Review

Left vocal cord paralysis after patent ductus arteriosus ligation: A systematic review

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Educational aims

The reader will be able to

- Appreciate that left vocal cord paresis (LVCP) is a significant side-effect of surgical closure of PDA in neonates born preterm.
- Appreciate the clinical importance of performing postoperative laryngoscopy in all infants born preterm exposed to surgical closure of PDA.
- Understand that LVCP can present with a wide variety of clinical symptoms in the neonatal period and later in life.
- Understand the risks of misdiagnosing LVCP.

ARTICLE INFO

ABSTRACT

Context: Extremely premature (EP) infants are at increased risk of left vocal cord paralysis (LVCP) following surgery for patent ductus arteriosus (PDA).
Objective: A Systematical Review was conducted to investigate the incidence and outcomes of LVCP after PDA ligation in EP born infants.
Data sources: Searches were performed in Cochrane, Medline, Embase, Cinahl and PsycInfo.
Study selection: Studies describing EP infants undergoing PDA surgery and reporting incidence of LVCP were included.
Data extraction and synthesis: Study details, demographics, incidence of LVCP, diagnostic method and reported outcomes were extracted. DerSimonian and Laird random effect models with inverse variance weighting were used for all analyses.
Study appraisal: The Newcastle-Ottawa scale for observational studies was used for quality assessment.
Results: 21 publications including 2067 infants were studied. The overall pooled summary estimate of LVCP incidence was 9.0% (95% CI 5.0, 15.0). However, the pooled incidence increased to 32% when only infants examined with laryngoscopy were included. The overall risk ratio for negative outcomes was higher in the LVCP group (2.20, 95% CI 1.69, 2.88, $p = 0.01$) compared to the non-LVCP-group.
Conclusions: Reported incidence of LVCP varies widely. This may be explained by differences in study designs and lack of routine vocal cords postoperative assessment. LVCP is associated with negative outcomes in EP infants. The understanding of long-term outcomes is scarce. Routine laryngoscopy may be necessary to identify all cases of LVCP, and to provide correct handling for infants with LVCP.
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Introduction

The ductus arteriosus fails to close spontaneously in up to 40–65% of extremely premature infants [1,2]. A patent ductus arteriosus (PDA) shunts blood back from the descending aorta into the pulmonary artery, potentially causing systemic hypoperfusion and pulmonary over circulation [3].

PDA surgical ligation is currently the second-line of treatment, and it is used when the medical treatment has failed or is contra-indicated [4,5]. Up to 20–30% of extremely premature infants with a clinically significant PDA undergo surgical PDA ligation [1,6,7]. This can be done by applying a small metal clip or by using a suture. Because of its close proximity to the ductus arteriosus [8], the left recurrent laryngeal nerve may be injured during surgery, causing both left vocal cord paresis or paralysis (LVCP). Early symptoms of LVCP are stridor, hoarseness, weak cry and feeding difficulties [9,10]. However, symptoms can be weak or even absent. In fact, LVCP can be unnoticed unless specifically looked for postoperatively for example via [11] flexible nasolaryngoscopy. This procedure allows visualization of the larynx without the use of anaesthetics [12] and is the recommended diagnostic method for LVCP in infants [13,14]. Known risk factors for LVCP after surgical PDA ligation are low gestational age at birth (GA) [11], low birth weight (BW) [15] and low weight at surgery [11,16]. Thus, extremely premature infants undergoing surgical PDA ligation have an increased risk of iatrogenic nerve damage compared to other premature infants [17]. A recent metaanalysis reported large discrepancies between studies regarding the incidence of LVCP in infants and children undergoing cardiothoracic surgery for congenital heart disease [16]. Some of this variability could potentially be explained by inconsistencies regarding postoperative vocal cord evaluation between studies [16].

The objectives of this study are to (1) determine the incidence of LVCP after surgical PDA ligation in extremely premature infants, (2) determine study level characteristics that may explain the wide incidence variation reported by different studies and (3) explore short- and long-term consequences and/or associated co-morbidities of LVCP in extremely premature born infants.

Methods

Protocol and registration

We registered the review protocol in the PROSPERO International prospective register of systematic reviews under the identification number CRD42016029921 (Supplemental File 1) and followed the checklist for Preferred Reporting Items for Systematic Reviews and Meta analyses (PRISMA, Supplemental File 2) [18].

Eligibility criteria

We included studies of extremely premature infants born at gestational age ≤28 weeks and/or ≤1000 g birthweight diagnosed with PDA, and reported cases of LVCP following surgical PDA ligation. We excluded studies with less than 80% of extremely premature infants or lacking a description of a subpopulation of extremely premature infants. Eligible study designs were cohort or case-control. Case reports, case series, narrative reviews, letters, editorials, commentaries and abstracts were excluded. Outlined in Supplemental File 3.

Literature search strategy

We searched the following databases from their inception through December 19, 2015: MEDLINE, Embase, PsycINFO, Cinahl and the Cochrane Library. The search was updated on December 20th, 2016 without additional included citations. In collaboration with a librarian (G.A), M.S.E. developed a highly sensitive search strategy for MEDLINE, using search terms relevant to the population and intervention (e.g., extremely premature infants, patent ductus arteriosus ligation). To identify grey literature, we searched Open Grey and Google Scholar. We searched Prospero and Clinical trials.gov for ongoing studies, and reference lists of relevant reviews and citations of included studies to identify other potentially relevant references. The search strategy was modified for the other databases. No restrictions were placed on publication date, study design or language. We describe the complete search strategy in Supplemental File 4.

Study selection

Two investigators (M.S.E. and S.M.) independently conducted the initial screening of references identified by the search strategy. Titles and abstracts were retained for full-text review if one of the investigators identified the study as being potentially eligible. Two investigators (M.S.E. and O.D.R.) independently screened the remaining full text references. Any disagreements were resolved by consensus, and a third investigator (S.M.) was consulted if consensus was not met.

Data abstraction

One investigator (M.S.E.) abstracted data from the selected studies, while another investigator (O.D.R.) over-read the abstracted data for inconsistencies. Disagreements regarding data abstracted were resolved by consensus between the two authors. The following data were extracted: Author details, year of publication, study methods, key characteristics of participants, intervention details, control conditions, incidence LVCP, diagnostic method and outcomes.

In addition, study authors were contacted for additional information if needed. They were asked about full text versions of abstracts, assessment method for LVCP, or information about number of extremely premature infants in the cohort, potentially allowing us to perform sub-analysis of incidence of LVCP in extremely premature infants.

Quality assessment of individual studies

Two investigators (M.S.E. and N.R.O.) independently assessed methodological quality of identified studies using the Newcastle-Ottawa Quality Assessment Scale (NOS) [19]. This is a quality measure tool for observational studies recommended by Cochrane [20] that assesses methodological quality by assigning points up to a maximum of nine points for the least risk of bias in three domains: (1) selection of study groups (four points); (2) comparability of groups (two points); and (3) ascertainment of exposure and outcomes (three points). We provide further details on the use of NOS for this Systematic Review in Supplemental File 5. Disagreements were resolved by consensus or through a third investigator (O.D.R).

