liver up	All cases	3[15,50(p20),71]	72/136	39/118	1.96 (1.14–3.37)	0	.01
	Left	2[15,17]	24/68	21/78	1.41 (0.68–2.95)	0	.36
GA at delivery	All cases	7[15,50,52,58,59,62,71]	381	202	0.10 (−0.14 to 0.35)	0	.41

CHD, congenital heart disease; PH, pulmonary hypertension; OR, odds ratio; MD, mean difference; O-E, observed-to-expected; LHR, lung/head ratio; GA, gestational age.
Data are n or n/N unless otherwise specified.

Table 4. Proposed Predictors for Need for Extracorporeal Membrane Oxygenation in Fetuses With Congenital Diaphragmatic Hernia

Variable	CDH Type	No. of Studies	ECMO	No ECMO	OR or MD (95% CI)	I^2	*P*
Mean O-E TFLV	All cases	4[23,49,57,69]	206	99	−10.08 (−13.54 to −6.62)	0	<.001
Mean O-E LHR	All cases	4[17,23,49,69]	182	97	−9.88 (−14.44 to −5.33)	30	<.001
	Left	2[23,71]	107	26	−12.75 (−22.53 to −2.97)	56	.01
LHR less than 1	Left	3[41,46,48]	14/37	24/45	0.49 (0.20–1.19)	54	.12
Mean PPLV	All cases	3[23,42,62]	57	82	−9.81 (−13.56 to −6.06)	34	<.001
Liver up	All cases	6[17,41,46,48,65,69]	74/102	137/291	2.70 (1.60–4.57)	0	<.001
	Left	4[17,41,46,48]	26/38	73/155	1.97 (0.83–4.66)	0	.12
Mean GA at delivery	All cases	4[17,23,49,69]	182	97	0.14 (−0.27 to 0.54)	0	.50

CHD, congenital heart disease; ECMO, extracorporeal membrane oxygenation; OR, odds ratio; MD, mean difference; O-E, observed-to-expected; TFLV, total fetal lung volume; LHR, lung/head ratio; PPLV, percentage of predicted lung volume; GA, gestational age.
Data are n or n/N unless otherwise specified.

cases of CDH in predominantly European centers, only 5% of patients undergoing fetoscopic endotracheal balloon occlusion and 29% of those in the control group were placed on ECMO.[85] This is in comparison with the recent report from the North American Fetal Therapy Network (NAFTNet) centers that compared outcomes of fetoscopic endotracheal balloon occlusion with those of expectant management from 2008 to 2020, in which ECMO rates in fetoscopic endotracheal balloon occlusion and expectantly managed cases of severe left-sided CDH were 36% and 57%, respectively.[86] The current ECMO practice patterns in Canada have lower rates of use compared with the United States and Europe.[87] Extracorporeal membrane oxygenation practice patterns also have changed over time, particularly in the past decade. All studies but one[18] included participants' data from before 2013 (ie, more than a decade ago), for which authors could not generate subgroup analysis for studies that had participants only from recent years.

The strengths of this study include a comprehensive search strategy along with a quality assessment performed according to current guidelines for high-quality systematic review.[26,38] We limited our study population and analysis to prenatal expectant management cases, excluding fetal-intervention-only populations. We were able to complete subgroup analysis for left-sided CDH cases.

Limitations of our study include the inclusion of mostly retrospective studies, study heterogeneity, methodologic concerns related to blinding in fetal imaging and interpretation, and selection bias in lower-quality studies. Additionally, there are notable limitations in measurement methodology, reproducibility, and institution-specific protocols for ultrasound and MRI measurements of CDH lesions and fetal lung volumes, which have changed substantially over the timeframe included in our review. We were unable to include every investigated prenatal imaging finding in the literature unless at least two studies reported outcomes in association with it. There was variation in the baseline characteristics and methodologic quality of the studies included; this variation may have altered the described rates of survival, need for ECMO, and especially the development of subsequent PH. The evolving care patterns for indications for ECMO and variation by center and country could not be directly addressed. The timing of postnatal CDH surgical repair and neonatal intensive care unit protocols for management also varied between and within centers. These are all factors that influence the ability to predict survival or the need for a specific intervention.

In conclusion, this systematic review and meta-analysis found that lung volume measurements can predict survival and need for ECMO among cases of isolated fetal CDH. There were limited data on need for ECMO and the development of persistent PH, limiting this portion of analysis. Future research may focus on standardized antenatal assessment measures of CDH, as well as standardization of postnatal criteria for initiation of ECMO and determination of persistent PH.

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