Meta-Analysis of Risk Factors for Bronchopulmonary Dysplasia in Preterm Infants (Postprint)

Authors: Yu Zhumei, Liu Annuo, Xiao Juan, Tang Yuxia, Yu Li, Tong Huanhuan

Date: 2022-08-01T00:00:00+00:00

Abstract

Background Bronchopulmonary dysplasia (BPD) is the most common serious pulmonary disease in preterm infants, representing injury to the immature lung from multiple factors. Identifying risk factors for BPD is crucial for developing preventive strategies. Currently, there remains controversy regarding the risk factors for BPD, and few related systematic reviews have been conducted both domestically and internationally.

Objective To systematically analyze the risk factors for BPD occurrence in preterm infants.

Methods A computerized search was conducted for literature on risk factors for BPD in preterm infants in China National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Biomedical Literature Database (CBM), VIP, PubMed, Embase, Web of Science, and Cochrane Library, with the search period from database inception to October 2021. Statistical analysis was performed using RevMan 5.3 and Stata 15.1 software.

Results A total of 23 studies were included. The pooled OR (95% CI) results for each risk factor from meta-analysis were as follows: Prenatal factors: chorioamnionitis 1.46 (1.18, 1.80), gestational hypertension 1.26 (1.15, 1.37), premature rupture of membranes 1.18 (1.10, 1.26). Perinatal factors: low birth weight 0.79 (0.76, 0.83), low gestational age 0.80 (0.73, 0.87), SGA 2.64 (1.85, 3.77), endotracheal intubation in delivery room 2.50 (1.39, 4.50), 5-min Apgar score <7 2.47 (1.36, 4.47), male sex 1.49 (1.43, 1.55). Postnatal factors: mechanical ventilation >7 days 7.99 (4.47, 14.29), surfactant 3.46 (1.96, 6.11), RDS 3.40 (2.01, 5.75), postnatal steroid use 2.42 (1.93, 3.03), PDA 1.96 (1.38, 2.79), sepsis 1.82 (1.36, 2.44), NEC 1.62 (1.18, 2.22), mechanical ventilation 1.59 (1.28, 1.96).

Conclusion Chorioamnionitis, gestational hypertension, premature rupture of membranes, low birth weight, low gestational age, SGA, endotracheal intubation

in delivery room, 5-min Apgar score <7, male sex, mechanical ventilation >7 days, surfactant, RDS, postnatal steroid use, PDA, sepsis, NEC, and mechanical ventilation are risk factors for BPD occurrence in preterm infants. Medical staff should promptly identify and manage these related risk factors to prevent BPD in preterm infants.

Full Text

Meta-analysis of Risk Factors for Bronchopulmonary Dysplasia in Premature Infants

Yu Zhumei[12], Liu Annuo[1]*, Xiao Juan[2], Tang Yuxia[3], Yu Li[3], Tong Huanhuan[2]

[1]School of Nursing, Anhui Medical University, Hefei 230032, China
[2]Department of Neonatology, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, China
[3]Department of Pediatrics, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, China

Corresponding author: Liu Annuo, Professor; E-mail: w971002y@sohu.com

Funding: Pediatric Nursing Teaching Team (Project No.: 2020jxtd128)

Abstract

Background: Bronchopulmonary dysplasia (BPD) is the most common serious pulmonary disease in premature infants, representing injury to the immature lung from multiple factors. Identifying risk factors for BPD is crucial for developing prevention strategies. Current evidence regarding BPD risk factors remains controversial, and few relevant systematic reviews exist domestically or internationally.

Objective: To systematically analyze risk factors for BPD in premature infants.

Methods: We comprehensively searched Chinese databases (CNKI, Wanfang, CBM, VIP) and English databases (PubMed, Embase, Web of Science, Cochrane Library) for literature on BPD risk factors from inception to October 2021. Statistical analysis was performed using RevMan 5.3 and Stata 15.1 software.

Results: Twenty-three studies were included. The pooled odds ratios (95% CI) for each risk factor were:

Prenatal factors: chorioamnionitis 1.46 (1.18, 1.80), gestational hypertension 1.26 (1.15, 1.37), premature rupture of membranes 1.18 (1.10, 1.26).

Perinatal factors: low birth weight 0.79 (0.76, 0.83), low gestational age 0.80 (0.73, 0.87), SGA 2.64 (1.85, 3.77), delivery room intubation 2.50 (1.39, 4.50), 5-min Apgar score <7 2.47 (1.36, 4.47), male sex 1.49 (1.43, 1.55).