Synthesis of results

We statistically pooled results when ≥2 studies were present for the same outcome. A pooled proportion of the incidence of LVCP including 95% confidence intervals (CIs) was calculated. Incidence was calculated by dividing the number of reported cases of LVCP by the total number of PDA ligated infants in each study, not

divided by the number of cases examined by laryngoscopy. DerSimonian and Laird random effect model with inverse variance weighting was used for all analyses. A Freeman–Tukey Double Arcsine Transformation was used to stabilize the variances prior to pooling for incidence estimates. For the analysis of and/or associated co-morbidities, we pooled studies using random effects models estimating risk ratios and 95% confidence intervals. Due to the small number of studies reporting consequences and/or associated co-morbidities, we did not attempt to stratify when significant heterogeneity was present. Heterogeneity between studies was tested for both incidence proportion and consequences with Cochrane's Q and I-squared. High heterogeneity was indicated by a Q p-value <0.10 or I-squared >50%. When substantial heterogeneity was present, we attempted to explain heterogeneity by stratifying by a priori covariates. Publication bias was assessed by visual inspection of the funnel plot and an Egger's test for the main analysis of occurrence of LVCP. All analyses were conducted using Stata 14.0 (College Station, TX).

Results were synthesized descriptively if a quantitative synthesis was not feasible. We placed greater emphasis on the evidence coming from studies with more precise estimates of effect. We also focused on documenting and identifying patterns of the intervention across outcome categories. We analyzed potential reasons for inconsistencies in treatment effects across studies by evaluating differences in method of assessment, intervention and study design.

Results

Study selection

The literature search identified 1985 unique records. Many of these (1815 or 91.4%) were excluded by title and abstract screen. In addition, we were not able to retrieve the full texts of 37 abstracts. Full-texts of 133 publications were reviewed of which, 112 were excluded resulting in 21 studies included in the review [11,15,17,21–40]. The selection process is outlined in Fig. 1. Reasons for exclusions of publications were: No description of LVCP after PDA surgery (n = 84), and/or less than 80% extremely premature infants or no subgroup of extremely premature infants described (n = 22), no PDA surgery (n = 2), not appropriate study design (n = 2), duplicate (n = 1) or chapter in book (n = 1). Reasons for exclusions are detailed in Supplemental File 6.

Study characteristics

Descriptions of study characteristics including study-population, exposure, diagnostic method and outcomes are provided in Table 1. The majority of study designs were cohort studies (n = 20), and one [23] was a case–control study.REF 23 here 17 studies were retrospective and four were prospective. Seven studies [11,15,17,23,33,35,37] aimed at measuring the incidence of LVCP following PDA ligation, and seven studies [15,22,23,32,33,35,37] at detecting risk-factors/co-morbidities or outcomes following LVCP after PDA ligation. Half of the included studies [21,24,25,27–30,34,39,40] did not report or reported unclearly how LVCP was assessed. Specifically, six studies [15,17,22,32,36,41] assessed via laryngoscopy only symptomatic infants, examining laryngoscopically all infants after PDA ligation [11,23,33,35,37].

The pooled mean GA at birth between the 21 included studies was 25.6 (range of means 24.5–27.1) weeks and the pooled mean BW was 816.5 (range of means 679–1040) g. The pooled mean surgical age of the 12 studies reporting this was 22.0 (range of means 12–57) days. The pooled mean surgical weight of the 8 studies reporting it was 933.1 (range of means 722–1404) g. There were 8 studies that included a higher maximum GA/BW range. However, all of these included more than 90% extremely premature infants [24,29,34,41] and/or a described subgroup of extremely premature infants [11,17,23,36] and therefore, were used in our analyses.

Six studies [11,15,17,22,23,35] compared GA and BW in children with and without LVCP. Only five of these [11,15,22,23,35] were included in this meta-analysis (Figs. 2 and 3), as one study [17] did not report variations from the mean. Infants with LVCP had 1.2 weeks (95% CI −2.01, −0.39, I^2: 70.4%, p = 0.009) lower GA, and 175.5 g (95% CI −321.5; −29.6; I^2: 82.7%, p < 0.001) lower BW.
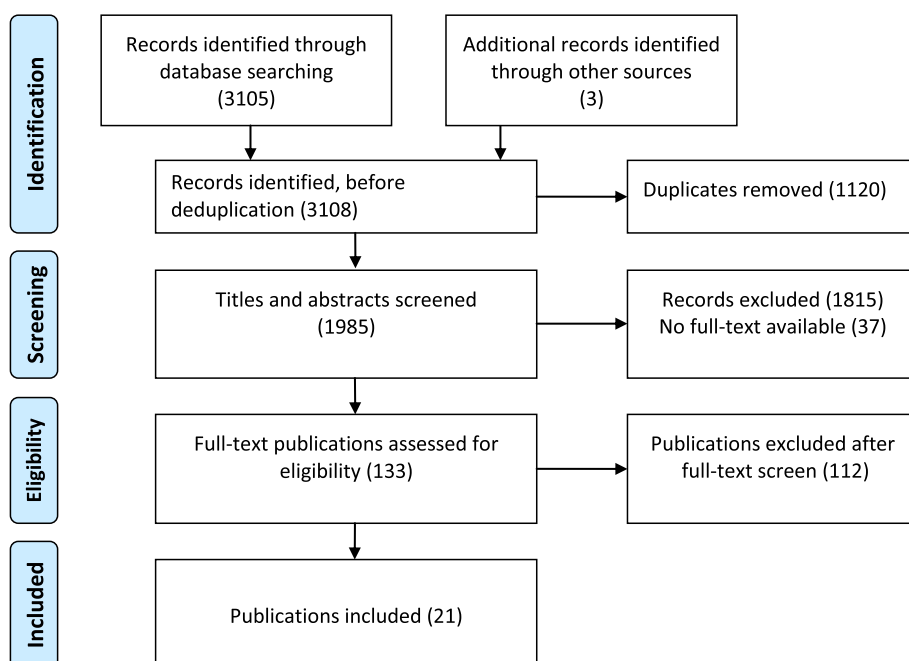

Fig. 1. Flow diagram of study selection.

Table 1
Characteristics of studies and participants included in the analyses.

