Lung size and liver herniation predict the need for extra corporeal membrane oxygenation but not pulmonary hypertension in isolated congenital diaphragmatic hernia: a systematic review and meta-analysis

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ABSTRACT

Objectives: To identify antenatal predictors of persistent pulmonary hypertension (PPH) and need for extracorporeal membrane oxygenation (ECMO) in fetuses with congenital diaphragmatic hernia (CDH).

Material and Methods: We performed a systematic literature review of antenatal diagnostic tests in fetuses with isolated CDH. The target conditions were PPH within 28 days of life and the need for ECMO. Quality of studies was assessed with the QUADAS-2 tool. Meta-analysis was performed when at least three studies reported on the same test. Sensitivity analysis was performed according to prenatal management of CDH (tracheal occlusion versus expectant management).

Results: Thirty-eight studies met the inclusion criteria. Fifteen reported on the incidence of PPH only, 19 on the need of ECMO only, and 4 on both outcomes. The general quality of the studies was moderate; most studies were retrospective (61%) and single-centre series (92%). One study included only fetuses undergoing tracheal occlusion, 22 only fetuses expectantly managed in utero, and 15 included both populations. We could not identify antenatal predictors of PPH. The need for ECMO was predicted by parameters indicative of lung size: lung-to-head ratio (LHR, relative risk for LHR<1: 1.65; 95% confidence interval 1.27 to 2.14) and observed-to-expected LHR (standardized mean difference -0.70; 95% confidence interval -0.98 to -0.42) measured by ultrasound and observed-to-expected total lung volume (standardized mean difference -1.00; 95% confidence interval -1.52 to -0.48) by magnetic resonance. Liver herniation was also associated with an increased risk of ECMO (relative risk 3.04; 95% confidence interval 2.23 to 4.14). These results were confirmed in a sensitivity analysis on studies including only expectantly managed cases. The data on vascular assessment for the prediction of PPH could not be pooled, as most of the parameters were evaluated in a single series or by a single investigator.

Conclusions: In fetuses with CDH, lung size and liver herniation predict the need for ECMO. A predictor for PPH is still lacking. Further studies aiming at diagnosing impaired vascular development in utero should therefore be developed.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a life-threatening condition mainly because of neonatal respiratory failure due to lung hypoplasia and persistent pulmonary hypertension (PPH)[1-4]. PPH is caused by an abnormal transition of fetal to neonatal circulation[5]. The persist**ently** elevated pulmonary vascular resistance causes right-to-left shunting of de-oxygenated blood to the systemic circulation, resulting in arterial hypoxia[6, 7] and, ultimately, right ventricular failure with systemic hypotension and obstructive shock[8, 9].

Unlike for other causes of neonatal respiratory failure, infants with CDH often present with refractory PPH resistant to inhaled nitric oxide (iNO)[10, 11]. When maximal medical therapy has failed, one may resort to extracorporeal membrane oxygenation (ECMO)[12] though there is a lack of evidence for its efficacy[13]. The main concerns with ECMO are the occurrence of hemorrhagic and ischemic cerebral lesions resulting in later neurological and neurodevelopmental dysfunction[14, 15]. Several studies also reported an effect of ECMO on non-neurological short term problems with feeding, growth and lung function[16, 17].

Given the severity and potential morbidity of PPH as well as the potential side-effects of ECMO, different research groups have searched for antenatal predictors to personalize the prognosis for women carrying a fetus with severe CDH. Ultrasound (US) and magnetic resonance imaging (MR) have both been used to assess the degree of lung hypoplasia and lung vascularization. Best validated are US measurement of the lung size, which permits to express parenchymal lung development as a function of what is expected[18, 19]. Conversely, much less attention has been paid to assessment of lung vascularization and prediction of postnatal cardiovascular function[20, 21].

The aim of the present study was to identify predictors of PPH and ECMO by systematic

review of the literature.

METHODS

This study was done according to the guidelines of systematic reviews Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[22] and of the Synthesizing Evidence from Diagnostic Accuracy Tests (SEDATE)[23]. The protocol of the review was registered in the PROSPERO registry (CRD 42015027272).

2.1. Search strategy

A computerized literature search for antenatal diagnostic studies predicting occurrence of PPH or need for ECMO was performed in Medline via PubMed, in EMBASE, Web of Science and The Cochrane Central Register of Controlled Trials (CENTRAL) to identify studies published from inception to June 2015. The electronic search strategy included both Medical Subject Headings (MeSH) and keywords (free text words), and is available in the Online Supplement. Endnote X7 (Thomson Reuters, Carlsbad, CA, US) was used to eliminate duplicate reports. Reference lists and topic-related reviews were checked manually to identify further relevant papers.

