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RISK FACTORS FOR BRONCHOPULMONARY DYSPLASIA IN NEONATAL INTENSIVE CARE UNITS: AN INTEGRATIVE REVIEW

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Abstract: Introduction: Bronchopulmonary dysplasia is one of the main comorbidities associated with prematurity, characterized as a chronic lung disease that affects premature babies exposed to prolonged use of oxygen and mechanical ventilation. Despite the high mortality rate, surviving neonates often have severe physiological and biochemical alterations. Understanding the predisposing factors makes it possible to improve prevention, diagnosis and treatment practices, thereby reducing neonatal morbidity and mortality and optimizing the care provided to newborns in situations of risk. Objective: To deepen our understanding of the risk factors for the development of Bronchopulmonary Dysplasia. Methodology: This is an integrative review of articles indexed in the electronic databases Medline/Pubmed, Latin American and Caribbean Literature in Health Sciences (Lillacs), Scientific Electronic Library Online (SciELO) and the Virtual Health Library (VHL). The bibliographic analysis was carried out between September and November 2024, using the descriptors: "Bronchopulmonary Dysplasia"; "Prematurity"; "Risk Factors". The search strategy was based on their different combinations, using the Boolean operator AND and/or OR. The inclusion criteria were original articles in Portuguese, English and Spanish, published in the last 10 years. Letters to the editor, reviews, opinion articles, literature reviews, reflection studies, editorials and duplicate works were excluded. Results: Bronchopulmonary Dysplasia results from multiple risk factors, related to the prenatal, perinatal and postnatal periods. In the prenatal period, maternal variables such as maternal smoking and pre-existing hypertension stand out. The perinatal and postnatal periods include extreme prematurity, low birth weight and prolonged mechanical ventilation, as well as lung infections and conditions such as patent ductus arteriosus. Qualified assistance from intensive care unit staff is essential to reduce cases and

deaths, since recognizing risk factors allows for targeted and effective interventions. Conclusion: Bronchopulmonary dysplasia is associated with multiple risk factors, highlighting the importance of early interventions, individualized strategies and standardized clinical protocols. Continued research is essential to improve practices and reduce neonatal morbidity and mortality.
Keywords: Bronchopulmonary Dysplasia; Prematurity; Risk Factors.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) remains one of the main comorbidities associated with prematurity, being a chronic lung disease that affects premature babies exposed for long periods to prolonged oxygen and mechanical ventilation. First described by Northway *et al.* in 1967, BPD initially appears in premature infants with hyaline membrane disease. These babies, despite the high mortality rate, survived but developed severe alterations to the mucous membranes, alveoli and pulmonary vascular system due to prolonged exposure to high ventilatory pressures and oxygen (Al Mandhari *et al.*, 2024; Li *et al.*, 2015; Gomez *et al.*, 2018).

With advances in neonatal care and improved survival rates, a "new BPD" has emerged, characterized by interrupted alveolar development, less fibrosis and a more diffuse inflammatory pattern. The definition and classification of BPD have undergone several revisions over the years, the most widely used being the definition proposed by the National Institute of Child Health and Human Development (NICHD) Workshop (Al Mandhari *et al.*, 2024; Gomez *et al.*, 2018).

BPD predisposes survivors to significant pulmonary, cardiovascular and neurodevelopmental morbidities, as well as being associated with high mortality. Children with this condition are at greater risk of developing chronic respiratory morbidity, manifested by asthma-like symptoms, as well as having reduced lung function compared to children born at term (Abushahin *et al.*, 2024).

Research has shown that the lower the gestational age (GA) and birth weight (BW), the more complex the care required, which results in an increase in neonatal hospital resources and costs, as well as a higher chance of death during the neonatal period. It should be noted that the neonatal period is a phase of extreme vulnerability in the lives of newborns, due to the various biological, environmental, social and cultural risks that influence their health and development (Lima *et al.*, 2022).

Despite advances in the identification of factors related to the development of BPD and in prevention strategies, the disease remains the most prevalent sequela among survivors of prematurity. Early identification of risk factors is essential to identify patients who may benefit from postnatal management and possible preventive therapies (Abushahin *et al.*, 2024; Gomez *et al.*, 2018).

The diagnostic criteria for BPD have evolved over the years, incorporating different parameters to more accurately classify the severity of the disease. Currently, a severity-based classification is used, in which infants who do not require oxygen are classified as having mild BPD; those who require less than 30% oxygen are diagnosed with moderate BPD; and those who require continuous positive pressure ventilation and/or more than 30% oxygen are considered to have severe BPD (Huang *et al.*, 2023; Gomez *et al.*, 2018).