Author, year, study design	Population demographics	Diagnostic method (LVCP)	Incidence of LVCP, cases/total (%)	Outcomes following LVCP
Alexander, 2009 Retrospective 1996–2005	All ELBW infants with PDA. 1: No treatment (N = 54): GA, 25.7 ± 1.9 wk; BW, 729.6 ± 169.6 g 2: Indomethacin (N = 82): GA, 26.3 ± 1.9 wk; BW, 758.2 ± 139.4 g 3: Primary surgery (N = 46): GA, 24.8 ± 1.5 wk; BW 678.7 ± 153.5 g 4: Indomethacin + surgery (N = 58): GA: 25.7 ± 1.8 wk; BW, 724.4 ± 139.7 g	NR	0/104 (0%)	NR
Benjamin, 2010 Retrospective 2004–2006	All ELBW infants, all PDA ligated. +LVCP (N = 22): GA, 24.5 ± 1 wk; BW, 722 ± 122 g; SA, 17 ± 8.7 d; SW, 722 ± 140 g. −LVCP (N = 33): GA, 24.8 ± 1.3 wk; BW, 728 ± 132 g; SA, 22 ± 14.5 d; SW, 798 ± 219 g	Laryngoscopy if symptoms (N = 25/55)	22/55 (40%)	Days of mechanical ventilation, bronchopulmonary dysplasia, reactive airway disease, gastrostomy tube, Nissen fundoplication, neurodevelopmental impairment, IVH
Clement, 2008[§] Retrospective 2003–2005	ELBW (N = 18) and VLBW (N = 5) infants, all PDA ligated. All LVCP was EP. +LVCP (N = 12): GA, 24.8 (24–26 wk); BW 725 (580–887 g); SA, 14.5 (6–31 d) −LVCP (N = 11): GA, 27 (25–31 wk); BW, 1040 (700–1540 g); SA, 13.8 (4–53 d)	Laryngoscopy (N = 20/23)	12/18 (67%)	Tube feeding, gastrostomy, hospital stay, readmission, ventilator support, supplemental oxygen, chronic lung disease
Ghosh, 1985 Retrospective 1979–1983	ELBW infants (N = 27/30). All infants (N = 30) were PDA ligated. GA, 27 (23–34 wk); BW, 811 (650–1620 g)	NR	1/30 (3.33%)	NR
Heuchan, 2012 Retrospective, 2001–2007	ELBW infants (N = 125), all PDA ligated. GA, 26 (IQR 25–27 wk); BW, 840 (IQR 730–1035 g)	NR	6/125 (4.8%)	NR
Hines, 2003[§] Retrospective, 1996–2002	EP infants (N = 94/100), 99/100 PDA ligated. GA: 25.6 (23–31 wk); BW, 859 (420–1500 g); SA, 16 (3–51 d)	Bronchoscopy if symptoms	5/94 (5.3%)	NR
Hutchings, 2013 Retrospective, 2005–2009	ELBW infants (N = 95/98)[*], all PDA ligated. GA, 26 ± 2wk; BW, 923 ± 394 g; SA, 29 ± 3 wk; SW, 1222 ± 506 g	NR	10/95 (10.5%)	NR
Ibrahim, 2015 Retrospective 2010–2014	ELBW infants (N = 120), all PDA ligated. Early ligation (N = 75): GA, 25 (22–28 wk); BW, 765 (607–923 g); SA, 12 (6–20 d); SW, 756 (646–900 g) Late ligation (N = 45): GA, 24.6 (22–27 wk); BW, 773 (620–901 g); SA, 30 (24–30 d); SW, 833 (690–990 g)	NR	1/120 (0.83%)	NR
Kang, 2013 Prospective 2004–2009	EP infants (N = 85/92), all PDA ligated. GA, 25 (23–36 wk); BW, 721 (462–2420 g); SA, 34 (10–94 d); SW, 1005 (627–3080 g)	NR	2/85 (2.4%)	NR
Lee, 2008 Retrospective 1994–2006	VLBW/ELBW infants (N = 94), all PDA ligated. GA, 26wk+3d ± 2 wk+1 d; BW: 869 ± 223 g	NR	0/94 (0%)	NR
Mandhan, 2009 Retrospective 1987–2005	ELBW infants (N = 145), all PDA ligated. GA, 25.5 ± 2.3 (24–36 wk); BW, 837.7 ± 277.2 (450–1000 g) SA, 14.1 ± 1.8 d; SW, 881.3 ± 338.1 g	NR	1/145 (0.7%)	NR
Natarajan, 2010 Retrospective 2004–2006	EP infants (N = 82), all PDA ligated. GA, 25.5 (23–28 wk); BW, 765 (484–1150 g); SA, 21 (5–58 d)	NR	0/82 (0%)	NR
Nichols, 2014 Retrospective 2001–2012	532 infants were PDA ligated. 66 were included in further analysis. +LVCP (N = 66): GA, 24.75 ± 1.6 wk; BW, 704.2 ± 185.6 g; SA, 18.4 ± 13.9 d	Laryngoscopy (N = 66/532)	66/532 (12.4%)	Stridor, dysphonia, tube feeding, bronchopulmonary dysplasia, IVH, retinopathy of prematurity, laryngomalacia, subglottic stenosis
Pereira, 2006 Prospective 2001–2004	Premature infants (N = 100), all PDA ligated. GA, 25 wk; BW, 740 g; SA, 23 d; SW, 914 g	Laryngoscopy (N = 61/100)	7/61 (11.5%)	Stridor, feeding difficulty, feeding tubes, weak cry
Robie, 1996 Retrospective 1990–1992	ELBW infants (N = 82), all PDA ligated. GA, 2.7 ± 1.74 (23–32 wk); BW, 756 ± 135 (420–1000 g)	NR	2/82 (2.4%)	NR
Røksund, 2010 Retrospective 1982–1985/ 2008–2009	EP infants with PDA. PDA-ligated (N = 13): SA, 12 (4–29 d) +LVCP (N = 7): GA, 27.1 ± 1.5 wk; BW, 874 ± 138 g −LVCP (N = 4): GA, 27.0 ± 2.9 wk; BW, 982 ± 283 g No surgery (N = 33): GA, 27.5 ± 1.4 wk; BW, 1051 ± 178 g	Laryngoscopy (N = 11/13)	7/11 (64%)	Ventilator treatment, oxygen treatment, measures of lung function, peak heart frequency, blood pressure, wheezing, severe stridor during heavy exercise
Rukholm, 2012 Retrospective 2003–2010	EP infants (N = 111), all PDA ligated. Results presented as mean (95% CI) +LVCP (N = 19): GA, 25.4 (24.8–26.0 wk); BW, 743.8 (665.4–822.1 g); SA, 22.7 (16.3–29.1 d); SW, 845.8 (766.5–925.2 g) −LVCP (N = 92): GA, 26.7 (26.0–27.5 wk); BW, 990 (858.4–1121.5 g); SA, 52.7 (23.8–81.6 d); SW, 1404 (966.3–1843.4 g)	Laryngoscopy (31/111)	19/111 (17.1%)	Gastroesophageal reflux syndrome, sepsis, bronchopulmonary dysplasia, gastric feeding tube, pneumonia, anemia of prematurity

Table 1 (continued)

Author, year, study design	Population demographics	Diagnostic method (LVCP)	Incidence of LVCP, cases/total (%)	Outcomes following LVCP
Smith, 2009[§] Prospective 2004–2007	EP infants (N = 60/86), all PDA ligated. All LVCP were <28 wk GA. +LVCP (N = 14): GA, 25.4 ± 1.2 wk; BW, 829 ± 205 g; SA, 27 ± 1.3 wk; SW, 911 ± 181 g −LVCP (N = 72): GA, 26. 9 ± 2.6 wk; BW, 1033 ± 414 g; SA, 29 ± 3.3 wk; SW, 1211 ± 449 g	Laryngoscopy (N = 86/89)	14/60 (23.3%)	Stridor, dysphonia
Spanos, 2009[§] Prospective 1995–2005	ELBW infants (N = 55/105), all PDA ligated. All cases of LVCP were EP. Results presented in median (mean absolute deviation) Suture: GA, 25.0 ± 2.0 wk; BW, 740 ± 288 g; SW, 1054 ± 626 g Clip: GA, 24.7 ± 1.3 wk; BW, 561 ± 169 g; SW, 762 ± 210 g	Laryngoscopy (N = 68/105)	13/55 (23.6%)	Hoarseness/stridor, aspiration, episodes of decreased oxygen saturation
Sørensen, 2010§ Retrospective 1998–2007	EP infants (N = 31/46), all PDA ligated. [*]3/3 infants with LVCP was EP Total: GA, 26 wk[+6,5d] (23[+6]–34 wk[+0 d]); BW, 943.5 (535–1793 g) <28 wk: (N = 31) GA, 25wk[+4,2d] BW, 788 g	NR Laryngoscopy if clinical suspicion[*]	3/31 (9.7%)	NR
Zbar, 1996[§] Retrospective 1991–1994	ELBW infants (N = 22/68), all PDA ligated. 5/22 with LVCP was EP. +LVCP (N = 6): GA, 26.3 wk; BW, 900 g −LVCP (N = 62): GA, 33.8 wk; BW, 2300 g	Laryngoscopy if symptoms	5/22 (22.7%)	NR

