Research Progress in Bronchopulmonary Dysplasia: A Narrative Review by Etiology

Shukri Omar Yusuf [ORCID], Peng Chen*

Department of Pediatrics, The Second Hospital of Jilin University, Changchun, China
Email: *c_p@jlu.edu.cn

Abstract

Background: Bronchopulmonary Dysplasia (BPD) is a chronic lung condition that primarily affects preterm infants. Genetic predispositions, environmental factors, prenatal, and postnatal risk factors have been associated with bronchopulmonary dysplasia. However, there is a lack of consensus regarding these factors. **Purpose:** To examine the available information on pathogenesis and summarize the points of agreement to generate concise information that can guide patient management and spur further research. **Method:** PubMed, Embase and Web of Science were used to search for studies that analyzed the risk factors associated with bronchopulmonary dysplasia between 2006 and 2022 with the key search terms "bronchopulmonary dysplasia, etiology, preterm birth, mechanical ventilation". **Results:** This study found that the pathogenesis of bronchopulmonary dysplasia is multifactorial, involving close interactions among these major etiological factors and other minor risk factors. A combination of mechanical ventilation, intrauterine factors, inflammation, genetic predispositions, insufficient surfactants, docosahexaenoic acid, and nutrition, among other minor risk factors, was all required in one way or another to influence BPD development. Therefore, studies should continuously update and incorporate the emerging information to assist frontline healthcare workers and generate qualitative data for clinical trial design and further research. **Conclusion:** Bronchopulmonary Dysplasia is different from other respiratory illnesses, and the pathogenesis of bronchopulmonary is multifactorial.

Keywords

Research Progress, Bronchopulmonary Dysplasia, Etiology, Preterm, Low Birth Weight

1. Introduction

Bronchopulmonary Dysplasia (BPD) is a progressive lung disease that primarily

affects premature infants. It results from an imbalance in the growing lung's damage and repair processes [1]. BPD is different from other respiratory illnesses because it has respiratory symptoms and histological findings like simple alveoli, less pulmonary vascularization, parenchymal fibrosis, and edema [2]. In premature infants, the alveoli are not mature enough to function independently. About 15 million premature infants are born globally, estimated to be about 1 in every 10 live births recorded. In China, the prevalence is about 1.26% [3]. The uncertainty surrounding BPD epidemiology and historical trends reflects a convergence of events, such as lack of awareness about the condition, discrepancies in its definitions, the increased survival rate among premature neonates previously susceptible to the disease, etc. Indeed, increased awareness of the prevalence of BPD can help inform preterm baby counseling, allow the product of professional guidance, and assist in the design of clinical trials to test new treatments [4]. In this disease in infants, the alveoli are not mature enough to function independently. As a result, lungs, airways, or bronchi are harmed, resulting in tissue destruction or dysplasia of the alveoli. These infants thus require long-term oxygen therapy to survive [5]. Preterm infants are those born alive before the 37th week of pregnancy. Preterm birth is divided into subcategories depending on gestational age:

1) Extremely preterm (less than 28 weeks)

2) Very preterm (28 to 32 weeks)

3) Moderate to late preterm (32 to 37 weeks) [6].

According to data from the Vermont Oxford Network, the number of preterm babies with BPD ranged from 4% to 58% in 2003. Birth weights (BW) for these babies were around 501 and 1500 g when they were born, and they have kept going up, especially for very premature babies who got help from perinatal medicine and neonatal intensive care [7]. Extremely preterm infants are the most vulnerable demography for BPD. Between 2012 and 2020, it was estimated that 40% - 45% of extremely preterm infants suffered from BPD [8]. This resulted in increased childhood mortality and severely affected the long-term health of the neonates, particularly their neurodevelopmental outcomes [9].