2.2. Selection of studies

The studies were selected in two phases. First, titles and abstracts of the listed articles were screened by one reviewer (FMR) using a high sensitivity-low specificity assessment of relevance. Then, full texts of the selected articles were independently assessed for their eligibility by two investigators (FMR and MPE), according to the inclusion and exclusion criteria described below. Disagreements between the reviewers were resolved by discussion or by a third reviewer (JD). In case of overlapping studies, only the largest and most complete data set was included.

2.2.1 Inclusion criteria

Both observational and interventional studies were retrieved for further analysis. No language

restriction was used. Studies and/or subgroups were only included if they adequately reported on study population, definition of prenatal tests and on postnatal outcome (PPH and ECMO). In case of missing information, the corresponding authors were contacted and asked to provide additional data using a standardized questionnaire.

A 'PIRT' (Patient-Index test-Reference test-Target condition), analogous to the 'PICO' (Patient-Intervention-Comparison-Outcome) for systematic reviews of interventional studies, was used to define the specific questions to be assessed[24, 25].

We only included studies on fetuses with isolated CDH (i.e. without associated anatomical malformations or genetic anomalies), regardless of the side of the defect and the degree of lung hypoplasia. Both cases that underwent fetal therapy and cases managed expectantly during pregnancy were included. Studies on all relevant tests were eligible for inclusion, if an accurate description of the technique was provided.

2.2.2 Exclusion criteria

We excluded studies which were case reports, reviews, articles with no full text available and studies reporting only outcomes beyond 1 month of life. Studies reporting on EXIT-to-ECMO were excluded. Patients who underwent termination of pregnancy, fetuses with associated major malformations or genetic problems, and cases lacking information on postnatal outcome were also excluded.

2.2.3 Target condition

Target conditions were: (a) PPH within 28 days of life; PPH was defined by the presence of tricuspid regurgitation, septal bowing, and continuous or dominant right-to-left shunt through a patent ductus arteriosus on cardiac ultrasound[26], or by a preductal–postductal saturation difference of 10% or higher[27]. Since PPH is an indication for initiating iNO or other vasodilators, studies reporting these type of neonatal outcomes were also included. (b) Need for ECMO, when applied according to consensus criteria[28, 29].

2.3. Quality appraisal

Two reviewers (FMR, MPE) independently assessed the methodological quality of each

included study with the QUality Assessment of Diagnostic Accuracy Studies 2 (QUADAS 2)[30]. Four domains, covering participant selection, index test, reference standard, and the flow of patients through the study, were rated for risk of bias (low, high, or unclear) and applicability concerns. Three additional items[31] were considered of interest to this review and were also scored. These additional items refer to the definition of the positivity threshold of the index test, treatment given between index test and reference standard, and observer variation. Discrepancies between the reviewers were resolved through consensus or through a third reviewer (JD). Agreement between the two reviewers was analyzed with the Cohen's Kappa test.

2.4. Data extraction and analysis

A pre-designed form was used for data extraction, which was done by two authors (FMR and MPE) independently. The selected studies were coded for participant characteristics, test characteristics and methodological aspects. Participant characteristics included study site, defect side, associated anomalies, degree of lung hypoplasia, prenatal and postnatal management. Test characteristics included the type of test, test methodology, cut-off point (if applicable), experience and number of the operators, gestational age at the test, type of reference standard, time and treatment between index test and reference standard. Methodological variables included study design (pro/retrospective) and duration, patient enrolment (consecutive or non-consecutive), sample size, inclusion/exclusion criteria, and type of statistical analysis.

The results of each study were reported individually. For dichotomous variables we extracted the diagnostic two-by-two table (true positive, false positive, true negative, and false negative index test results). Continuous variables, instead, were expressed as mean ± standard deviation (SD) or median (interquartile range (IQR)).

Subgroup analysis for PPH or use of vasodilators and need of ECMO was performed to test for differences between the two outcomes and guarantee homogeneity among the groups.

For all variables reported on by at least three studies, we performed a meta-analysis of the

results. Variables were tested for statistical heterogeneity by applying the I2 test. Results were expressed as relative risk (RR) for categorical measures and standard difference of the mean (SMD) for continuous measures. A random-effect model was used. For meta-analyses including at least ten studies, publication bias was analyzed by visual inspection of the funnel plot. MedCalc software (version 15.4) was used to carry out the statistical analyses.

RESULTS

3.1 Search results

The search strategy yielded 3,533 citations. Of these, 3,442 were excluded by review of the title and abstract as they failed to meet the inclusion criteria. The full article was reviewed in 91 cases of which 38 were included in the systematic review. The principal reasons for exclusion after full article examination were overlapping datasets (n = 17), not matching the review question (n = 16), and inclusion of a different study population (i.e. postnatal series, n = 5), next to a number of other reasons (n=15). Of the selected papers, 15 reported on the occurrence of PPH[20, 21, 26, 32-43], 19 on the need for ECMO[44-62], and 4 on both outcomes[63-66] (Figure 1). Seven corresponding authors provided relevant unpublished data[32, 35, 37, 55, 63, 64, 66].