Results given in mean ± standard deviation and/or range unless other is specified. GA; gestational age, BW; birth weight, SA; age at surgery, SW; weight at surgery. LVCP; left vocal cord paralysis, EP; extremely premature (≤1000 g/≤28 weeks), ELBW; extremely low birth weight (<1000 g), VLBW; very low birth weight (<1500 g), LBW: Low birth weight (<2500 g), Wk; weeks, g; gram, IVH; intraventricular hemorrhage, NR; not reported.
[§] Analysis of incidence of LVCP was performed based on a described subgroup of extremely premature children.
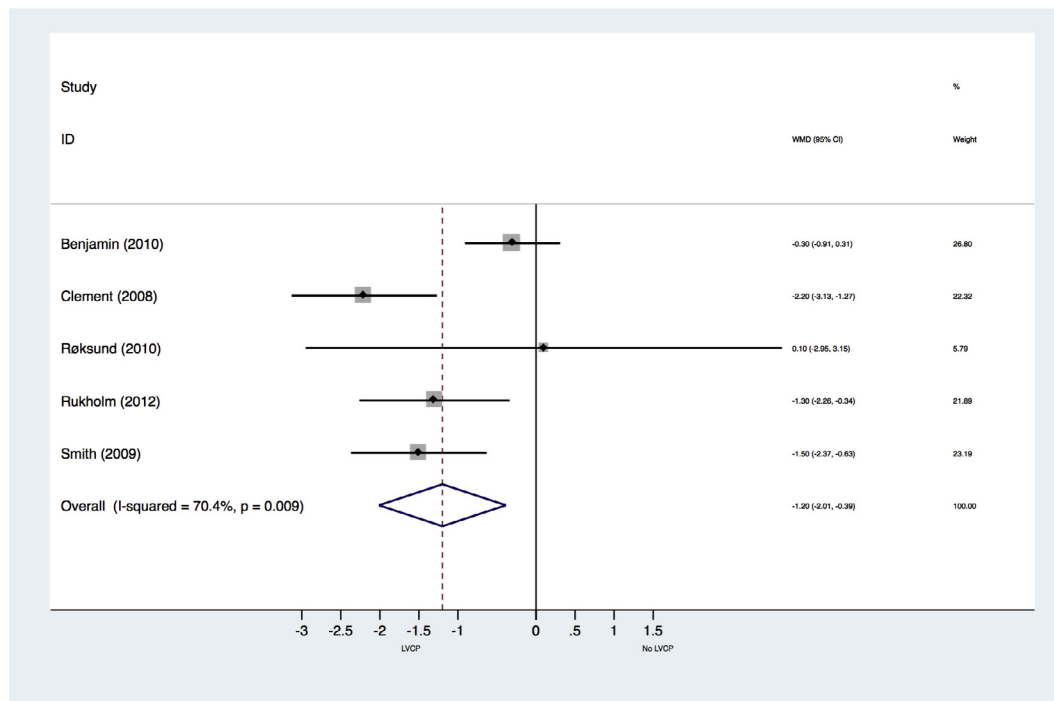[*] Additional information provided by author of the publication.

Fig. 2. Gestational age (weeks), weighted mean difference between infants with and without LVCP.

Analysis of reported incidence of left vocal fold paralysis

Twenty-one studies involving 2067 infants were included in analysis of the incidence of LVCP after PDA surgery (Fig. 4). Five studies [11,17,23,36,37], calculated the incidence of LVCP in a subgroup of extremely premature infants, not among all infants who underwent PDA ligation in the study. Reported incidence of LVCP ranged from 0% to 67% in the individual studies. The overall pooled incidence summary estimate was 9.0% (95% CI 5.0, 15.0). However, significant heterogeneity was present with an I^2 of 91.9% and Q p-value <0.01. No visual evidence was noted by visual inspection of the funnel plot, and the Egger's test (p = 0.26) also suggested that no publication bias was present.

Subgroup analyses

As shown in Fig. 5, heterogeneity decreased, and pooled reports of LVCP were impacted after stratifying by type of LVCP identification method The weighted pooled proportion of LVCP incidence was 2% (95% CI 0, 4%, I^2 = 72.2%, Q-p < 0.01) in studies not reporting or reporting unclearly how infants with LVCP after PDA ligation were evaluated [21,24,25,27–30,34,39,40]. The pooled incidence
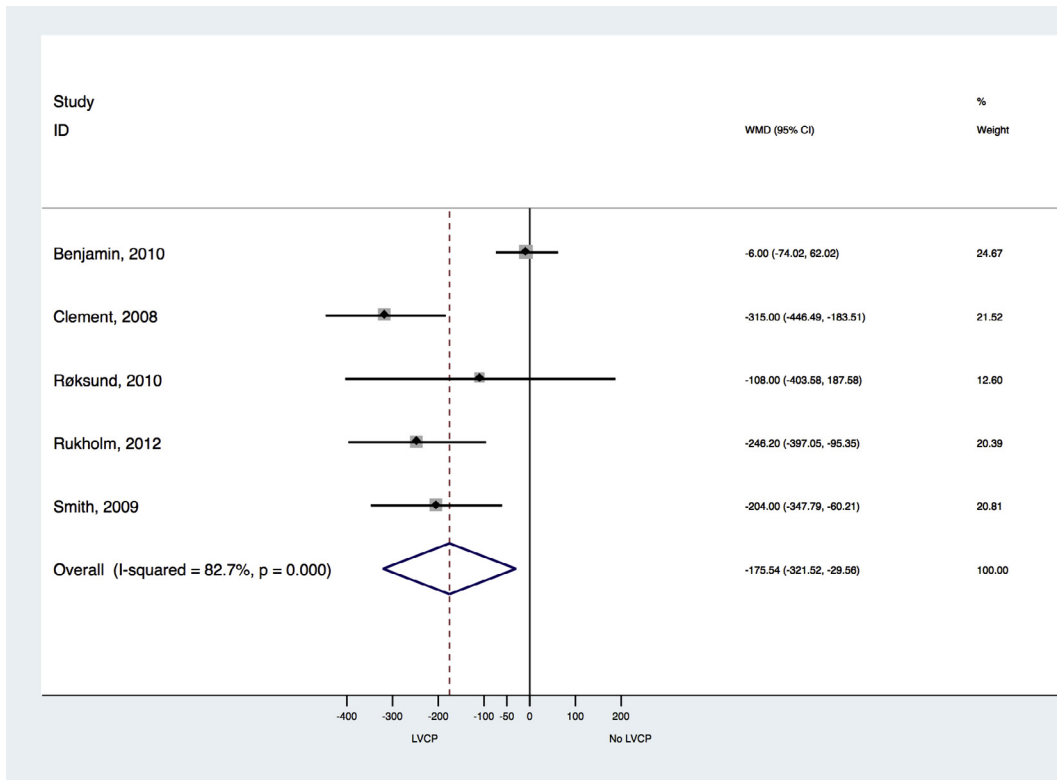
Fig. 3. Birth weight (g), weighted mean difference between infants with and without LVCP.
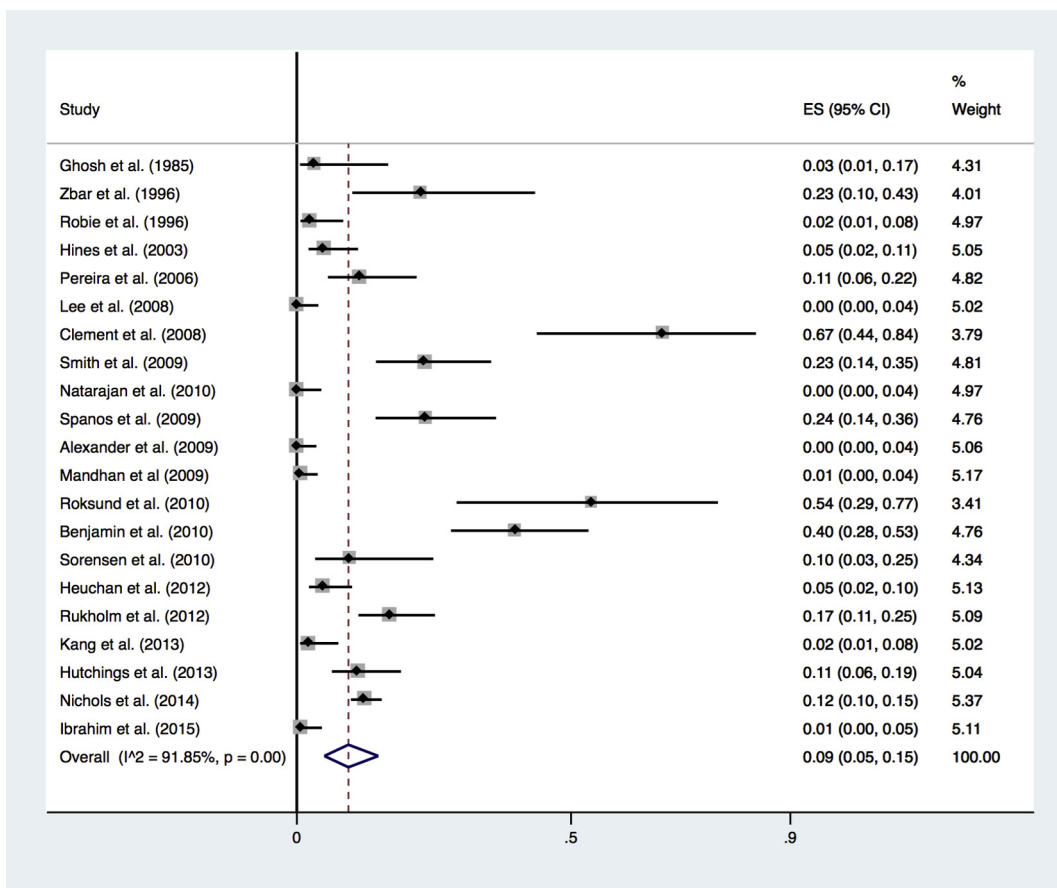