Postnatal factors: mechanical ventilation >7 days 7.99 (4.47, 14.29), surfactant 3.46 (1.96, 6.11), RDS 3.40 (2.01, 5.75), postnatal steroids 2.42 (1.93, 3.03), PDA 1.96 (1.38, 2.79), sepsis 1.82 (1.36, 2.44), NEC 1.62 (1.18, 2.22), mechanical ventilation 1.59 (1.28, 1.96).

Conclusion: Chorioamnionitis, gestational hypertension, premature rupture of membranes, low birth weight, low gestational age, SGA, delivery room intubation, 5-min Apgar score <7, male sex, mechanical ventilation >7 days, surfactant, RDS, postnatal steroids, PDA, sepsis, NEC, and mechanical ventilation are risk factors for BPD in premature infants. Healthcare providers should promptly identify and manage these risk factors to prevent BPD occurrence.

Keywords: premature infants; bronchopulmonary dysplasia; risk factors; systematic review; meta-analysis

---

According to WHO statistics, approximately 15 million infants are born preterm worldwide annually, with preterm complications being the leading cause of death among children under five years old. Bronchopulmonary dysplasia (BPD) is the most common complication in premature infants, resulting from the combined effects of multiple risk factors. With rapid advances in contemporary perinatal medicine and neonatal care technology, the survival rates of premature infants —particularly very preterm and extremely preterm infants—have significantly improved, leading to a global increase in BPD incidence. Reports indicate that BPD occurs in 10%-89% of extremely preterm infants worldwide each year. BPD not only increases respiratory morbidity, medication use, and readmission rates in premature infants but also causes adverse short-term and long-term outcomes such as neurodevelopmental impairment, severely affecting quality of life for years and imposing substantial economic and psychological burdens on families. Currently, no specific treatment for BPD exists, making it crucial to investigate its risk factors to fundamentally reduce its incidence. While many single-center studies on BPD risk factors have been conducted, multi-center studies offer broader case coverage, more representative samples, and greater generalizability. Therefore, this study collected published multi-center studies on BPD risk factors from domestic and international sources for meta-analysis to provide evidence for clinical prevention and management of BPD in premature infants.

1. Methods

1.1 Search Strategy

We systematically searched the Cochrane Library, PubMed, Embase, Web of Science, CNKI, Wanfang Database, CBM, and VIP for literature on

BPD risk factors from inception to October 2021. We used a combination of subject headings and free-text terms. Chinese search terms included: "premature infant/immature infant/low birth weight infant," "bronchopulmonary dysplasia/bronchopulmonary dysplasia/perinatal bronchopulmonary dysplasia/chronic lung disease of newborn," and "risk factor/high-risk factor/influencing factor/related factor/predictive factor." English search terms included: "Infant, Premature OR Premature OR Preterm Infants OR Infant, Low Birth Weight OR low birth weight infants" AND "bronchopulmonary dysplasia OR BPD OR chronic lung disease" AND "risk factor OR dangerous factors OR influencing OR relevant factors OR predictive factor." We also performed secondary searches of references from included studies to identify additional eligible research.

1.2 Inclusion Criteria

Studies were included if they: (1) enrolled premature infants with gestational age $ $32 weeks and/or birth weight $ $1500 g; (2) were multi-center observational studies, including case-control and cohort studies; (3) examined risk factors for BPD in premature infants published domestically or internationally; (4) had BPD occurrence as the outcome measure; and (5) provided clear BPD diagnostic criteria.

1.3 Exclusion Criteria

We excluded: (1) duplicate publications; (2) studies with incomplete data or where original data could not be obtained even after contacting authors; and (3) studies not published in Chinese or English.

1.4 Literature Screening and Data Extraction

Two researchers independently screened literature, extracted data, and cross-checked results. Discrepancies were resolved through discussion or consultation with a third researcher. Screening involved reviewing titles and abstracts to exclude obviously irrelevant studies, followed by full-text review for final inclusion. For unreported but critical information, we contacted original study authors when possible. Extracted data included: (1) basic study information (first author, publication year, country, number of centers); and (2) baseline characteristics and influencing factors (study type, sample size, diagnostic criteria, and influencing factors).