3.2 Characteristics and quality of the included studies

Details on the design, setting, population, index test and definition of the target condition are provided in Supplementary Table S1. Thirty-five studies (92%) were single-center, and 23 (61%) were retrospective. Of the studies reporting on PPH, only 16% (3/19) restricted the analysis to left-sided CDH and 79% (15/19) to cases expectantly managed during pregnancy. Studies on the need for ECMO, instead, included a more homogeneous population: 43% (10/23) included only fetuses with left-sided CDH and 96% (22/23) only fetuses not undergoing intra-uterine therapy. **Only one study reporting on PPH was limited to fetuses undergoing intra-uterine therapy[20].**

The quality assessment of the included studies is summarized in Figure 2 and Supplementary Figure 1. The agreement between the two reviewers in determining the risk of bias was good, with Kappa ranging from 0.797 to 0.901 for the different domains. Overall, the methodological quality was moderate. The domains with the highest risk of bias were domain 2, ‘Index test’, and domain 3, ‘Reference standard’. Gestational age at testing was not specified or broad in 21 studies (55%)[21, 34-39, 44, 45, 47-52, 54, 56-58, 65, 66]. In five papers (13%), the positivity threshold of the index test was not pre-specified[50, 53, 54, 63, 66]. Finally, 15 studies (39%) did not mention the blinding to the reference standard in the interpretation of the index

test[21, 35-37, 40-43, 47, 48, 58, 60, 62, 65, 66].

The proportion of studies with uncertain or high risk of bias in the 'Reference standard' domain was higher in studies reporting on PPH than in those reporting on the need of ECMO (89% vs 48%). The main cause of bias in the first group was the absence of a specified timing at the reference test for diagnosis of PPH. This was provided in the manuscript by a single author[63], and on request by another author[64].

3.3 Proposed predictors for PPH

Table 1 summarizes the antenatal tests for the prediction of PPH. These were mainly related to measurement of lung size, either with US or with MR. In detail, the most commonly proposed tests were the LHR, o/e LHR and o/e total lung volume (o/e TLV), reported in seven[20, 26, 35, 37, 41, 43, 63, 64], five[32, 33, 37, 41, 43] and in four studies[21, 26, 41, 43] respectively. Tests for direct assessment of the pulmonary vasculature, either anatomical or functional, have also been proposed[26, 32-34, 38-40]. However, all of them have been evaluated only in single case series, or in multiple case series from the same author (n=2). Still, a lower o/e contralateral pulmonary artery diameter and a lower contralateral vascularization index consistently predicted an increased risk of PPH[38-40]. Conversely, the side of the hernia consistently did not predict the occurrence of PPH in both studies where it was evaluated (n=2)[40, 43].

The predictive value of liver herniation was assessed in five studies[37, 43, 63, 64, 66], without consistency among the results from different series.

Figure 3 shows the forest plots of the association between all predictors evaluated in at least three series and PPH. Summary data from individual studies included in the meta-analysis are provided in Table S2. PPH was *not* significantly associated either with a LHR <1 (RR 1.44, 95% CI 0.42 to 4.95), or with a lower mean o/e LHR (SMD -0.06, 95% CI -1.18 to 0.07). However, for both tests we observed a high heterogeneity between studies. The results of the four studies on LHR that were not included in the meta-analysis, because reporting either odds ratios[26, 43], or mean LHR values[37, 41], were not homogeneous, with two studies demonstrating an association between low LHR and PPH and two with opposite results. Similarly, two

studies reporting on the predictive value of the o/e LHR were not included, because results were presented as odds ratios[33, 43]. In that case however, both studies did show an association between a lower o/e LHR and PPH. Results from studies on o/e TLV could not be pooled, because of high heterogeneity in the methodology for measuring o/e TLV (two studies with US[21, 41] and two with MR[26, 43]), in the study population and in the reporting of statistical results. The results were not consistent among studies, with three studies supporting the correlation of a lower o/eTLV with the occurrence of PPH[21, 41, 43], and one failing to show a significant association[26].

Finally, Figure 3C shows the forest plot for the association between liver position and PPH. Liver herniation did not significantly predict the occurrence of PPH (RR 1.39, 95% CI 0.821 to 2.35). Again, there was a high heterogeneity among studies (I2 = 96.51%, p=0.0001).