Fig. 4. Individual study and overall incidence of LVCP following patent ductus arteriosus surgery. ES; effect size.
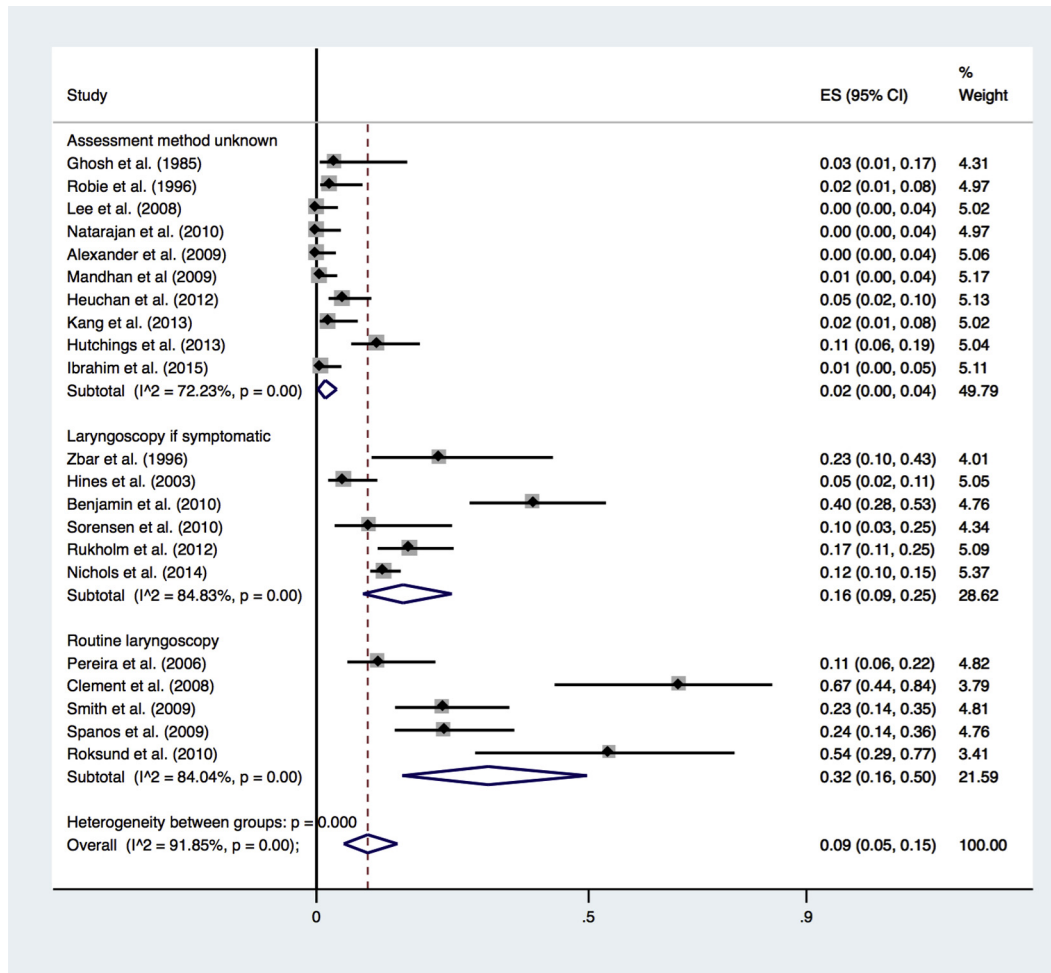
Fig. 5. Overall Incidence of LVCP, stratified by type of assessment method. ES; effect size.

was 16% (95% CI 9, 25%, I^2: 84.83%, Q-p < 0.01) in studies assessing symptomatic infants via laryngoscopy [15,17,22,32,36,41], and 32% (95% CI 16, 50%, I^2: 84.04%, Q-p < 0.01) in studies assessing all infants via laryngoscopy [11,23,33,35,37]. After the latter were stratified by retrospective ($n = 31$) [23,35] vs. prospective design ($n = 215$) [11,33,37] (Fig. 6), the heterogeneity decreased substantially in the retrospective studies (I^2: 48.94%, Q-p = 0.14; prospective studies I^2 was 74.47%, Q-p = 0.05). Retrospective studies had a higher pooled incidence of LVCP of 61.0% (95% CI 43, 78%) compared to prospective studies (19.0%, 95% CI 11, 28%). Heterogeneity was not reduced by stratification based on PDA surgical closure method (clip or suture, I^2 > 88%).

Analysis of reported comorbidities and/or consequences of LVCP

Eight of the 21 included studies reported consequences and/or comorbidities following LVCP after PDA ligation in extremely premature infants [11,15,17,22,23,33,35,37]. Six of these studies [11,15,22,23,35,37] were included in the meta-analysis because two lacked comparison group. Fig. 7 illustrates the consequences and/or comorbidities of LVCP following PDA ligation reported by two or more studies. Bronchopulmonary dysplasia (BPD) was reported by four studies [15,22,23,35] including 235 infants. The risk for BPD among premature infants with LVCP was increased; risk ratio (RR) = 1.60 (95% CI 1.29, 1.99, I^2: 0.0%, Q-p = 0.58). The need of enteral feeding via nasogastric tube or gastrostomy was reported in three studies [15,22,23] including 189 patients. This

risk was strong in premature infants with LVCP although imprecise due to small sample sizes (RR = 5.76 (95% CI 2.15, 15.46, I^2 = 0.0%, Q-p = 0.40). Two studies [11,37] including 115 patients reported stridor, and this risk was elevated (RR = 5.22 (95% CI 1.97, 13.86, I^2 = 20.2%, Q-p = 0.26) but imprecise. Asthma or reactive airway disease was reported by two studies [22,35] including 99 patients, and the risk of asthma was strong (RR = 2.45 (95% CI 1.52, 3.92, I^2 = 0.0%, Q-p = 0.58) and precise. The risk of aspiration, gastroesophageal reflux/gastroesophageal reflux syndrome or intraventricular hemorrhage were all reported by two or three studies [15,22,23] and included in the meta-analysis, but the pooled risks between individual studies were not statistically significant. Three studies [22,23,35] including 89 infants reported differences in total days spent on mechanical ventilation between infants with and without LVCP (Fig. 8). Infants with LVCP spent on average 16.5 days (95% CI: 8.57, 24.07, I^2 = 58.6%, p = 0.089) longer on mechanical ventilation.