1.5 Quality Assessment

Two researchers independently used the Newcastle-Ottawa Scale (NOS) for observational studies to evaluate included literature and cross-checked results. Disagreements were resolved through consultation with a third researcher. The NOS comprises three domains: selection (0-4 points), comparability (0-2 points),

and outcome assessment (0-3 points), with a total of 8 items and a maximum score of 9. Studies scoring $ $7 were considered high quality.

1.6 Statistical Analysis

We used RevMan 5.3 software for statistical analysis. The odds ratio (OR) was used as the effect measure, with 95% confidence intervals (95% CI) provided. Heterogeneity among studies was assessed using I^2. If $P > 0.1$ and $I^2 < 50\%$, indicating low heterogeneity, a fixed-effects model was used; otherwise, a random-effects model was applied, with sensitivity analysis performed to test result stability. Stata 15.1 software was used with Begg' s and Egger' s tests to quantitatively assess publication bias.

2. Results

2.1 Literature Search Results

The initial search yielded 9,948 articles. After removing 3,501 duplicates, 6,329 articles were excluded based on titles and abstracts according to inclusion and exclusion criteria. The remaining 118 articles underwent full-text review, resulting in final inclusion of 23 studies [7-29]. The literature screening flowchart is shown in Figure 1 [Figure 1: see original paper].

2.2 Characteristics and Quality of Included Studies

All 23 included studies were multi-center studies published between 1998-2021, including 21 cohort studies [7-15, 17-24, 26-29] and 2 case-control studies [16, 25]. A total of 106,557 premature infants were screened, with 33,508 BPD cases. All 23 studies had NOS scores $ $7, indicating overall high quality. Details are provided in Table 1 .

2.3 Meta-analysis Results

Twenty-three studies were included, with meta-analysis performed on 21 risk factors examined in $ $2 studies. Results showed that 17 risk factors had statistically significant pooled effect sizes ($P < 0.05$): chorioamnionitis, gestational hypertension, premature rupture of membranes, low birth weight, low gestational age, small for gestational age (SGA), delivery room intubation, 5-min Apgar score <7, male sex, mechanical ventilation >7 days, surfactant, respiratory distress syndrome (RDS), postnatal steroids, patent ductus arteriosus (PDA), sepsis, necrotizing enterocolitis (NEC), and mechanical ventilation. Four risk factors showed no significant association: antenatal steroids, preeclampsia, gestational diabetes, and retinopathy of prematurity (ROP). Detailed results are categorized and ranked by strength in Table 2 , with forest plots shown in Figure 2 [Figure 2: see original paper].

2.4 Sensitivity Analysis

Sensitivity analysis was performed for each risk factor. Results showed minimal change in effect size before and after changing models, indicating high stability and reliability of pooled results across both models. Details are provided in Table 3 .

2.5 Publication Bias Assessment

Begg' s and Egger' s tests were used to assess publication bias for risk factors with $ $5 included studies. Results showed no statistically significant differences ($P > 0.05$), suggesting low likelihood of publication bias. Details are provided in Table 4 .

3. Discussion

3.1 Prenatal Factors

Among six examined prenatal risk factors, maternal chorioamnionitis, gestational hypertension, and premature rupture of membranes were identified as major risk factors for BPD. The relationship between chorioamnionitis and increased BPD risk remains controversial. Our findings suggest chorioamnionitis is associated with increased BPD risk. The potential mechanism involves accelerated functional lung maturation following exposure to chorioamnionitis, which simultaneously increases the premature lung' s susceptibility to postnatal injury. Research indicates that placental inflammatory responses interact with vascular pathology and BPD pathogenesis. Intrauterine inflammation alters fetal lung development, with inflammation-mediated pulmonary vascular remodeling affecting contractile function, increasing pulmonary vascular resistance in persistent fetal circulation, and ultimately leading to BPD. Growing evidence suggests that pulmonary vessels promote alveolar growth and maintain alveolar structure after birth. Maternal factors that disrupt or impede angiogenesis may cause impaired pulmonary vascular development and alveolarization, thereby increasing BPD incidence. Maternal hypertension is associated with lower levels of vascular growth factors, which may explain its relationship with BPD. This study found BPD associated with premature rupture of membranes, likely due to reduced amniotic fluid, increased infection, and inflammatory responses that impair lung development and increase BPD incidence.