In the attempt to remove the confounding effect of intra-uterine therapy on the occurrence of PPH, we subsequently performed a sensitivity analysis on studies which only included patients managed expectantly in utero. This led to only two studies available for meta-analysis on LHR <1[35, 63] and mean o/e LHR[37, 41] and to three studies evaluating the predictive value of liver herniation[37, 63, 66]. Again the occurrence of PPH did not significantly correlate with a LHR <1 (RR 1.75, 95% CI 0.53 to 5.81), or a low o/e LHR (SMD -0.50, 95% CI -1.18 to 0.07), or with liver herniation (RR 1.57, 95% CI 0.96 to 2.56).

3.4 Proposed predictors for need for ECMO

Antenatal predictive tests for the need of ECMO are displayed in Table 2. Again, the most commonly proposed tests assessed lung size. The LHR was evaluated in eleven series[45, 50, 51, 54-58, 60, 63, 64], the o/eLHR in four[51, 55, 56, 58] and the o/e TLV in five[46, 55, 57, 58, 61] studies. Assessment of organs other than the lungs was also reported. Of these, the most common parameter was presence of liver herniation, which was evaluated in 11 studies[44, 45, 47, 50-52, 56, 57, 61, 64, 66] either with US (10 studies) or with MR (1 study). One study looked at the amount of liver into the chest as a predictor[47].

There was no consistency in any outcome of these studies in terms of predicting need for

ECMO. As for PPH, the side of the hernia was not associated with a difference in the occurrence of PPH in all the three studies where it was evaluated[47, 56, 61].

Meta-analysis was performed of studies evaluating the association of ECMO with LHR < 1 (n=6), lower mean LHR (n=4), mean o/e LHR (n=3), mean o/e TLV (n=3) (Figure 4), being these the only predictors reported in at least three series. A lower lung size significantly predicted the need of ECMO in all cases, with a pooled RR of 1.65 (95% CI 1.27 to 2.14) for LHR <1 and a pooled SMD of -0.73 (95% CI -1.07 to -0.42), -0.70 (95% CI -0.98 to -0.42) and -1.00 (95% CI -1.52 to -0.48) for mean LHR, mean o/e LHR and mean o/e TLV respectively. Summary data from individual studies included in the meta-analysis are provided in Table S2. Low heterogeneity was observed among different studies. One paper reporting the predictive value of LHR and o/e LHR was not included in the meta-analysis because the results were expressed as odds ratio[56]. In that study, the two tests did not predict the need of ECMO. One study was not included in the meta-analysis for o/e TLV because results were expressed as medians, yet its conclusions were consistent with the statistical pooling of the other studies[58].

Similarly, a meta-analysis of ten studies reporting on the presence of liver herniation demonstrated that liver herniation significantly predicted the need of ECMO (RR 3.04, 95% CI 2.23 to 4.14). There was no heterogeneity (I2 = 0%, p=0.596), neither evidence of publication bias (Supplementary Figure 2). One study[56] could not be pooled in the analysis, because of reporting only odds ratios. In that series, liver herniation was not associated with need for ECMO.

The association between ECMO and an LHR <1 (RR 1.67, 95% CI 1.26 to 2.23) or the presence of liver herniation (RR 3.01, 95% CI 2.21 to 4.11) was confirmed even when we removed from the analysis one study including patients who underwent FETO[64].

DISCUSSION

Acquiring evidence on antenatal predictors of outcome in rare congenital anomalies is a major challenge, first because of the low incidence of these conditions, and second because of a lack of standardization for testing and of adequately sized prospective studies. Additionally, there is lack of standardized time points for measurement, inconsistencies in perinatal management protocol, prenatal intervention, and effect of gestational age at delivery and postnatal events on the outcomes studied.

Prenatal prediction studies in CDH have been significantly boosted by the introduction of fetal therapy and when the condition is isolated, lung size and liver position can be used to predict lethal pulmonary hypoplasia to a certain extent[67, 68]. To further improve prediction, we here looked at other determinants of outcome: PPH is commonly associated with poor long term outcome[14, 69]. The need and relevance of assessing the risk for PPH prior to birth is acknowledged by experts[13]. Alongside PPH, severe ventilatory insufficiency may also lead to the use of ECMO[70] , which may in its own be an independent predictor of outcome due to the complications associated with this therapy[14].

Overall, we identified more than fifteen claimed predictors for each of these adverse outcomes. Most are direct or indirect measurements of lung size[21, 26, 32, 33, 35, 37, 40, 41, 43, 45, 46, 48-51, 53-58, 60-66], either using MR or US. Other indicators concern herniation of abdominal organs into the thorax, among which the most commonly evaluated was liver herniation[36, 40, 43-45, 47, 50, 51, 56, 57, 61, 64, 66, 71], either categorized as absent or present or quantified. For the prediction of PPH, attempts to directly assess pulmonary vasculature include measurements of the pulmonary arterial diameters[26, 39, 40], studies of flow in the pulmonary arteries[33, 34, 72] –with or without hyperoxygenation- or more complex three-dimensional power Doppler techniques[38, 40, 41]. These indicators however were only assessed by a single author or reported inconsistent findings[73]. For most of these variables, a normative study on healthy fetuses, enabling a more comprehensive interpretation of the results, is also lacking. Ultimately, the vast majority of the

studies reporting on PPH presented an uncertain or high risk of bias mainly due to an unspecified or broad range of gestational age at execution.