Additional analysis

Additional pooling of data was not performed because of the 21 included studies had non-uniform reporting of data among or less than two studies reported a given outcome. For example, only one study followed children beyond the age of ten years. Data from additional analyses are presented in Table 2. Significant differences between subjects with and without LVCP as regards neonatal outcomes were reported for neonatal sepsis [15], initial length of hos-
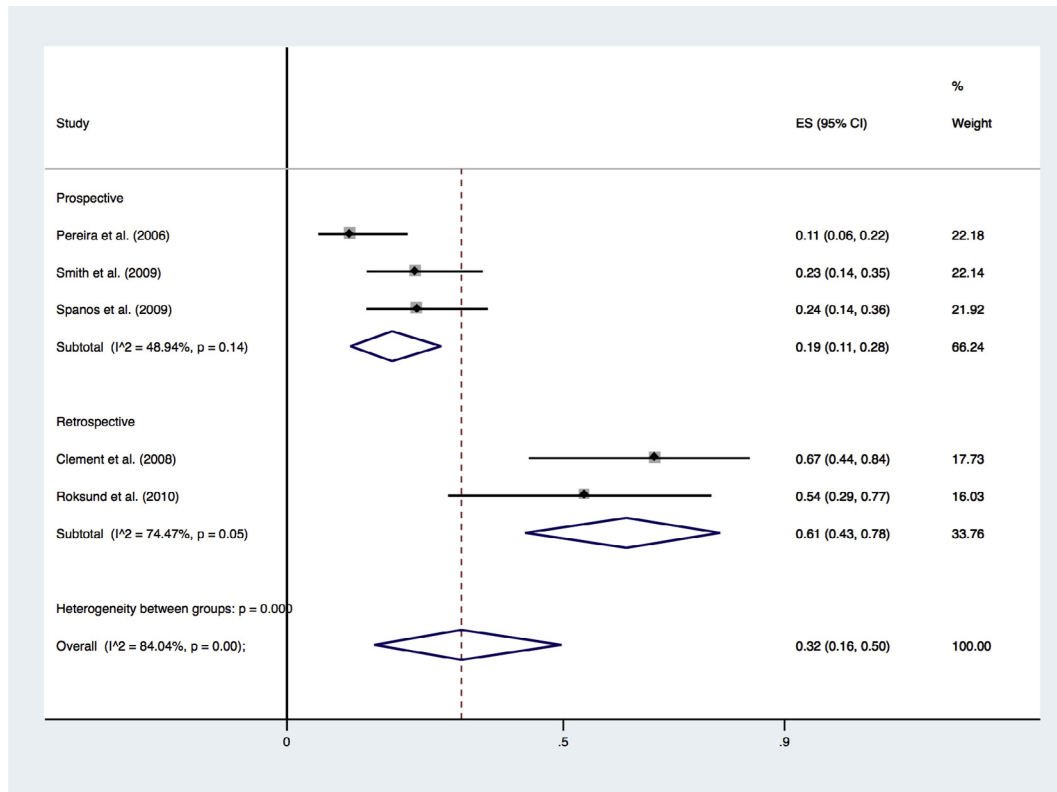
Fig. 6. Overall incidence of LVCP among studies routinely assessing patients with laryngoscopy. ES; effect size.

pital stay [23], dysphonia [11,37] and subjects undergoing gastroe-sophageal reflux disease surgery [22]. One study [35] reported follow-up data after discharge and found significantly more airway obstruction as measured by spirometry in the LVCP group.

Quality assessment

Assessment of quality in the included studies is summarized in Supplemental File 7. Seventeen studies (81%) scored 4 out of 9 possible stars. Two studies [21,35] had a control group of extremely premature infants with PDA who did not undergo PDA ligation, and scored three additional stars (7/9) for selection and comparability. The only study [11] earning a star for assessment of outcome examined 97% of infants with laryngoscopy postoperatively. One study [37] scored only three stars, because 35% of patients were lost to follow-up and not accounted for. No studies examined infants for LVCP preoperatively and therefore, all studies missed a potential star for demonstrating that the outcome of interest was not present at the start of the study.

Discussion

The overall pooled incidence of LVCP after PDA ligation in extremely premature children was 9.0%. However, the incidence varied widely (0–67%) between studies. Higher incidence was seen in studies that examined *all* children with laryngoscopy after ligation (32%), and in studies with a retrospective design (61%) compared to those with a prospective design (19%). Results revealed a scarcity of follow-up studies that could provide further knowledge on short- and long-term outcomes. However, based on analyses of the available outcome data, we found that infants with LVCP, overall, had a significantly higher risk of negative outcomes. Further prospective research analyzing confounding factors is needed.

To our knowledge, this is the first systematic review that focused on identifying the incidence of LVCP after PDA ligation in extremely premature infants. A strength of this study is that the aim and search strategy were restricted to one type of cardiothoracic surgery and we only included studies describing extremely premature infants. Thus, our search strategy was more specific compared to a previous systematic review [16] on LVCP that included various types of cardiothoracic surgery in infants and children. In addition, we had no language restrictions, and our search identified new research on the topic.

Low gestational age, low birth weight and low weight at surgery are known risk factors for LVCP [11,15,17]. Therefore, we expected a high LVCP pooled incidence in this research as we only included studies describing extremely premature infants. However, our overall LVCP pooled incidence is similar (9.0% vs 8.7%) to that reported by Strychowsky et al. [16], in a sub-analysis of 21 studies investigating incidence of LVCP after PDA ligation in infants and children. Congruent results between these two meta-analyses could be due to the expectedly high proportion of extremely premature infants in studies investigating consequences of surgical PDA ligation. Of note, about half of the studies included by Strychowsky et al. [16,11,15,17,22,23,25,33,35–37,40] (*n* = 11) were also included in our meta-analysis.