According to consensus, BPD in immature lungs is associated with postnatal hyperoxia, invasive mechanical ventilation (IVM), pulmonary insufficiency, and other predisposing factors [10]. Factors responsible for BPD are both prenatal and postnatal. Prenatal factors include hypertension in pregnancy, maternal obesity, gestational diabetes, etc., while postnatal factors include lung injury, low birth weight, and low gestational age. Genetic predispositions have also been explored. A mix of inherited and environmental factors is believed to influence BPD [11]. There are three severity levels in BPD: mild, moderate, and severe. In severe forms, different levels of lung airway resistance result in varying time constants [12]. And also, the degree of breathing support and the necessity for extra oxygenation is used to determine the severity [13].

Despite postnatal factors like low birth weight, hyperoxia, and mechanical ventilation that increase BPD risk, epidemiological research indicates that pre-

natal factors are the most important etiological risk factors for the disease [14].

Premature delivery and low birth weight are the two most significant risk factors associated with bronchopulmonary dysplasia [15] [16]. Estimates show that BPD is diagnosed in nearly 80% of neonates between 22 - 24 weeks, while only about 20% of those delivered after 28 weeks of pregnancy have BPD [17]. According to one study, premature membrane rupture one week or more before delivery is associated with a threefold increase in the risk of developing BPD [18]. After adjusting for many other perinatal variables, smoking, preeclampsia, poorer socioeconomic position, and birth weight z-score, employed as a marker for fetal growth restriction, are the most connected to BPD development among the various prenatal factors [19]. At the same time, the postnatal risks are prolonged mechanical ventilation, sepsis, intrauterine growth restriction, and supplementary oxygen, among others [20]. **Figure 1** shows the Prenatal and postnatal variables. Given the continued lack of consensus on these etiological factors, this review aims to examine the information accumulated so far on the etiology of BPD and summarize the points of agreement to generate concise information that can guide patient management and spur further research.

2. Etiology of Bronchopulmonary Dysplasia

BPD is a disease with complex pathogenesis causing inflammation, cell death, and changes to the extracellular matrix, which affect lung growth, function, immunity, alveolarization, and vascularization, and make it harder for the lungs to repair and grow back [21]. Depending on the several factors that lead to lung damage in the preterm, various abnormalities in the bronchi, epithelial surfaces, mesenchyme, and pulmonary vasculature are likely to have a role in an infant's classification as having BPD. In many infants, the lung injury that leads to BPD begins with abnormal lung development before birth (for example, when the lungs are tiny for their gestational period, chorioamnionitis, and tobacco exposure) [22]. When combined with other risk factors such as surfactant inadequacy,
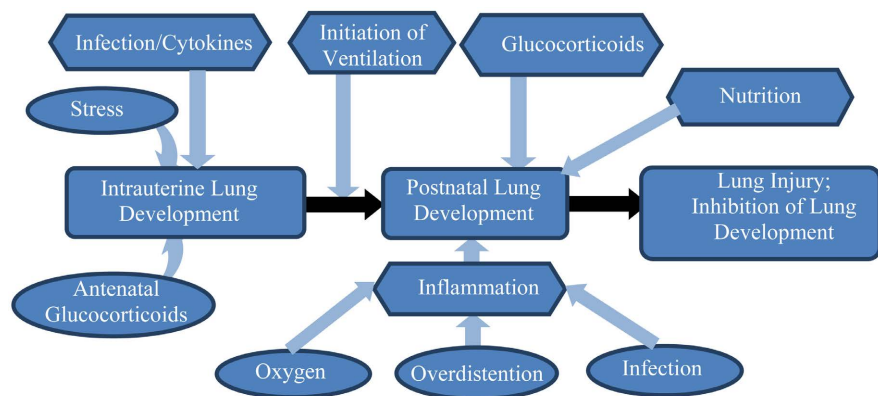

Figure 1. Prenatal and postnatal variables are shown in this diagram describing the pathophysiology of BPD. Adapted from Jobe AH. The new BPD: an arrest of lung development. Source: Pediatric Research (1999), 46: 641.

ventilation-associated lung injury, nutritional deficiency, oxygen radical's toxicity, perinatal and postnatal infections, and inflammatory conditions, the vicious circle of lung injury hinders pulmonary vasculature development, eventually leading to BPD [23]. This section examines the key etiology and how they lead to BPD development.

