BMJ Open

Severe bronchopulmonary dysplasia in extremely premature infants: a scoping review protocol for identifying risk factors

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To cite: Kato S, Ito M, Saito M, *et al*. Severe bronchopulmonary dysplasia in extremely premature infants: a scoping review protocol for identifying risk factors. *BMJ Open* 2022;**12**:e062192. doi:10.1136/bmjopen-2022-062192

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-062192).

Received 21 February 2022
Accepted 20 April 2022

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ABSTRACT

Introduction The remarkable improvement in the long-term prognosis of extremely premature infants has led to an increase in the number of cases of bronchopulmonary dysplasia (BPD). BPD affects pulmonary function and developmental outcomes, resulting in high chronic health burdens for infants and their families over the years. Therefore, identifying its risk factors in the early period of life and exploring better prophylactics and treatment strategies are important.

The objectives of our scoping review are to screen available evidence, identify perinatal risk factors involved in the development and severity of BPD and devise a novel disease classification system that can predict long-term prognosis.

Methods and analysis Eligibility criteria are as follows: articles published from 2002 to 2021; studies conducted in developed countries; articles written in English (PubMed) or Japanese (Ichushi); randomised controlled trials, prospective/retrospective cohort studies or case-control studies; extremely premature infants born before 28 weeks of gestational age; and articles in which endpoint was severe BPD as classified by the National Institute of Child Health and Human Development.

We will screen the titles and abstracts of studies identified by independent reviewers using the population-concept-context framework. After a full-text review and data charting, we will provide the perinatal risk factors for severe BPD along with the risk ratio or odds ratio, 95% confidence interval and p values.

Ethics and dissemination Institutional review board approval is not required due to the nature of the study. The results of this review will be disseminated through peer-reviewed publications and presentations at relevant conferences.

Protocol V.1, 22 September 2021

Trial registration number UMIN000045529.

Strengths and limitations of this study

⇒ The present scoping review includes Japanese literature that has contributed significantly in improving our understanding of the pathophysiology of bronchopulmonary dysplasia, which are not yet known to most neonatologists worldwide.
⇒ This review will follow the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping reviews, ensuring transparent process.
⇒ Stakeholders and experts will be consulted throughout the review process.
⇒ A quality assessment of the articles included in the scoping review will not be performed as it is outside of the framework of this scoping review.

INTRODUCTION

Rationale

Bronchopulmonary dysplasia (BPD) is one of the most important chronic morbidities associated with prematurity.[1 2] BPD requires prolonged respiratory support and is a cause of airway hypersensitivity[3] and obstructive pulmonary disease.[4] This leads to an increased incidence of rehospitalisation,[5] neurodevelopmental impairment[6] and pulmonary hypertension.[7–9] These events result in high chronic health burdens for infants and their families over the years.[8] Due to significant improvement in the long-term prognosis of extremely premature infants,[10] there is now an increase in BPD cases. Identifying the risk factors for BPD in these premature infants and exploring better prophylactics and treatment strategies is important to prevent deterioration of health and to avoid serious sequelae.

Since BPD affects not only pulmonary function but also developmental outcomes, a classification that can predict long-term prognosis is required. The BPD classification, proposed by the National Institute of Child Health and Human Development (NICHD) in 2001,[11] which is based on clinical symptoms and treatment, has been widely used. However, the association between severity classified by the NICHD classification and infants' long-term prognosis has not been well determined,[12]

partly because the NICHD classification is consensus based. In Japan, a BPD classification based on aetiology and chest X-ray appearance was established in 1992.[13] An association between the Japanese classification and the long-term outcome has been reported,[14] although to date, it has been popular only in Japan.[15] We expect that unknown factors might fill the gaps in BPD definitions by incorporating the NICHD classification and the Japanese classification. Furthermore, since the introduction of antenatal corticosteroid and surfactant replacement therapy, the phenotype of BPD has changed,[16] and more premature newborns are managed with non-invasive positive pressure ventilation.[17 18] New modalities of respiratory support, such as using a high-flow nasal cannula, have also become popular.[19] In this 'new BPD' era, the classification of BPD also needs to be revised, to better reflect changes in these phenotypes and management.

Objectives

Taken together, we hope to develop a new BPD classification based on our original classification, which is internationally acceptable. Therefore, the objective of this scoping review is to screen available evidence and identify perinatal risk factors involved in the development and severity of BPD and to establish a novel disease classification for BPD, which can be useful in predicting long-term prognosis.