LVCP assessment methods could partly explain the large between-studies variability in the reported incidence of LVCP [16]. For example, our results showed that the incidence of LVCP was substantially higher in studies routinely assessing all infants postoperatively via laryngoscopy (32%), compared to those that performed laryngoscopy only in symptomatic infants (16%). The pooled incidence of LVCP was only 1% in studies with unclear or unreported vocal cord assessment method. Strychowsky et al. [16] found a weighted pooled proportion for LVCP of 39% in studies that assessed infants and children by laryngoscopy after PDA liga-
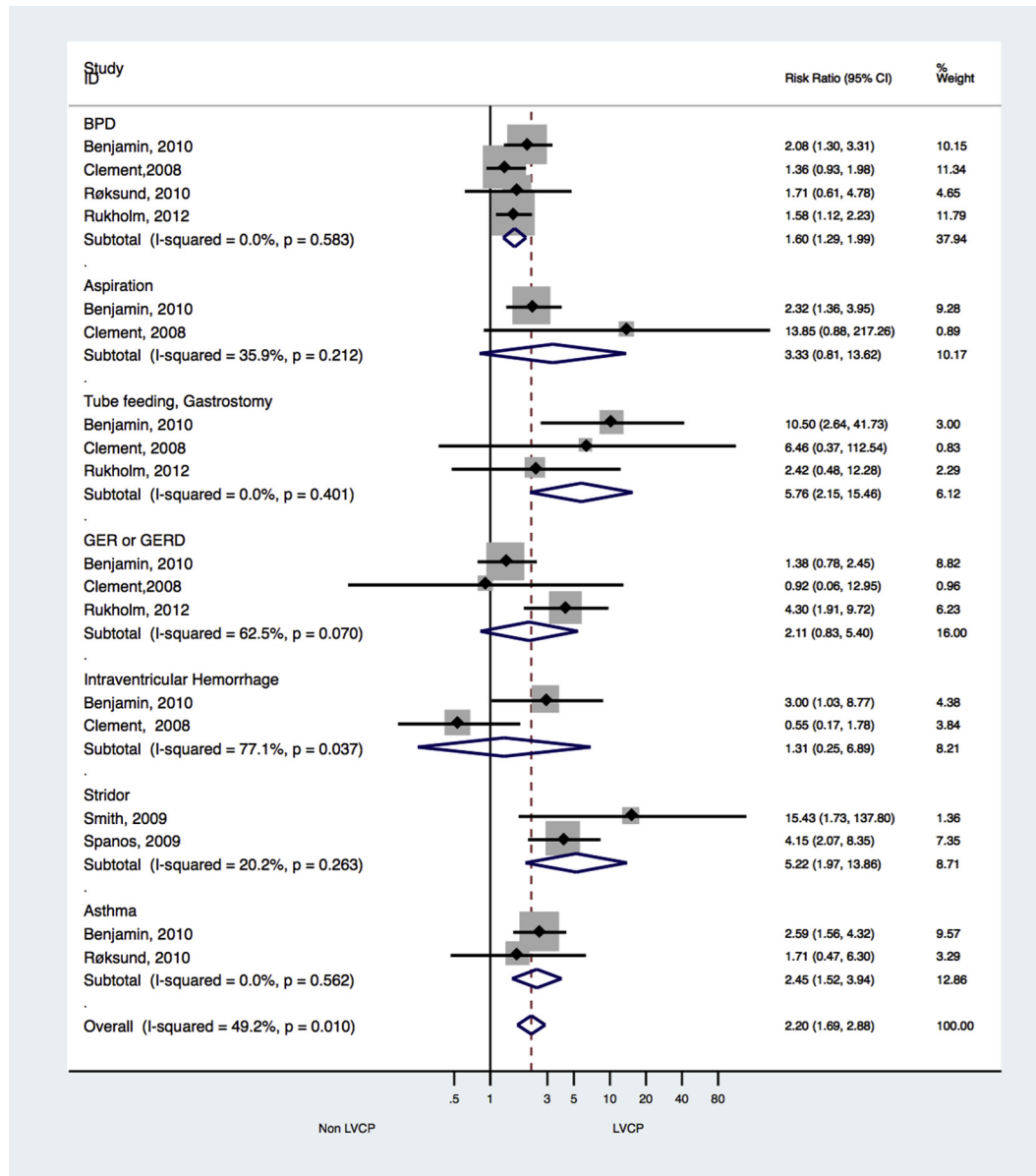
Fig. 7. Individual studies and overall risk of consequences and/or comorbidities of LVCP.

tion. As five of six studies [11,17,22,23,35,37] used in Strychowsky's analysis were included in our analysis, congruent results are not surprising. We chose to exclude one study [22] from our sub analysis because only symptomatic infants were examined via laryngoscopy. This exclusion contributed to a slightly lower weighted pooled proportion of LVCP in our study (32% vs. 39%). This variability in reported incidence may be due to the transient nature of LVCP symptoms in infants. It seems clear that the methods of assessment significantly impact incidence reports, and that LVCP may be undetected unless routinely looked for via laryngoscopy [11,32,33,38,42]. In addition, some infants presenting with typical symptoms of LVCP, such as stridor and dysphonia, may not have LVCP when examined via laryngoscopy [11,22,37]. This stresses the point that symptom-based diagnosis of LVCP is not reliable, may cause misleading rates of postoperative LVCP incidence and also may lead to misdiagnoses and erroneous management of these infants.

Preoperative laryngoscopy was not performed in all but one study [15]. Considering that extremely premature infants referred to PDA surgery are critically ill and may require intubation before surgery [15,43,44], preoperative laryngoscopy may be difficult and unethical to perform [43,44]. Lack of preoperative assessment of the vocal cords may confuse the postoperative LVCP incidence rates, as other potential causes of LVCP among infants exists. For example, cases of idiopathic or neurological causes of LVCP have been reported among neonates [9,10,44]. Moreover, a large PDA can possibly compress the left recurrent laryngeal nerve and lead to injury [45]. In addition, findings of vocal cord paralysis would have been equally distributed between the right and left side should intubation have caused direct injury to the vocal cord. However, this was not the case in any of the included studies. Theoretically, one may speculate that a partial preoperative paralysis of the left recurrent laryngeal nerve due to a large pulsating PDA, or a partial paralysis of the left recurrent laryngeal nerve due to perioperative traction on the nerve, may lead to a transient immobilization of the left side of the larynx, and thus predispose the left side of the larynx to postoperative intubation trauma. However, this needs to be addressed in properly designed studies.
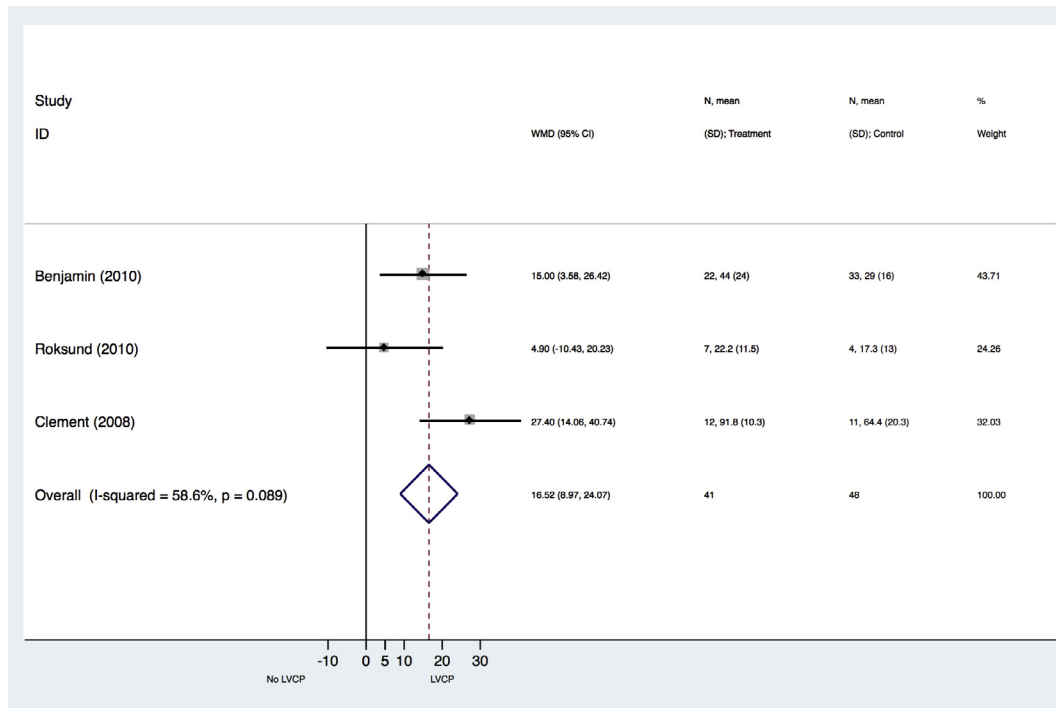
Fig. 8. Duration of ventilation (total number of days). Weighted mean difference between infants with and without LVCP.