3.2 Perinatal Factors

Our results identified low birth weight, low gestational age, SGA, delivery room intubation, 5-min Apgar score <7, and male sex as major risk factors. Birth weight and gestational age are the strongest predictors of BPD, with incidence and severity inversely proportional to both. Research shows that among infants with BPD, nearly 95% are very low birth weight infants and nearly 80% are born at 22-24 weeks' gestation. When premature lung development is in the canalicu-

lar or saccular stage, it is vulnerable to oxidative stress injury, with lung immaturity being a key factor in BPD development. Therefore, strengthening perinatal care to prolong gestational age is crucial for short-term outcomes and long-term prognosis in very preterm and very low birth weight infants. SGA' s impact on BPD development also appears related to inhibited lung growth, potentially involving altered pulmonary angiogenesis. Rocha et al. analyzed data from 11 Portuguese tertiary neonatal centers on infants born at 24-30 weeks' gestation and found, after adjusting for other BPD risk factors, a significant association between SGA and BPD [OR=5.2, 95%CI:(1.46, 18.58), P<0.01], consistent with our findings. Delivery room intubation was associated with increased BPD risk. Lung injury may occur during resuscitation; inadequate mask positive pressure ventilation in the critical first minutes after birth can lead to persistent hypoxia and bradycardia requiring emergency intubation. Studies show that centers with high delivery room intubation rates tend to have higher ventilation rates and BPD incidence, making it essential to strengthen delivery room resuscitation strategies and reduce intubation rates. A 5-min Apgar score <7 was a risk factor, likely because infants with low scores experience birth asphyxia and inadequate systemic organ perfusion, leading to increased pulmonary vascular resistance, reduced pulmonary blood flow, pulmonary vascular remodeling, and impaired lung development. Current research indicates male infants have higher BPD risk, possibly because male fetuses produce dihydrotestosterone that damages surfactant production, leading to RDS and increased BPD incidence.

3.3 Postnatal Factors

Our findings indicate that postnatal therapeutic measures including mechanical ventilation, mechanical ventilation >7 days, surfactant, postnatal steroids, and complications including RDS, PDA, sepsis, and NEC are major risk factors. Mechanical ventilation was a major risk factor with a clear dose-response effect, with mechanical ventilation >7 days showing a particularly strong association [OR=5.2, 95%CI:(3.634, 11.804), P<0.01]. Experimental evidence demonstrates clear links between mechanical ventilation-induced barotrauma and volutrauma and pathological structural and inflammatory changes in animal lungs that mimic human BPD. Prolonged mechanical ventilation not only disrupts lung development causing alveolar arrest but also mediates inflammatory lung injury, leading to pulmonary infection that further increases BPD risk in a vicious cycle. Therefore, actively preventing and controlling pulmonary infections while reducing and shortening mechanical ventilation is crucial. Pulmonary surfactant is a complex mixture of phospholipids and surfactant proteins, with lipid and protein synthesis depending on type II alveolar cell differentiation occurring in late gestation. Incomplete type II cell differentiation leads to surfactant deficiency and RDS in premature infants. While exogenous surfactant improves survival, it also increases the number of infants at risk for BPD. Our results suggest postnatal steroid treatment actually increases BPD development, possibly because steroids are administered only to the most severely ill infants. Although steroids may temporarily improve lung function early in lung dis-

ease, long-term pulmonary outcomes may worsen. However, this interpretation should be cautious due to the small number of included studies. "Classic BPD" occurs primarily in infants with RDS, mainly due to surfactant deficiency requiring early mechanical ventilation or oxygen therapy in immature lungs, leading to oxidative stress injury, pulmonary vascular remodeling, and pulmonary fibrosis, ultimately progressing to BPD. The mechanism for oxygen-induced ductal constriction is immature in premature infants, and persistent ductal patency is closely associated with BPD development, with longer PDA duration increasing BPD risk. Systemic inflammation from sepsis interacts with lung development, causing alveolar hypoplasia and pulmonary vascular malformation—the histological features of BPD—with this association well-established. Jung et al. conducted a prospective cohort study identifying sepsis as a high-risk factor for BPD in extremely low birth weight infants, particularly late-onset sepsis with multiple episodes or fungal infection. Therefore, infection control is key for BPD prevention, requiring strict hand hygiene and aseptic technique. NEC increased BPD risk, likely because subsequent inflammation from intestinal ischemia and necrosis causes lung injury, though more large-sample studies are needed to verify this conclusion due to limited included literature.