We were only able to perform a meta-analysis of studies reporting on lung size and liver herniation. Surprisingly, the results on the two target conditions were conflicting. We found a three-fold increase in the risk for ECMO when the liver was herniated and a 1.7 fold increase when the LHR was <1.0. However, smaller lung size or liver herniation were not associated with an increased risk of PPH. There are many possible explanations for this. First, the number of studies included in the meta-analyses for PPH was much lower than those for ECMO, thus reducing the statistical power to detect a difference. Second, we observed significant heterogeneity among studies reporting on PPH, perhaps due to a more heterogeneous study population: unlike studies on ECMO, most studies (>80%) concerning PPH included left- and right-sided CDH cases, with some (20%) including both fetuses managed expectantly and by invasive fetal surgery. Finally, a lack of consistency in the timing of post-natal assessment of PPH even further complicated the analysis: only two studies reported the exact timing of echocardiographic evaluation of PPH. Standardization of the time point of assessment for PPH is important as its incidence decreases during the first weeks of life[74]. Later evaluations may exclude neonates with severe PPH who died in the early postnatal periods introducing ascertainment bias. Similarly, some studies report only on PPH refractory to first line therapy (iNO), thus cases resolved after initial therapy were not included hence PPH incidence being underestimated. Finally, resorting to ECMO may be influenced by other aspects of post-natal management, including ventilation modality or access to alternative treatments for PPH, and ECMO can be started for respiratory failure other than PPH[75].

The strengths of our study include a very sensitive search strategy and a rigorous study selection and quality assessment in line with the most recent guidelines for conduct and reporting of systematic reviews. This is the first study to investigate the prediction value of prenatally relevant morbidity indicators for PPH. Our review nevertheless also has limitations. Although a substantial number of studies was included, many predictors were only

assessed by a single research group, thereby limiting our ability to pool data and limiting the statistical power in detecting heterogeneity and publication bias across studies. Furthermore, adjustments for potential confounding factors, like side of the hernia and intrauterine management, were not consistent across studies. To increase the homogeneity among study populations we performed a sub-analysis of studies only including patients managed expectantly in utero, confirming the results previously obtained. However, this further reduced the number of pooled studies, especially in the analysis of tests for PPH. Finally, the reviewed literature spans a 30 year time period (1984–2015), which has seen dramatic changes in perinatal practice influencing directly the outcome parameters.

Despite these limitations, this systematic review condenses the existing knowledge on prenatal prediction of PPH and need for ECMO, whilst concurrently providing direction for future research. It definitively demonstrates the need for larger (collaborative) studies to adjust for bias. It also highlights the need for standardized prenatal assessment methods, at standardized time points in gestation alongside standardization of postnatal criteria and time points of assessment of PPH.

In conclusion, our meta-analysis demonstrates that ECMO can be reliably predicted by liver position and lung size, but we failed to identify a reliable predictor of PPH.

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CONFLICTS OF INTEREST

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The Authors declare no other conflict of interest.

Table 1: Proposed predictors for PPH

Index test	Technique	Number of studies	Consistency among studies
LHR	US	6	No
o/e LHR	US	5	No
Lung/thorax ratio	US	2	No
o/e contralateral lung area	US	1	/
TLV/FBW	US	2	No
TLV	MR	1	
o/e TLV	US/MR	4	No
Pulmonary artery PI	US	1	/
Pulmonary artery ΔPI after hyperoxygenation	US	1	/
Pulmonary artery AT/ET	US	1	/
Vascularization index	US	2	Yes: associated
Flow index	US	1	/
Quantitative lung index	US	1	/
o/e Pulmonary artery diameter	US	2	Yes: associated
McGoon index	MR	1	/
Prenatal pulmonary hypertension index	MR	1	/
Liver herniation	US/MR	5	No
Liver/Thorax ratio	US	1	/
Stomach position	US	1	/
Nuchal translucency	US	1	/
Side	US	2	Yes: not associated
GA at diagnosis	N.A.	1	/
GA at delivery	N.A.	2	No
Interval balloon removal-delivery	N.A.	1	/

LHR: lung-to-head ratio; o/e: observed/expected; TLV: total lung volume; FBV: fetal body volume; PI: pulsatility index; AT/ET: acceleration time/ejection time; GA: gestational age; US: ultrasound; MR: magnetic resonance; N.A.: not applicable.