Table 2
Additional analysis.

Study	Outcomes	LVCP	No LVCP	*p*-Value
Respiratory outcomes				
Spanos, 2009	Episodes of decreased O_2-saturation, N (%)	2/13 (15)	4/54 (7)	0.48
Roksund, 2010	Forced expiratory volume (FEV1), % of predicted	71.9%	83.3%	<0.05[*]
Roksund, 2010	Flow through middle half of forced vital capacity, % of predicted	51%	83%	<0.05[*]
Roksund, 2010	Peak expiratory flow, % of predicted, mean (95% CI)	76.4 (63–90)	102.5 (92–113)	>0.05
Roksund, 2010	Forced vital capacity, % of predicted, mean (95% CI)	99.1 (85–113)	98.0 (83–113)	>0.05
Roksund, 2010	Maximal oxygen uptake, % of reference, mean (95% CI)	96.2 (83–110)	96.3 (72–121)	>0.05
Laryngeal outcomes				
Roksund, 2010	Dysphonia, N (%)	6/7 (85.7)	1/4 (25.0)	0.07
Smith, 2009	Dysphonia, N (%)	9/14 (20.5)	8/72 (11)	<0.001[*]
Spanos, 2009	Dysphonia, N (%)	9/13 (69)	9/54 (17)	<0.001[*]
Nichols, 2014	Dysphonia, N (%)	51/66 (77.3)	–	
Nichols, 2014	Laryngomalacia, N (%)	26/66 (38)	–	
Nichols, 2014	Subglottic stenosis, N (%)	3/66 (5)	–	
Feeding outcomes				
Benjamin, 2010	Nissen fundoplication, N (%)	9/22 (41)	1/33 (3)	0.001[*]
Other outcomes				
Benjamin, 2010	Hospital stay (total days)	148.2	96.8	<0.001[*]
Benjamin, 2010	Neurodevelopmental IMPAIRMENT (18–22 months)	10/22 (56)	8/11 (36)	0.34
Benjamin, 2010	Intraventricular hemorrhage (grade 3 or 4), N (%)	8/22 (36)	4/33 (12)	0.05
Clement, 2008	Readmission within 12 months, N (%)	6/12 (50)	2/11 (18)	0.19
Nichols, 2014	Retinopathy of prematurity, N (%)	50/62 (81)	–	
Rukholm, 2012	Retinopathy of prematurity, N (%)	8/19 (42.1)	22/92 (23.3)	0.154
Rukholm, 2012	Sepsis, N (%)	14/19 (73.7)	36/92 (39.1)	0.010[*]
Roksund, 2010	Peak heart rate, beats per minute, mean (95% CI)	185.0 (178–183)	196.3 (188–206)	>0.05

[*] Marks significant difference (*p* < 0.05) between groups as reported in individual publications. Two exceptions are *p*-values for Dysphonia from Smith et al. (2009) and Roksund et al. (2010), as these values were calculated based on Odds Ratios by authors of this Systematical Review.

Differences in study design could also have impacted the between study variability in reported LVCP incidence. The three prospective studies [11,33,37] included in our analysis had a substantially lower incidence of LVCP compared to the two retrospective studies [23,35]. A possible explanation for this could be due to the fact that surgeons participating in prospective studies may be more cognizant of the risk of recurrent laryngeal nerve damage and therefore, more cautious during surgery. However, Carpes

et al. [44] described a *higher* odd of damaging the recurrent laryngeal nerve upon visualization of the nerve during surgery. This observation could imply that the laryngeal nerve is vulnerable to low impact trauma such as traction, and that efforts made to avoid damaging to the nerve could actually be harmful.

We found that a range of adverse outcomes or comorbidities were associated with LVCP. As several studies [23,32,33,37,38] have reported low rates (0–33%) of recovery, infants are thus left with a potential for life-long sequelae. Undetected LVCP that is confused with other medical conditions could theoretically lead to inappropriate and potentially harmful treatment choices. Infants with LVCP can present with symptoms such as apneas or increased work of breathing associated with stridor. Such symptoms might leave infants susceptible for prolonged hospital stay, and prolonged and possibly unnecessary mechanical ventilation in the misbelief that they suffer from lung disease [22,23,33,35]. In turn, such unnecessary treatment can complicate subsequent handling of the baby and also lead to acute and chronic pulmonary problems, e.g., BPD [43,46]. Early LVCP detection could theoretically allow use of less invasive ventilatory support, such as CPAP, and thus facilitate better airflow despite laryngeal obstruction.

In older children symptoms of LVCP have been confused with symptoms of asthma [35]. These children have been treated with medications instead of receiving treatment for their actual condition. Therefore, we propose that laryngoscopy should be performed before hospital discharge in infants who have undergone surgical PDA ligation.

Benefits versus disadvantages of surgical ligation of PDA have been debated in recent years [6,47–50]. Surgical ligation has been associated with a range of morbidities [11,23,51–54]. Extremely premature infants undergoing surgical PDA ligation are often the most vulnerable and at risk of a range of morbidities [55]. We can hardly study the consequences of PDA surgery and LVCP without facing the problem of selection bias or confounding by surgical indication as infants selected for surgical ligation may have a higher baseline risk for comorbidities [50]. We suggest that future studies prospectively enroll extremely premature infants undergoing PDA ligation and explore possible short and long-term consequences of LVCP. Future studies should also perform routinely pre- and postoperative laryngoscopy examinations, use matched controls, and try to control for selection bias.

Study limitations

Our study has several strengths including an exhaustive search, a rigorous protocol driven approach, and meta-analytical analyses of potentially important subgroups. The major limitation of this study, similar to many meta-analyses, lies in the data on which it was based; i.e., the wide heterogeneity and the varying approach between the included studies. However, we were able to explain some of this heterogeneity that could also be utilized to speculate over issues of clinical interest.

Conclusion

The pooled incidence of LVCP after PDA ligation in extremely premature infants was 9%, with a wide heterogeneity depending on the method used for LVCP assessment and study design. Unfortunately, routine laryngoscopy is rarely performed in relation to PDA ligation, preventing identification of all cases of PDA-related LVCP. A range of adverse outcomes and/or comorbidities were found to be associated with LVCP; however, the full picture of this still remains unknown due to lack of systematic follow-up studies.

Early recognition of LVCP seems to be of significant clinical value, which supports routine laryngoscopy performed after PDA ligation.

Contributors' statements

All authors contributed to conceptualization and design of the study, reviewed and revised the manuscript, approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ms. Engeseth performed the search, screening of titles, abstracts and full-text records, data abstraction, quality assessment, contributed to meta-analysis and drafted the initial manuscript.

Dr. Maeland performed titles and abstract screen of records.

Professor Røksund performed full-text screen of articles and contributed to data abstraction.

Dr. Olsen performed quality-assessment of articles.

Dr. Goode performed the meta-analysis and contributed to draft of the original manuscript.

Professor Halvorsen participated in quality assessment and as a clinical neonatologist he secured clinical relevance and interpretation of the findings.

Directions for future research

- Prospective multi-center cohort study including all infant born preterm undergoing PDA surgical closure to determine the incidence and risk factors of LVCP.
- Investigate the mechanisms of injury that leads to LVCP in infants born preterm exposed to surgical closure of PDA.
- Investigate clinical symptoms and outcomes of LVCP after surgical closure of PDA in infants born preterm with, both during their NICU hospitalization and later in life.
- Develop therapies aimed at alleviating symptoms and restoring laryngeal function in ex-preterm children with LVCP after surgical closure of PDA.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.prrv.2017.11.001.

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