2.1. Mechanical Ventilation (MV)

Mechanical Ventilation (MV) is used in critically ill patients for many reasons. Still, the most prevalent ones are to ease breathing effort and ensure enough gas exchange until the underlying sickness is treated. On the other hand, ventilation therapy has been shown to injure the lungs and increase mortality [24]. The main way to treat severe neonatal respiratory failure is to give the baby supportive care and MV. However, lung damage can be caused and made worse by MV on its own. Ventilator-induced lung injury (VILI) is the medical term for when your lungs get injured after using your ventilator. VILI is a big risk factor for bronchopulmonary dysplasia in very low birth weight (ELBW) babies (BPD) [25].

Extremely preterm neonates (<28 weeks) are often put on mechanical ventilation (MV) to support breathing. Although this is a necessary practice, it has well-documented negative effects on the infant's health. Therefore, it is not a secret to scientists that hyperoxia is harmful to the lungs [26]. The risk of developing BPD increases with longer exposure to MV. In preterm neonates with extremely low birth weight exposed to more than six weeks of MV, mortality risk increases 8-fold. The risk rises by thirteen times when stratified for only cardiorespiratory causes [27]. Every extra week a neonate spends on MV raises the risk of developing BPD by 2.7 fold. In addition, long-term use of an endotracheal tube for invasive artificial breathing has been linked to several negative consequences, including chronic upper and lower respiratory tract disorders [28].

2.2. In Utero Factors

2.2.1. Preeclampsia

Preeclampsia is a pregnancy-induced complication characterized by high blood pressure, the protein in the urine, and swelling of the legs is a controversial subject in the etiology of BPD. The recent findings that tie Preeclampsia to abnormal changes in the maternal vasculature and the concept that BPD is essentially a disease of abnormal pulmonary vasculature development have created a plausible link between the two conditions [29]. Preeclampsia affects 2% - 8% of all pregnancies worldwide [30]. Various cohorts of infants born to preeclampsia mothers have been studied and have made sharply opposite conclusions on its association with BPD. Soliman *et al.* and O'Shea *et al.* studied a total of 1702 children born to preeclampsia moms and concluded that the condition was not connected with BPD [31]. Interestingly, a meta-analysis of large population-based studies discovered a negative relationship between Preeclampsia and

BPD. Subgroup analysis found that exposure to Preeclampsia was protective against BPD for neonates > 31 weeks of gestation [32]. On the contrary, Hansen *et al.*, Wilmink *et al.*, and Zkan *et al.* evaluated 735 babies with Preeclampsia and found that it was a major factor in BPD development [33]. Therefore, whether Preeclampsia is a positive or negative predictor for BPD remains unclear. However, both conditions share a similar origin: blood vasculature.

2.2.2. Chorioamnionitis (CA)

Chorioamnionitis is a bacterial infection of the placenta and amniotic fluids, which is the most often-recognized cause of preterm delivery and is connected to BPD etiology [34]. Previously, chorioamnionitis is a condition caused by an intrauterine infection that can develop at any stage of pregnancy. Chorioamnionitis was referred to as amniotic fluid infection syndrome [35]. Waterberg *et al.* discovered a relationship between chorioamnionitis and an increased risk of persistent lung sickness, but not between RDS and chorioamnionitis. Researchers hypothesized that exposure to chorioamnionitis accelerated functional lung maturation but increased the lungs' premature susceptibility to postnatal injury. However, the evidence for this hypothesis was ambiguous, and further studies undertaken over the last two decades discovered that chorioamnionitis was related to a lower incidence of BPD and RDS [36]. It is a common cause of preterm delivery due to its induced intrauterine inflammation and comorbidities such as mechanical ventilation, respiratory distress syndrome, supplemental oxygen, parenteral nutrition, and early-onset sepsis. Combined, these factors predispose the baby to an increased risk of developing BPD [37]. These infants usually have much lower birth weights and gestational age than their unexposed counterparts [38]. The risk of developing respiratory distress syndrome modulates the likelihood of developing BPD in infants exposed to chorioamnionitis. Watterberg *et al.* suggested that histological chorioamnionitis lowers the risk of developing respiratory distress syndrome but increases the risk of BPD [39]. A comprehensive meta-analysis by Villamor-Martinez and colleagues combining over 158 studies found a significant positive correlation between chorioamnionitis and BPD (OR, 2.32; 95% CI, 1.88 - 2.86; P < 0.001); both clinical and histologic chorioamnionitis were correlated with BPD [40].