The diagnosis of BPD is confirmed when a baby has been receiving oxygen for at least 28 days and requires positive pressure ventilation or oxygen support at 36 weeks postmenstrual age or at the time of discharge. Although the prevalence of BPD is high in premature babies, not all are affected and the severity of the disease can vary significantly between patients (Huang *et al.*, 2024).

In summary, given the complexity and importance of the subject, this study aims to deepen our understanding of the risk factors for developing BPD. A better understanding of these factors will make it possible to improve prevention, diagnosis and treatment strategies, contributing to a reduction in neonatal morbidity and mortality and improving the quality of care provided to newborns in situations of risk.

METHODOLOGY

This integrative literature review analyzes recent studies to guide future research, allowing up-to-date knowledge on the subject to be identified. Its purpose is to provide a comprehensive overview to aid decision-making, optimize clinical practice and highlight gaps for further investigation.

In this analysis, the methodological path proposed by Marconi & Lakatos (2021) was followed, going through six stages: elaboration of the triggering research question together with the elaboration of hypotheses, literature search following criteria for the selection of articles, organization and categorization of the findings, evaluation of the studies that were included in the study, interpretation of the results, followed by the presentation of the review.

The delimitation of the study and the objectives to be achieved were carried out in the formulation of the triggering question, using the strategy with the mnemonic PICo for non-clinical research, with "P" being the population, "I" Interest, and "Co" for the context of the investigation in question (Chart 1). Thus, the following research question was adopted: What risk factors are involved in the occurrence of BPD in neonatal units?

Acronym	Definition	Application
P	Population	Neonates
I	Interest	Risk factors for bronchopulmonary dysplasia
Co	Context	Intensive care

Table 1: Application of the PICo strategy.

The bibliographic survey was carried out in September 2024, in the following data sources: Medline/Pubmed, Latin American and Caribbean Literature in Health Sciences (Lillacs), Scientific Electronic Library Online (SciELO) and Virtual Health Library (VHL).

The search used descriptors in Health Sciences (DeCS) and Medical Subject Headings (MeSH): "Bronchopulmonary Dysplasia"; "Prematurity"; "Risk Factors". The search strategy was based on their different combinations, using the Boolean operator AND and/or OR in the respective data sources.

After selecting the articles, it was possible to construct the PRISMA flowchart with the identification, screening, eligibility and inclusion data of the studies. The inclusion criteria were: studies available in full, focusing on bronchopulmonary dysplasia in newborns in the Neonatal Intensive Care Unit (NICU), in Portuguese, English and Spanish, with a time frame of the last 10 years. Studies such as letters to the editor, reviews, opinion articles, literature reviews, reflection studies, editorials and duplicate studies were excluded.

Among the titles searched according to the descriptors, 2,060 articles were obtained. However, after applying the inclusion and exclusion criteria, 571 studies remained, which were reduced to 60 after reading the titles. Finally, after reading the articles in full, assessing their eligibility and relevance to the research topic, only 9 articles remained (Figure 1).

The data was organized by drawing up a table, in which the following information was presented: the year of publication of the study, the journal in which it was submitted, the title of the article followed by the names