METHODS AND ANALYSIS

Eligibility criteria

Articles that meet the following eligibility criteria will be included: published between January 2002 and August 2021; studies conducted in developed countries; articles written in English or Japanese; randomised controlled trials, prospective/retrospective cohort studies or case-control studies; involved participants who were extremely premature infants born before 28 weeks of gestational age; and in which the endpoint was severe BPD classified by the NICHD definition. We will exclude descriptive research design studies as well as animal model and in vitro studies. We will also exclude studies that evaluated congenital airway diseases such as diaphragmatic hernia and congenital pulmonary airway malformations. This will enable us to restrict the objectives to BPD, which is, naturally, prematurity related. Protocols (a type of publication) will also be excluded from the analysis. We will omit studies with less than 500 participants to ensure the quality of literature included in this scoping review. In addition, we will focus more on the latest literature to reflect changes in pathophysiology and treatment of severe BPD.

Literature search

The search strategy for PubMed and a Japanese database 'Ichushi' is shown in the online supplemental appendix to identify eligible studies with the assistance of an expert librarian. We considered it important to include the Japanese database because considerable literature on the pathogenesis, risk factors, treatment and prognosis of BPD has been published in Japanese. The Ichusi database also contains many publications that have contributed to the establishment of the Japanese BPD classification. A search was conducted in October 2021. The final search results were imported into Endnote, and duplicates were removed. The database search returned 7954 studies. Of these, 4925 records were excluded due to duplication and prespecified conditions, as defined above.

Selection of sources of evidence

We will screen the titles and abstracts of the studies identified in the initial search by independent reviewers (SK, MI, MS and NM), using the population-concept-context framework (table 1) to determine which articles meet the inclusion criteria.[20]

We will subsequently conduct a full-text review of potentially relevant articles. Disagreements among the reviewers will be discussed and selection will be decided by consensus. The reference lists of the included articles will be screened for primary studies that may have been missed by the search strategy. After a full-text review, data will be extracted from all selected studies, including risk factors for severe BPD, such as chorioamnionitis, being small for gestational age, and bubbly and cystic appearance of the lungs on chest X-ray. The study selection process will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Table 1 PCC framework of this scoping review

Population	Extremely premature infants born before 28 weeks of gestational age
Concept	Identifying risk factors associated with severe BPD classified by the NICHD definition
	RCTs, prospective/retrospective cohort studies or case–control studies
Context	Studies conducted in developed countries
	Written in English or Japanese
	Exclude congenital airway disease

BPD, bronchopulmonary dysplasia; NICHD, National Institute of Child Health and Human Development; PCC, population concept context; RCTs, randomised controlled trials.

Data charting process

We will collect data on the following study characteristics using a data collection form (online supplemental material 1):

1. Study title and authors.
2. Study design.
3. Year of publication. The assessment year will be extracted, as some studies were conducted over several years, and the first year will be recorded.
4. Country of origin.
5. Sample size.
6. BPD information: we will collect details of information regarding BPD as the endpoint in studies.
7. Outcome measures: the outcome measures in the studies will be extracted. They will be categorised as follows: antenatal therapy (eg, antenatal corticosteroid), maternal condition (chorioamnionitis), neonatal condition (sex, gestational age, birth weight, small for gestational age), morbidities (patent ductus arteriosus, sepsis), neonatal therapy (nutrition, invasive respiratory support, oxygen, postnatal steroid and caffeine), respiratory and neurodevelopmental outcomes.
8. Covariates/confounding factors: covariates/confounding factors used in the main analysis will be charted.
9. Relationship between main exposure and endpoints: the main finding of the relationship between the main exposure and endpoint will be described (hazard ratio, odds ratio, relative risk, etc).

Any modifications to the data extraction strategy will be reported in the results section of the final scoping review.

Synthesis of results

The detailed search results will be collated and summarised through tables or figures. Adjustment to the data reporting scheme will be made as needed, based on the findings. We will conduct a scoping review following the PRISMA-ScR checklist.[21]

Ethics and dissemination

Institutional review board approval is not required because of the nature of the methodology used in the analysis. A final report will be publicised and disseminated through a peer-reviewed journal and presentation at relevant conferences. The University Hospital Medical Information Network—Clinical Trial Registry (UMIN-CTR) was satisfied with the ICMJE criteria and registered the review protocol for clinical trial registration.

Patient and public involvement

The patients and the public have not been involved in the design and review process. However, they will be asked to join the consensus-building process before publishing a novel useful disease classification for BPD. We have been consulting stakeholders and experts throughout the review process.