Table 2: Proposed predictors for need for ECMO

Index test	Technique	Number of studies	Consistency among studies
LHR	US	11	No
o/e LHR	US	5	No
Lung/thorax ratio	US	1	/
TLV	MR	2	No
TLV/FBV	MR	1	/
TLV growth rate	MR	1	/
o/e TLV	MR	5	No
o/e contralateral TLV	MR	1	/
PPLV	MR	1	/
Liver herniation	US/MR	10	No
% liver herniation	MR	1	/
Liver/thorax ratio	MR	1	/
Stomach position	US/MR	3	No
Bowel position	MR	1	/
Side	N.A.	3	Yes: not associated
GA at diagnosis	N.A.	2	No
GA at delivery	N.A.	4	No
Birthweight	N.A.	2	No

LHR: lung-to-head ratio; o/e: observed/expected; TLV: total lung volume; FBV: fetal body volume; PPLV: percent predicted lung volume; GA: gestational age; US: ultrasound; MR: magnetic resonance; N.A.: not applicable.

FIGURES LEGENDS

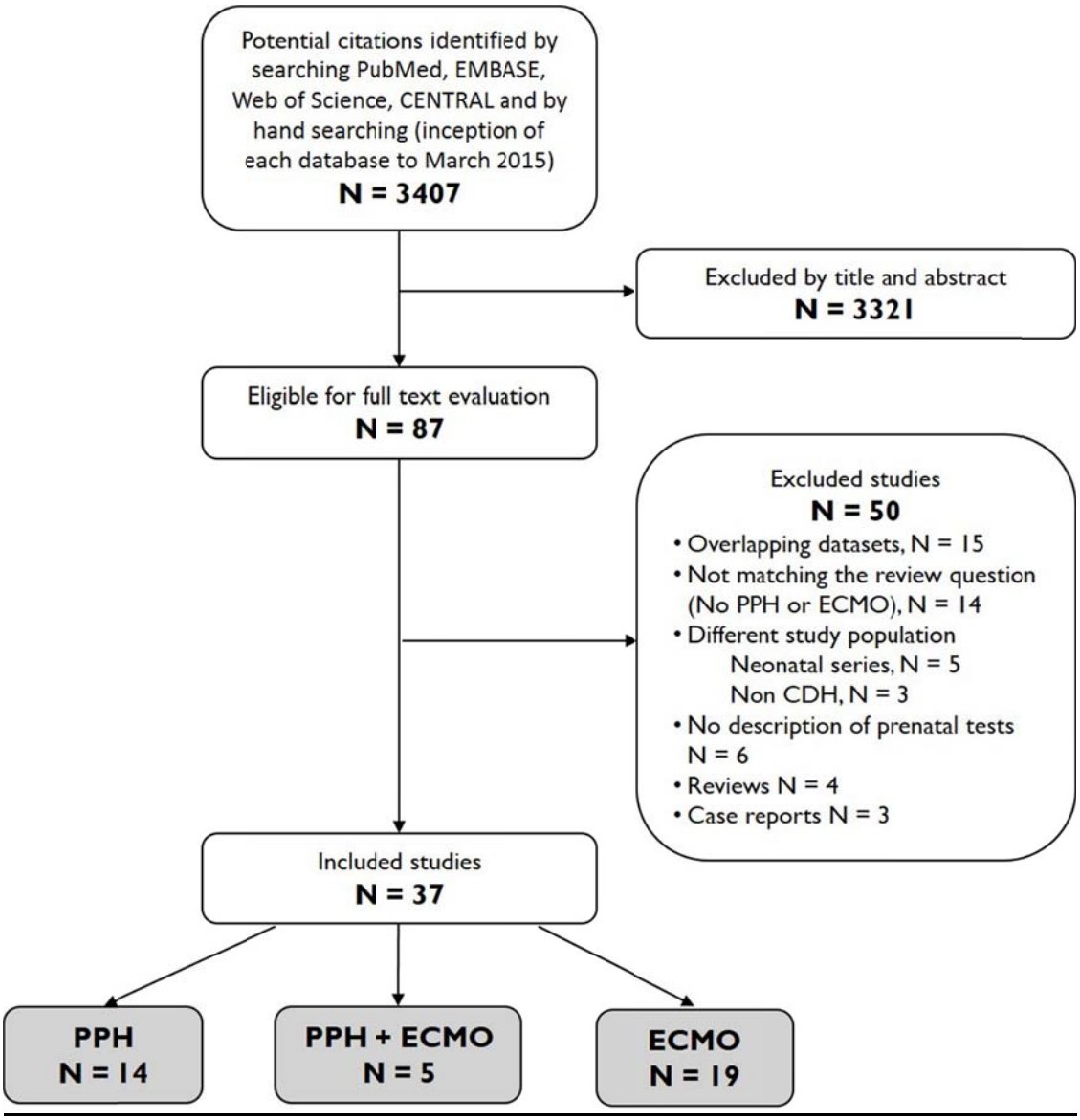

Figure 1: The preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of studies selection.