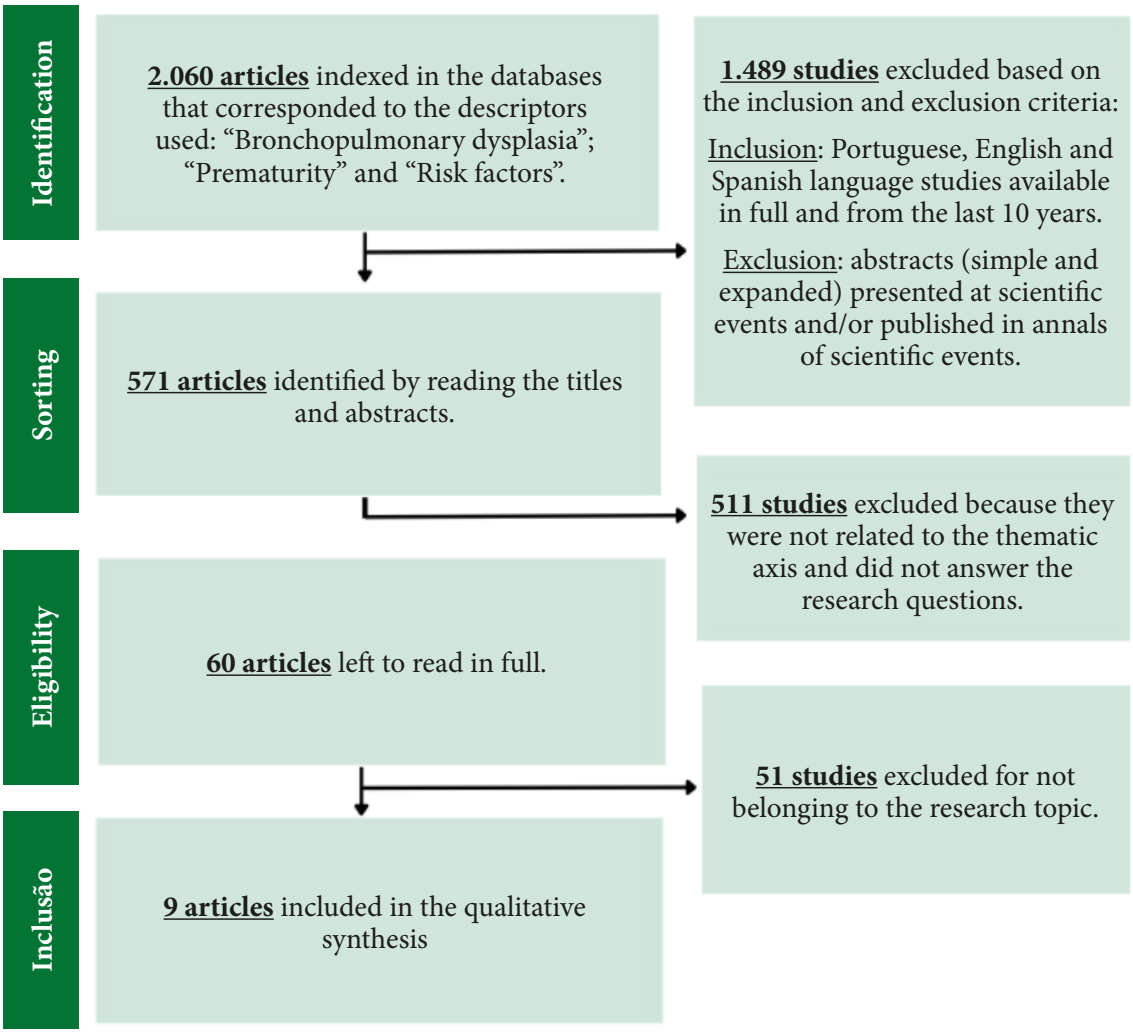

Figure 1. Flowchart for selecting articles for the Integrative Review based on PRISMA ADAPTED.

Title	Authors, year	Results	Level of Evidence
A risk factor analysis on disease severity in 47 premature infants with bronchopulmonary dysplasia	Li, Y. *et al.* (2015)	The data showed that the most relevant risk factors that could influence the severity of BPD were low birth weight, early gestational age, chorioamnionitis, fertile history, cholestasis and abnormal coagulation function.	IV
Antenatal Determinants of Bronchopulmonary Dysplasia and Late Respiratory Disease in Preterm Infants	Morrow L. A. *et al.* (2017)	They found that maternal smoking before birth increased the chances of having a baby with moderate or severe BPD by 2.02 times. Maternal smoking was also associated with prolonged need for mechanical ventilation and the use of respiratory support during NICU stay, as well as with late respiratory disease during infancy. Additional risk factors for BPD in this cohort also included lower gestational age at birth, lower birth weight *z* scores, white race and pre-existing maternal hypertension.	IV
Bronchopulmonary Dysplasia: Comparison Between the Two Most Used Diagnostic Criteria	Gomez P. E. *et al.* (2018)	The incidence of BPD using the NIH criteria is 80% higher when compared to the Shennan definition, with an estimated difference of 32%. Associated with either definition are the following risk factors: birth weight, gestational age, male gender, intrauterine growth restriction, low Apgar scores, intubation in the delivery room and additional doses of surfactant. Babies classified as without BPD by the Shennan criteria are more likely to go home on oxygen compared to those classified as without BPD by the NIH criteria.	IV