Chorioamnionitis is not yet known to be a significant independent risk for BPD. Studies that have attempted to do so have found difficulties controlling all the confounders. Additionally, several kinds of research have indicated that in the absence of sepsis, chorioamnionitis quickens lung development, reducing reliance on mechanical ventilation and oxygen supplementation hence attenuating BPD [41]. To clarify this phenomenon, Ballard *et al.* revealed in a 25-year cohort study that sepsis, rather than chorioamnionitis, was associated with developing moderate to severe BPD in very low birth weight infants after controlling for gestational age. To truly make a conclusive remark on this subject, future studies should attempt to control all the confounding comorbidities associated with chorioamnionitis to determine if it is an independent factor for BPD.

2.2.3. Smoking

Smoking during pregnancy is strongly associated with BPD. Studies on this subject suggest that babies exposed to intrauterine smoke and born weighing less than 1500 g are at increased risk of developing BPD [42]. When babies were delivered to smoking moms were hypoxic, they had a faster ventilatory deceleration and reached the lowest oxygen saturation of less than [43]. As a result of hypoxic stimulation, the decrease in minute volume is more pronounced [44]. This maladaptive conduct could be explained by the infant's constant prenatal hypoxia exposure, which results in persistent, maladaptive behaviors. An incorrectly activated respiratory neural network underpins the biphasic ventilatory response [44]. Preterm birth and impaired lung function in the offspring are well-established risks of Smoking during pregnancy [45].

Studies on animal models have produced strong evidence linking antenatal Smoking to detrimental effects on lung development. Embryonic exposure to nicotine, the active ingredient in cigarettes, has been shown to disrupt stem cell differentiation, induce alveolar hypoplasia, impair lung branching morphogenesis, increase airway reactivity and induce early immune dysregulation [46]. Furthermore, the epigenetic modifications induced by nicotine could affect DNA methylation patterns and hence modify the likelihood of future generations acquiring lung disease [46]. As a result, one of the essential roles of maternal Smoking in the pathophysiology of BPD is as a trigger for preterm birth.