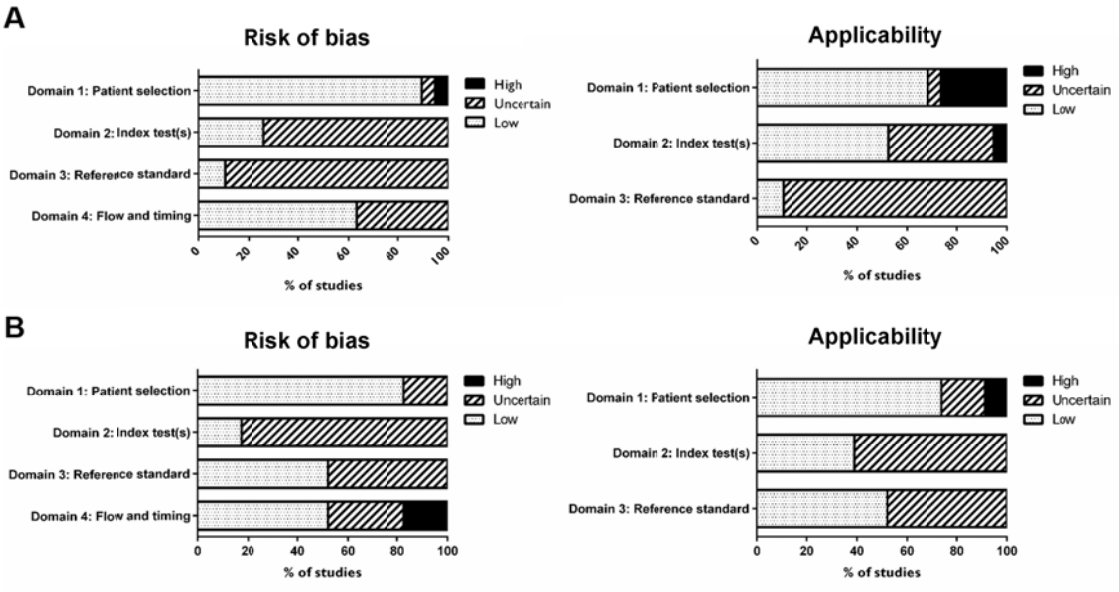

Figure 2: Summary of methodological quality of studies according to QUADAS-2 tool concerning risk of bias and applicability about each domain, presented as percentages across included studies. (A): studies reporting on PPH; (B) studies reporting on the need for ECMO. Studies reporting on both outcomes are included in both rows of this figure.

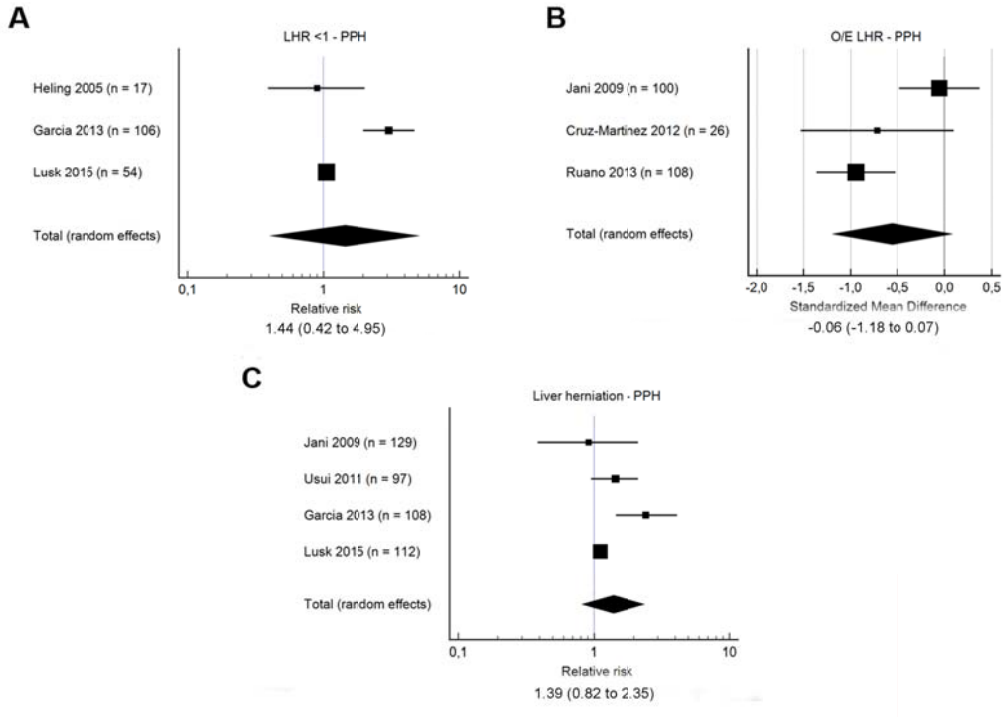

Figure 3: Forest plots of relative risk or standardized mean difference for the association of need of PPH and LHR <1 (A), mean o/e LHR (B) and liver herniation

(C). The exact relative risk (95% confidence interval) or standardized mean difference (95% confidence interval) is reported below each forest plot.