3.4 Limitations and Future Directions

This study has several limitations: (1) Large variations in sample sizes and outcome definitions across included studies created some heterogeneity; (2) Excluding single-center studies due to their low generalizability and high bias risk may have limited comprehensiveness; (3) Small numbers of included studies for some exposure factors limit the analysis. Therefore, future multi-center studies are needed to further clarify relationships between various risk factors and BPD.

Conclusion

This meta-analysis identified the following major risk factors for BPD in premature infants: prenatal factors (chorioamnionitis, gestational hypertension, premature rupture of membranes); perinatal factors (low birth weight, low gestational age, SGA, delivery room intubation, 5-min Apgar score <7, male sex); and postnatal factors (mechanical ventilation >7 days, surfactant, RDS, postnatal steroids, PDA, sepsis, NEC, mechanical ventilation). BPD is a chronic lung disease in premature infants resulting from multiple factors, with severe short-term and long-term sequelae and mortality in very low birth weight infants. Healthcare providers should identify high-risk infants and implement early prevention and control measures targeting these risk factors to reduce BPD incidence and improve outcomes.

Author Contributions

Yu Zhumei was responsible for manuscript writing and takes responsibility for the article; Tang Yuxia and Yu Li were responsible for conception, design, fea-

sibility analysis, and manuscript revision; Xiao Juan and Tong Huanhuan were responsible for data collection, extraction, analysis, and quality assessment; Liu Annuo was responsible for final review and overall quality control.

Conflict of Interest

This article has no conflict of interest.

References

[1] World Health Organization: Preterm Birth. https://www.who.int/news-room/fact-sheets/detail/preterm-birth.

[2] Islam J Y, Keller R L, Aschner J L, et al. Understanding the Short- and Long-Term Respiratory Outcomes of Prematurity and Bronchopulmonary Dysplasia [J]. American Journal of Respiratory and Critical Care Medicine, 2015, 192(2): 134-56. DOI:10.1164/rccm.201412-2142PP.

[3] Stoll B J, Hansen N I, Bell E F, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012 [J]. Jama, 2015. DOI:10.1001/jama.2015.10244.

[4] Siffel C, Kistler K D, Lewis J F M, et al. Global incidence of bronchopulmonary dysplasia among extremely preterm infants: a systematic literature review [J]. Journal of Maternal-Fetal & Neonatal Medicine, 2021, 34(11): 1721-31. DOI:10.1080/14767058.2019.1646240.

[5] Thebaud B, Goss K N, Laughon M, et al. Bronchopulmonary dysplasia [J]. Nat Rev Dis Primers, 2019, 5(1): 78. DOI:10.1038/s41572-019-0127-7.

[6] Mandell Erica W, Kratimenos P, Abman Steven H, et al. Drugs for the Prevention and Treatment of Bronchopulmonary Dysplasia [J]. Clinics in Perinatology, 2019, 46(2): 291-310. DOI:10.1016/j.clp.2019.02.011.

[7] Abele-Horn M, Genzel-Boroviczeny O, Uhlig T, et al. Ureaplasma urealyticum colonization and bronchopulmonary dysplasia: a comparative prospective multicentre study [J]. European journal of pediatrics, 1998, 157(12): 1004-11. DOI:10.1007/s004310050987.

[8] Marshall D, Kotelchuck M, Te, Bose C, et al. Risk Factors for Chronic Lung Disease in the Surfactant Era: A North Carolina Population-based Study of Very Low Birth Weight Infants [J]. Pediatrics, 1999, 104(6): 1345-50. DOI:10.1016/j.jallcom.2006.10.053.

[9] Pi-Ying T, Chyong-Hsin H, Han-Yang H, et al. Risk Factors for Chronic Lung Disease in Very Low Birth Weight Infants: A Five-Year Multicenter Study in Taiwan [J]. Clinical Neonatology, 2005, 12(1): DOI:10.7098/CN.200507.0013.

[10] Tapia J L, Agost D, Alegria A, et al. Bronchopulmonary dysplasia: incidence, risk factors and resource utilization in a population of South Ameri-

can very low birth weight infants [J]. Jornal de pediatria, 2006, 82(1): 15-20. DOI:10.1590/S0021-75572006000100005.

[11] Henderson-Smart D J, Hutchinson J L, Donoghue D A, et al. Prenatal predictors of chronic lung disease in very preterm infants [J]. ARCHIVES OF DISEASE IN CHILDHOOD-FETAL AND NEONATAL EDITION, 2006, 91(1): 40-5. DOI:10.1136/adc.2005.0722.