2.3. Inflammation

Inflammation has a crucial role in the etiology and progression of bronchopulmonary dysplasia. BPD-associated inflammatory processes are often persistent and continuously pro-inflammation, creating an environment for its development. Neutrophils, macrophages, and various pro-inflammatory mediators invade the neonatal airways and pulmonary tissues, destroying the alveolar capillaries in the process [47]. The trachea aspirates of premature neonates who were mechanically ventilated show many polymorphonuclear leukocytes and macrophages. These babies were later diagnosed with BPD. Premature children developing BPD had pro-inflammatory monocytes and greater levels of interleukin (IL-1) cytokines in their tracheal aspirates. In tracheal aspirates about preterm respiratory distress syndrome babies that develop BPD, pro-inflammatory cytokines such as interleukins (IL-6, IL-1b), and tumor necrosis factor-alpha (TNF-a), as well as the chemokines CCL2, CCL7, CCL8, and IL-8 (CXCL8), are found [48]. Inflammation caused by infections, toxic oxygen radicals, various lipid mediators, and potent proteases could thus be responsible for the acute lung injury seen in BPD. Continuous inflammation affects wound healing, inhibits alveolarization, and interferes with the development of the pulmonary vasculature of the immature lungs in very preterm infants. This is a perfect recipe for BPD. For a comprehensive assessment of the role of inflammation in BPD, readers are referred to Shahzad 2016 study [49]. The pathogenesis of BPD through Inflammation is summarized in Figure 2.
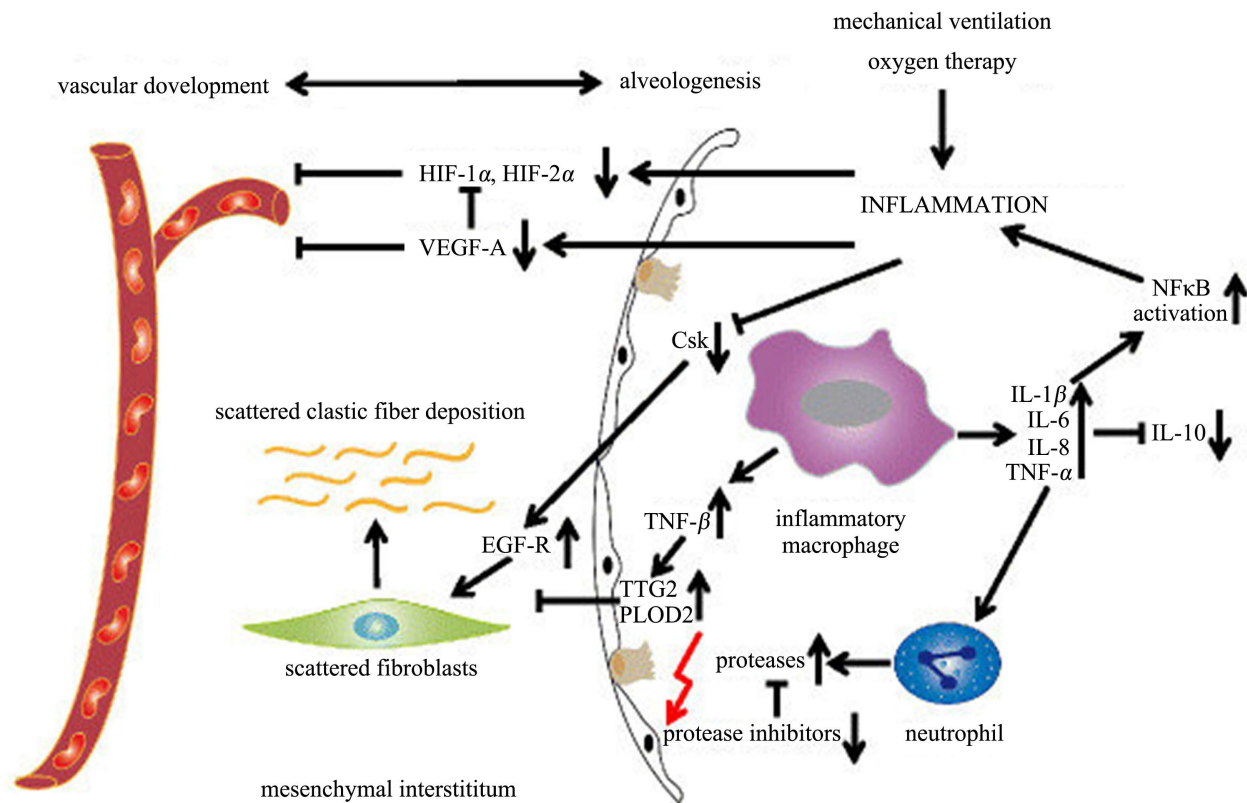
Figure 2. Pathogenesis of BPD: influence of the pulmonary inflammatory response on the premature lung. The plan outlines the impact of the pulmonary inflammatory response on alveolar and vascular development and the major components of lung development in the mesenchymal interstitium. fromShahzad *et al.* Molecular and Cellular Pediatrics (2016) 3: 23. Copyright: Public Library of Science, 2016. Disclaimer and Creative Commons Attribution License accessible from: http://creativecommons.org/licenses/ by/4.0/.