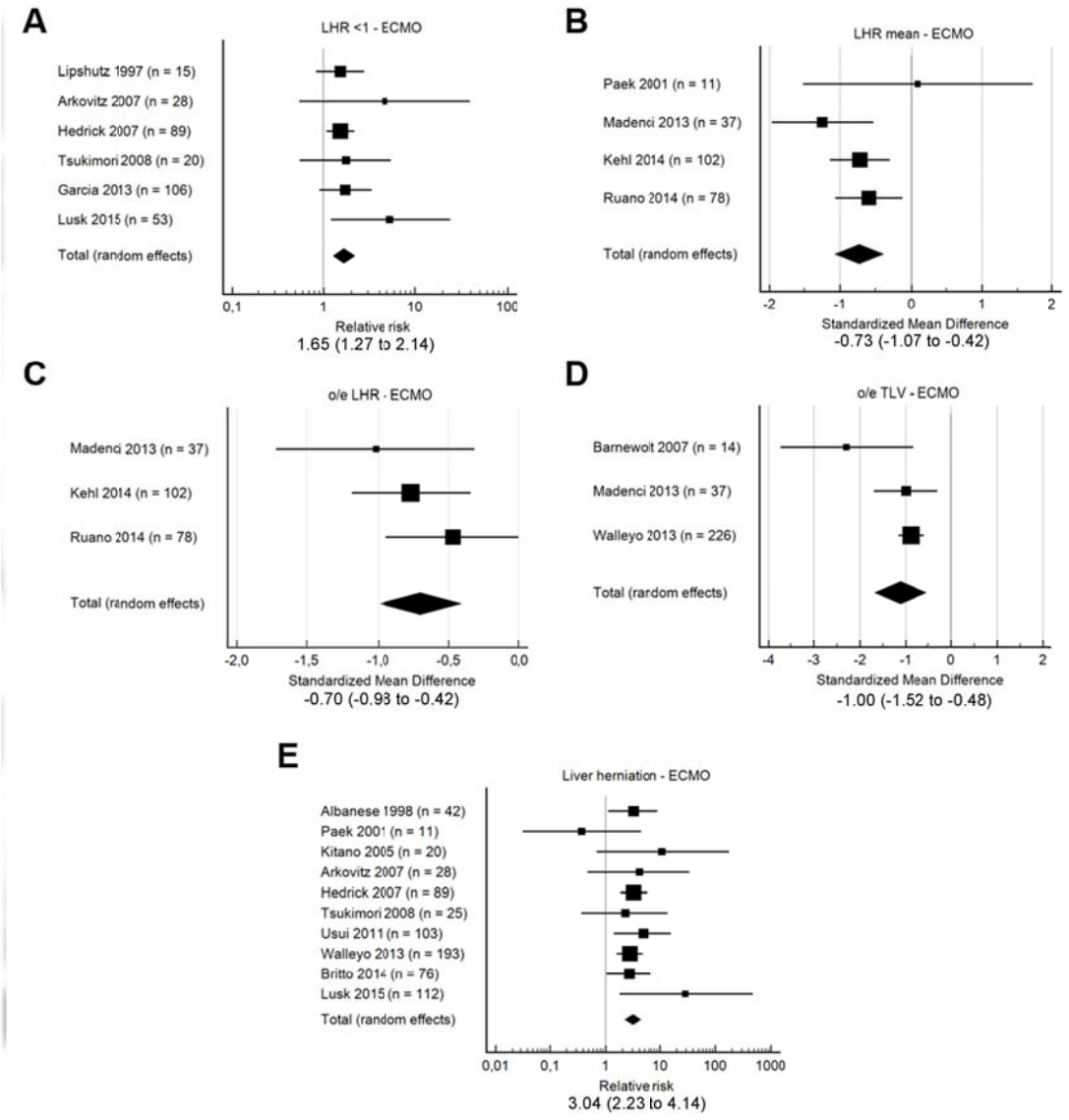

Figure 4: Forest plots of relative risk or standardized mean difference for the association of need of ECMO and, respectively, LHR <1 (A), mean LHR (B), mean o/e LHR (C), o/e TLV (D) and presence of liver herniation (E). The exact relative risk (95% confidence interval) or standardized mean difference (95% confidence interval) is reported below each forest plot.

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