[12] Guimaraes H, Rocha G, Vasconcellos G, et al. Risk factors for bronchopulmonary dysplasia in five Portuguese neonatal intensive care units [J]. Rev Port Pneumol, 2010, 16(3): 419-30. DOI:10.1016/s0873-2159(15)30039-8.

[13] Farstad T, Bratlid D, Medbo S, et al. Bronchopulmonary dysplasia - prevalence, severity and predictive factors in a national cohort of extremely premature infants [J]. Acta Paediatr, 2011, 100(1): 53-8. DOI:10.1111/j.1651-2227.2010.01959.x.

[14] Gortner L, Misselwitz B, Milligan D, et al. Rates of Bronchopulmonary Dysplasia in Very Preterm Neonates in Europe: Results from the MOSAIC Cohort [J]. Neonatology, 2011, 99(2): 112-7. DOI:10.1159/000313024.

[15] Gagliardi L, Bellu R, Lista G, et al. Do differences in delivery room intubation explain different rates of bronchopulmonary dysplasia between hospitals? [J]. Archives of Disease in Childhood Fetal, 2011, 96(1): F30. DOI:10.1136/adc.2010.183905.

[16] Rojas M X, Rojas M A, Lozano J M, et al. Regional variation on rates of bronchopulmonary dysplasia and associated risk factors [J]. ISRN pediatrics, 2012, 2012: 685151. DOI:10.5402/2012/685151.

[17] Yen T A, Yang H I, Hsieh W S, et al. Preeclampsia and the Risk of Bronchopulmonary Dysplasia in VLBW Infants: A Population Based Study [J]. PLoS One, 2013, 8(9): 7. DOI:10.1371/journal.pone.0075168.

[18] Klinger G, Sokolover N, Boyko V, et al. Perinatal risk factors for bronchopulmonary dysplasia in a national cohort of very-low-birthweight infants [J]. Am J Obstet Gynecol, 2013, 208(2): 9. DOI:10.1016/j.ajog.2012.10.876.

[19] N. V, Tolia, Karna, et al. The Effect of the National Shortage of Vitamin A on Death or Chronic Lung Disease in Extremely Low-Birth-Weight Infants [J]. JAMA Pediatrics, 2014. DOI:10.1001/jamapediatrics.2014.1353.

[20] Lapcharoensap W, Gage S C, Kan P, et al. Hospital Variation and Risk Factors for Bronchopulmonary Dysplasia in a Population-Based Cohort [J]. Jama Pediatr, 2015, 169(2): e143676. DOI:10.1001/jamapediatrics.2014.3676.

[21] Rocha G M, Lima F F D, Machado A P, et al. Hypertensive Disorders during Pregnancy and Risk of Bronchopulmonary Dysplasia in Very Preterm Infants [J]. Thieme Publishing, 2019, (02). DOI:10.1055/S-0038-1667174.

[22] Valenzuela-Stutman D, Marshall G, Tapia J L, et al. Bronchopulmonary dysplasia: risk prediction models for very-low-birth-weight infants [J]. Journal

of Perinatology, 2019, 39(9): 1275-81. DOI:10.1038/s41372-019-0430-x.

[23] Jung Y H, Park Y, Kim B I, et al. Length at birth z-score is inversely associated with an increased risk of bronchopulmonary dysplasia or death in preterm infants born before 32 gestational weeks: A nationwide cohort study [J]. PLoS One, 2019, 14(5): 12. DOI:10.1371/journal.pone.0217739.

[24] Jung E, Lee B S. Late-Onset Sepsis as a Risk Factor for Bronchopulmonary Dysplasia in Extremely Low Birth Weight Infants: A Nationwide Cohort Study [J]. Sci Rep, 2019, 9: 7. DOI:10.1038/s41598-019-51617-8.

[25] 江苏省新生儿重症监护病房母乳质量改进临床研究协作组. 多中心回顾性分析极低及超低出生体重儿支气管肺发育不良的临床特点及高危因素 [J]. 中华儿科杂志, 2019, 57(01): 33-9. DOI:10.3760/cma.j.issn.0578-1310.2019.01.007.

[26] Shin S H, Shin S H, Kim S H, et al. The Association of Pregnancy-induced Hypertension with Bronchopulmonary Dysplasia - A Retrospective Study Based on the Korean Neonatal Network database [J]. Sci Rep, 2020, 10(1): 6. DOI:10.1038/s41598-020-62595-7.