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	Jung Y. H. *et al.* (2019)	Decreased birth weight z-score, decreased birth length z-score, low gestational age and male gender were significantly associated with an increased risk of BPD or death before 36 weeks of post-menstrual age.	IV
The high-risk factors of different severities of bronchopulmonary dysplasia (BPD) based on the National Institute of Child Health and Human Development (NICHD) diagnosis criteria in 2018	Jian M. *et al.* (2021)	Congenital heart disease, hemodynamically significant patent ductus arteriosus, mechanical ventilation ≥ seven days, reintubation, pneumonia, especially multiple microbial lung infections, and *Klebsiella pneumoniae pneumonia* are significantly associated with the severity of BPD and can be considered as predictive events for moderate and severe BPD.	IV
Comprehensive Analysis of Risk Factors for Bronchopulmonary Dysplasia in Preterm Infants in Taiwan: A Four-Year Study	Huang L. Y. *et al.* (2023)	They found that low gestational age, low birth weight, infection, ventilator use and nitric oxide inhalation were important risk factors for BPD. In addition, the indicators of small-for-gestational-age babies, male gender and endotracheal intubation or cardiopulmonary brain resuscitation at initial resuscitation are more likely to be associated with the development of moderate to severe BPD.	IV
Risk factors for severe bronchopulmonary dysplasia in a Chinese cohort of very preterm infants	Huang J. *et al.* (2024)	This study found a prevalence of BPD of 36.0% among very preterm babies with a birth weight of <1500 g, of whom a high percentage had mild/moderate BPD. Lower gestational age and birth weight correlated with greater severity of BPD. Very preterm babies who received invasive mechanical ventilation for ≥7 days had a higher chance of BPD than those who did not. Erythrocyte transfusion of ≥3 times, hemodynamically significant patent ductus arteriosus and nosocomial infection were significantly correlated with an increased risk of BPD. The delay in starting enteral feeding and the long duration needed to reach total caloric intake (110 kcal/kg/day) were the independent risk factors for BPD. Our study identified the use of prenatal corticosteroids as a protective factor for moderate to severe BPD.	IV
Incidence and Predictors of Bronchopulmonary Dysplasia Development and Severity Among Preterm Infants Born at 32 Weeks of Gestation or Less	Abushahin A. *et al.* (2024)	Extreme prematurity and extremely low birth weight remain the strongest predictors of BPD due to the underdevelopment of lung structures. Our study showed that infants with adequate weight for gestational age, presence of patent ductus arteriosus at birth or first echocardiography, late-onset sepsis and use of invasive ventilation were significant risk factors for the incidence of BPD in infants with gestational age ≤ 32 weeks and birth weight < 1500 g.	IV
Prevalence, Severity Patterns and Risk Factors of Bronchopulmonary Dysplasia in Preterm Infants Younger than 32 Weeks of Gestation in a Tertiary Center in Oman	Al Mandhari H. *et al.* (2024)	This study did not identify any significant prenatal risk factors related to BPD. However, multiple perinatal and postnatal factors were associated with BPD, such as lower birth weight, lower gestational age at birth, lower Apgar scores, resuscitation at birth, mechanical ventilation and longer duration of mechanical ventilation. Other comorbidities of prematurity were also associated with BPD.	IV

Chart 2: Articles selected for the integrative review.

of the authors, the results and finalized by the classification as to the level of evidence, which hierarchizes publications by external evidence based on seven levels. Level I - meta-analysis or systematic reviews of clinical trials; II - randomized or controlled experiments; III - clinical trials without randomization, but well-designed; IV - cohort or case-control studies with study design; V - systematic review of qualitative or descriptive studies; VI - research derived from single studies with a qualitative or descriptive approach; VII - opinion articles by authorities or expert committees with no basis in clinical research (Galvão, 2006).

As this was a qualitative study, which used a secondary, publicly accessible database as its data source, it was not necessary to obtain approval from a Research Ethics Committee to carry out the study. However, it can be inferred that the ethical precepts in terms of structure, references and regulations were maintained.

RESULTS AND DISCUSSION

The study sample consisted of 9 primary scientific articles dealing with bronchopulmonary dysplasia, published in journals between 2014 and 2024. Based on the organization of the articles included, a prevalence of 29.3% can be observed in each of the years 2017 and 2020. However, with regard to the content exposed, selected and included in the review, after thorough reading and analysis of the results, they were synthesized into categories for discussion of the research.

The report "Born Too Soon: Decade of Action on Premature Birth", launched by the World Health Organization (WHO) in 2023, highlights premature births as one of the main causes of serious illnesses and neonatal deaths in the world. Prematurity is a global public health challenge, and the initiative seeks to reduce premature births and improve neonatal care. In this context, identifying predictors of BPD is essential to prevent complications and deaths associated with the condition (WHO, 2023).