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Contributors This study was conceptualised by HN, EO and FN. All authors contributed to the scope and design of the review. EO developed our search strategy via consultation with a medical librarian at St. Luke's International University. SK, MI, MS and NM will perform screening, data charting and data synthesis of the studies. SK prepared the first draft, and all other authors provided substantial inputs toward the development of the final version. EO, FN and HN provided feedback on the methodology. All authors approved the final version of the manuscript.

Funding This research is supported by the Research Program on Rare and Intractable Diseases, Health, Labor, and Welfare Sciences Research Grants (21FC0101).

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Stoll BJ, Hansen NI, Bell EF, *et al*. Neonatal outcomes of extremely preterm infants from the NICHD neonatal research network. *Pediatrics* 2010;126:443–56.
2 Shah PS, Lui K, Sjörs G, *et al*. Neonatal outcomes of very low birth weight and very preterm neonates: an international comparison. *J Pediatr* 2016;177:144–52.
3 Motoyama EK, Fort MD, Klesh KW, *et al*. Early onset of airway reactivity in premature infants with bronchopulmonary dysplasia. *Am Rev Respir Dis* 1987;136:50–7.
4 Fawke J, Lum S, Kirkby J, *et al*. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the EPICure study. *Am J Respir Crit Care Med* 2010;182:237–45.
5 Smith VC, Zupancic JAF, McCormick MC, *et al*. Rehospitalization in the first year of life among infants with bronchopulmonary dysplasia. *J Pediatr* 2004;144:799–803.
6 Schmidt B, Asztalos EV, Roberts RS, *et al*. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. *JAMA* 2003;289:1124–9.
7 Arjaans S, Haarman MG, Roofthooft MTR, *et al*. Fate of pulmonary hypertension associated with bronchopulmonary dysplasia beyond

36 weeks postmenstrual age. *Arch Dis Child Fetal Neonatal Ed* 2021;106:45–50.
8 Lapcharoensap W, Bennett MV, Xu X, *et al*. Hospitalization costs associated with bronchopulmonary dysplasia in the first year of life. *J Perinatol* 2020;40:130–7.
9 Humayun J, Löfqvist C, Ley D, *et al*. Systematic review of the healthcare cost of bronchopulmonary dysplasia. *BMJ Open* 2021;11:e045729.
10 Helenius K, Sjörs G, Shah PS, *et al*. Survival in very preterm infants: an international comparison of 10 national neonatal networks. *Pediatrics* 2017;140:e20171264.
11 Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163:1723–9.
12 Hines D, Modi N, Lee SK, *et al*. Scoping review shows wide variation in the definitions of bronchopulmonary dysplasia in preterm infants and calls for a consensus. *Acta Paediatr* 2017;106:366–74.
13 Ogawa Y, Fujimura M, Goto A, *et al*. Epidemiology of neonatal chronic lung disease in Japan. *Acta Paediatr Jpn* 1992;34:663–7.
14 Hirata K, Nishihara M, Shiraishi J, *et al*. Perinatal factors associated with long-term respiratory sequelae in extremely low birthweight infants. *Arch Dis Child Fetal Neonatal Ed* 2015;100:F314–9.
15 Namba F, Fujimura M, Tamura M. Bubbly and cystic appearance in chronic lung disease: is this diagnosed as Wilson-Mikity syndrome? *Pediatr Int* 2016;58:251–3.
16 Jobe AJ. The new BPD: an arrest of lung development. *Pediatr Res* 1999;46:641–3.
17 Hutchison AA, Bignall S. Non-Invasive positive pressure ventilation in the preterm neonate: reducing endotrauma and the incidence of bronchopulmonary dysplasia. *Arch Dis Child Fetal Neonatal Ed* 2008;93:F64–8.
18 Isayama T, Iwami H, McDonald S, *et al*. Association of noninvasive ventilation strategies with mortality and bronchopulmonary dysplasia among preterm infants: a systematic review and meta-analysis. *JAMA* 2016;316:611–24.
19 Sand L, Szatkowski L, Kwok T'ng Chang, *et al*. Observational cohort study of changing trends in non-invasive ventilation in very preterm infants and associations with clinical outcomes. *Arch Dis Child Fetal Neonatal Ed* 2022;107:150–5.
20 Peters MDJ, Godfrey C, McInerney P. Chapter 11: Scoping Reviews (2020 version). In: Aromataris E, Munn Z, eds. *JBI manual for evidence synthesis, JBI*, 2020. https://synthesismanual.jbi.global
21 Tricco AC, Lillie E, Zarin W, *et al*. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med* 2018;169:467–73.