[27] Nakashima T, Inoue H, Sakemi Y, et al. Trends in Bronchopulmonary Dysplasia Among Extremely Preterm Infants in Japan, 2003-2016 [J]. J Pediatr, 2021, 230: 119-+. DOI:10.1016/j.jpeds.2020.11.041.

[28] Faleh I E, Faouzi M, Adams M, et al. Bronchopulmonary dysplasia: a predictive scoring system for very low birth weight infants. A diagnostic accuracy study with prospective data collection [J]. European Journal of Pediatrics, 2021, 180(8): 2453-61. DOI:10.1007/s00431-021-04054-2.

[29] Li S J, Feng Q, Tian X Y, et al. Delivery room resuscitation and short-term outcomes of extremely preterm and extremely low birth weight infants: a multicenter survey in North China [J]. Chin Med J, 2021, 134(13): 1561-8. DOI:10.1097/cm9.0000000000001499.

[30] Northway W H, Rosan R C, Porter D Y. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia [J]. New England Journal of Medicine, 1967, 276(7): 357. DOI:10.1056/NEJM196702162760701.

[31] Jobe A H, Bancalari E. Bronchopulmonary dysplasia [J]. American Journal of Respiratory & Critical Care Medicine, 2001, 163(7): 1723-9. DOI:10.1164/ajrccm.163.7.2011060.

[32] Higgins R D, Jobe A H, Koso-Thomas M, et al. Bronchopulmonary Dysplasia: Executive Summary of a Workshop [J]. J Pediatr, 2018, 197: 300-8. DOI:10.1016/j.jpeds.2018.01.043.

[33] Villamor-Martinez E, Alvarez-Fuente M, Ghaazi A M T, et al. Association of Chorioamnionitis With Bronchopulmonary Dysplasia Among Preterm Infants [J]. Jama Network Open, 2019, 2(11). DOI:10.1001/jamanetworkopen.2019.14611.

[34] Hartling L, Liang Y, Lacaze-Masmonteil T. Chorioamnionitis as a risk factor for bronchopulmonary dysplasia: a systematic review and meta-analysis [J]. Archives of Disease in Childhood -Fetal & Neonatal Edition, 2012, 97(1): F8. DOI:10.1136/adc.2010.210187.

[35] 原晋芳, 韩彤妍. 绒毛膜羊膜炎与早产儿肺部疾病研究进展 [J]. 中华实用儿科临床杂志, 2019, 34(10): 3. DOI:10.3760/cma.j.issn.2095-428X.2019.10.018.

[36] Thébaud B, Abman S H. Bronchopulmonary dysplasia: where have all the vessels gone? Roles of angiogenic growth factors in chronic lung disease [J]. American Journal of Respiratory and Critical Care Medicine, 2007, 175(10): 978-85. DOI:10.1164/rccm.200611-1660PP.

[37] Lignelli E, Palumbo F, Myti D, et al. Recent advances in our understanding of the mechanisms of lung alveolarization and bronchopulmonary dysplasia [J]. AJP Lung Cellular and Molecular Physiology, 2019, 317(6). DOI:10.1152/ajplung.00369.2019.

[38] Rozance P J, Seedorf G J, Brown A, et al. Intrauterine growth restriction decreases pulmonary alveolar and vessel growth and causes pulmonary artery endothelial cell dysfunction in vitro in fetal sheep [J]. Am J Physiol-Lung Cell Mol Physiol, 2011, 301(6): L860-L71. DOI:10.1152/ajplung.00197.2011.

[39] Rocha G, De Lima F F, Machado A P, et al. Small gestational age very preterm infants present a higher risk of developing bronchopulmonary dysplasia [J]. Journal of neonatal-perinatal medicine, 2019, 12(4): 419-27. DOI:10.3233/npm-180129.

[40] Kakkilaya V, Jubran I, Mashruwala V, et al. Quality Improvement Project to Decrease Delivery Room Intubations in Preterm Infants [J]. Pediatrics, 2019, 143(2): 10. DOI:10.1542/peds.2018-0201.

[41] Cai H, Jiang L, Liu Y, et al. Development and verification prediction model of bronchopulmonary dysplasia in very low birth weight infants [J]. Translational pediatrics, 2021, 10(10): 2533-43. DOI:10.21037/tp-21-445.

[42] Silveyra P, Fuentes N, Bauza D R. Sex and Gender Differences in Lung Disease [J]. Advances in Experimental Medicine and Biology, 2021. DOI:10.1007/978-3-030-68748-9_{14}.