Extreme prematurity and low birth weight (LBW) have emerged as the main risk factors for the development of BPD and have been reiterated in several studies analyzed. Al Mandhari *et al*. (2024) pointed out that the prevalence of BPD in premature infants under 32 weeks is consistent in different locations, but the specific risk factors and severity rates vary, suggesting the influence of socioeconomic aspects and neonatal protocols. Abushahin *et al*. (2024) reinforced the relationship between prematurity and greater severity of BPD, highlighting prolonged use of invasive mechanical ventilation as one of the main predictors.

In addition, the association between reduced GA, PN and postnatal factors, such as the need for intubation and mechanical ventilation, has been shown by several studies. Li *et al*. (2015) and Jian *et al*. (2021) also identified pulmonary infections and patent ductus arteriosus as aggravating factors of BPD, while Gomez *et al*. (2018) highlighted that distinct diagnostic criteria, such as those of the NICHD, are more effective for stratifying cases and guiding personalized interventions.

Prenatal factors such as maternal smoking and hypertension were associated with a higher risk of BPD, according to Morrow *et al*. (2017). The study revealed that smoking significantly increases the need for prolonged respiratory support, as well as aggravating respiratory morbidities in childhood. In addition, Jung *et al*. (2019) observed that intrauterine growth restriction, assessed by the z score of birth weight and length, intensifies the risk of respiratory complications.

Diagnostic criteria also have an impact on the identification and management of BPD. Gomez *et al*. (2018) and Jian *et al*. (2021) showed the superiority of the NICHD criteria for differentiating mild, moderate and severe cases, highlighting the importance of standardization in clinical practice. These criteria incorporate variables such as duration of respiratory support and other comorbidities such as pulmonary hemorrhage and congenital heart disease.

Another relevant aspect was the influence of perinatal factors, such as the delay in starting enteral nutrition and the prolonged need for mechanical ventilation, as pointed out by Huang *et al*. (2024). These factors not only prolong hospitalization, but also increase the severity of BPD, especially in neonates with lower birth weight and GA.

In the findings of Huang *et al*. (2023), determinants such as small-for-GI babies, male gender and the need for initial resuscitation stood out as predictors of BPD. In addition, the studies highlighted the role of early interventions and multidisciplinary management in the context of neonatal units.

The absence of a significant association with prenatal factors in some studies, such as the research by Al Mandhari *et al*. (2024), suggests that postnatal morbidities play a more central

role in the progression of BPD. This points to the need for close monitoring of infections and respiratory support in the first days of life.

In addition, the importance of prenatal corticosteroid therapy as a preventive strategy for BPD is highlighted. According to studies such as Huang *et al*. (2024), the administration of corticosteroids before birth has been shown to be effective in accelerating lung development and reducing the need for ventilatory support in the first days of life. However, it is essential that this intervention is carried out carefully, considering the potential adverse effects and its suitability to the clinical profile of each pregnant woman.

Another crucial point discussed was the impact of socioeconomic and regional factors on neonatal care. Studies such as those by Al Mandhari *et al*. (2024) and Jian *et al*. (2021) highlighted that variations in protocols and available resources directly influence clinical outcomes, pointing to the need for public policies that reduce disparities in neonatal care.

Finally, the findings highlight the complexity of BPD as a multifactorial condition that requires an integrated and individualized approach. The diversity of risk factors identified reinforces the importance of standardized protocols and ongoing research to improve management and prevent complications.

CONCLUSION

The findings of this study reinforce that this condition results from multiple risk factors, such as extreme prematurity, LBW and prolonged mechanical ventilation, as well as pulmonary infections and conditions such as patent ductus arteriosus. These factors highlight the need for early interventions and individualized neonatal care strategies.

The study also pointed out the relevance of practices such as prenatal corticotherapy and the careful use of non-invasive ventilation, while revealing a lack of standardization in diagnostic and therapeutic criteria, such as those proposed by the NICHD. This highlights the need to unify clinical protocols and implement public policies to reduce regional and socioeconomic disparities in neonatal care.

In view of this, further research into BPD is essential in order to identify more effective preventive and therapeutic strategies, considering the long-term impact of this condition on the quality of life of neonates. It is suggested that future studies should investigate the interaction between genetic and environmental factors, as well as exploring emerging technologies that could contribute to reducing the morbidity and mortality rates associated with BPD.

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