[43] Mokres L M, Parai K, Hilgendorff A, et al. Prolonged mechanical ventilation with air induces apoptosis and causes failure of alveolar septation and angiogenesis in lungs of newborn mice [J]. Ajp Lung Cellular & Molecular Physiology, 2010, 298(1): L23-35. DOI:10.1152/ajplung.00251.2009.

[44] Whitsett J A, Wert S E, Weaver T E. Diseases of Pulmonary Surfactant Homeostasis [J]. Annual Review of Pathology, 2015, 10(1): 371-93. DOI:10.1146/annurev-pathol-012513-104644.

[45] Clyman R I, Hills N K, Liebowitz M, et al. Relationship between Duration of Infant Exposure to a Moderate-to-Large Patent Ductus Arteriosus Shunt and

the Risk of Developing Bronchopulmonary Dysplasia or Death Before 36 Weeks [J]. American Journal of Perinatology, 2020, 37(02): 216-23. DOI:10.1055/s-0039-1697672.

Figure 1 [**Figure 1: see original paper**] Flowchart of literature search

Figure 2 [**Figure 2: see original paper**] Forest plot of risk factors for bronchopulmonary dysplasia in premature infants

Note: 1. Chorioamnionitis; 2. Gestational hypertension; 3. Premature rupture of membranes; 4. Antenatal steroids; 5. Preeclampsia; 6. Gestational diabetes; 7. Low birth weight; 8. Low gestational age; 9. SGA; 10. Delivery room intubation; 11. 5-min Apgar score <7; 12. Male sex; 13. Mechanical ventilation >7 days; 14. Surfactant; 15. RDS; 16. Postnatal steroids; 17. PDA; 18. Sepsis; 19. NEC; 20. Mechanical ventilation; 21. ROP

```
Study or SubgroupAbele-Horn等 1998Shin等 2020Nakashima等 2021Total (95% CI)Heterogeneity: Ta

Study or SubgroupGortner等 2011Klinger等 2013Lapcharoensap等 2015Total (95% CI)Heterogeneity

Study or SubgroupXimena等 2012Lapcharoensap等 2015Total (95% CI)Heterogeneity: Chi$^{2}$ = (

Study or SubgroupStutman等 2019Li等 2021Total (95% CI)Heterogeneity: Tau$^{2}$ = 3.95; Chi$^

Study or SubgroupYen等 2013Rocha等 2019Total (95% CI)Heterogeneity: Tau$^{2}$ = 1.41; Chi$^{

Study or SubgroupLapcharoensap等 2015Rocha等 2019Total (95% CI)Heterogeneity: Tau$^{2}$ = 0.

Study or SubgroupMarshall等 1999Tai等 2005Guimarães等 2010Yen等 2013Total (95% CI)Heterogene

Study or SubgroupTai等 2005Yen等 2013Tolia等 2014Shin等 2020Total (95% CI)Heterogeneity: Tau

Study or SubgroupGortner等 2011Gagliardi等 2011Klinger等 2013Yen等 2013Lapcharoensap等 2015S

Study or SubgroupGagliardi等 2011Stutman等 2019Li等 2021Total (95% CI)Heterogeneity: Tau$^{2

Study or SubgroupAbele-Horn等 1998Marshall等 1999Tapia等 2006Farstad等 2011Stutman等 2019Fal

Study or SubgroupAbele-Horn等 1998Guimarães等 2010Yen等 2013Stutman等 2019Jung等 2019韩树萍等

Study or SubgroupAbele-Horn等 1998Farstad等 2011Euiseok等 2019Total (95% CI)Heterogeneity: C

Study or SubgroupTai等 2005Tapia等 2006Farstad等 2011Ximena等 2012Yen等 2013Stutman等 2019Eu

Study or SubgroupAbele-Horn等 1998Tai等 2005Tapia等 2006Guimarães等 2010Gagliardi等 2011Xime
```

Study or SubgroupTapia等 2006Stutman等 2019Total (95% CI)Heterogeneity: Tau^{2} = 0.04; Ch

Study or SubgroupAbele-Horn等 1998Marshall等 1999Tapia等 2006Ximena等 2012Tolia等 2014韩树萍

Study or SubgroupGuimarães等 2010Euiseok等 2019Total (95% CI)Heterogeneity: Tau^{2} = 0.22

Note: Figure translations are in progress. See original paper for figures.