T-regulatory cells (Treg) and their immunological phenotype and immunosuppressive properties are thought to play an important role in BPD development pathways. Many variables support this idea. First, Tregs are important mediators in the maintenance of immunological homeostasis. Second, Tregs are involved in many chronic inflammatory respiratory diseases. Changes in Treg frequency and suppressive activity in humans and animals are risk factors for infectious disease susceptibility and the development of inflammatory, autoimmune, and allergic disorders [50]. Third, immunoregulatory cell populations like Tregs are one-of-a-kind cells for understanding the complicated mechanics of the intrauterine to extrauterine transition. The immunological activities of the semi-allogeneic fetus have been tuned to minimize potentially harmful inflammation, resulting in neonatal immunosuppression. Moreover, the immunosuppressive T cells (Treg) are also known to influence BPD development [51].

2.4. Genetic Susceptibility

The advent of genome-wide association studies has facilitated research into a genetic association to diseases. Employing a similar technique, studies have shown that genes are linked to bronchopulmonary dysplasia [52]. The rs4351 al-

lele of the angiotensin-converting enzyme (ACE) genes, for example, has been related to BPD in neonates. It has been noted that this allele is frequently transmitted from parents of very preterm birth infants to their offspring with BPD, although its particular role in BPD is not yet fully elucidated. Similarly, the gene SPOCK2, responsible for extracellular matrix formation, has been associated with BPD. Polymorphism in its allele rs1245560 was significantly associated with BPD development in preterm infants in both white and black populations [52]. Studies on whole-exome sequencing of DNA from BPD and non-BPD samples revealed the existence of some rare but detrimental mutations in specific genes in BPD patients, creating a strong genetic link for the disease [53]. With the rapid advancement in genetic studies seen today, using tools such as DNA and RNA. Microarray technologies, high throughput sequencing platforms, and bioinformatics tools will uncover and define more genetic and epigenetic links.

3. Surfactant Insufficiency

Surfactant is a phospholipid and protein surface-active compound produced by type II alveolar cells to lower alveolar air-liquid surface tension and prevent end-expiratory alveolar collapse [54]. Surfactant, a phospholipid and protein combination (90 percent lipids, 5 - 10 percent proteins), decreases alveolar surface tension, enabling them to stay open [55]. When an insufficient surfactant is insufficient, each breath causes the small alveoli to collapse. As the alveoli break down, injured cells build up in the airways, making breathing even more difficult. Surfactant improves lung compliance by reducing the surface tension of the alveolar membrane at the air-liquid interaction, and different surfactant components have functions in cell signaling and defense. The majority of preterm babies suffer from surfactant deficiency [56]. Premature babies are more likely to develop bronchopulmonary dysplasia if they lack surfactant [57]. Surfactant protein D (SP-D) deficiency has been connected to the increase of bronchopulmonary dysplasia (BPD) in preterm newborns who need mechanical breathing [58]. Surfactant insufficiency is responsible for the etiology of BPD. However, this is not the case, so it needs a researcher to look if it's independent or not.

4. Docosahexaenoic Acid

Docosahexaenoic Acid (DHA) is a phospholipid in high central nervous system concentrations. A reduction in DHA levels in the neurodevelopment causes problems in neurogenesis, neurotransmitters metabolism, and poor learning and visual function in animals. The mean DHA levels in preterm babies were similar to those in term infants at delivery, indicating that these levels reflect levels in the developing fetus' blood throughout the third trimester. Consequently, preterm neonates should be maintained within this range during the postnatal period. Moreover, substantial reductions in mean DHA levels in preterm neonates were seen during the first postnatal week and remained for three weeks, and decreased postnatal DHA levels in premature infants were associated with an in-

creased risk of BPD [59]. A post-hoc study of the Trial to Improve Neurodevelopmental Outcomes (2001 to 2005) found that giving DHA supplements to pregnant mothers reduced supplementary oxygen requirements in newborns weighing less than 1250 g at birth 36 weeks after menopause [60].

5. Nutrition

Nutrition is critical for lung development and healing. However, it should be noted that malnutrition may begin in utero, making it a significant prenatal risk factor for BPD. Following a preterm delivery, various complications associated with acute immaturity make it difficult to get enough energy and nutritional intake [61]. There are many reasons for development failure and malnutrition in BPD newborns. The primary and most serious reason is a break in nutritional assistance after birth. Delays in commencing and progressing to complete enteral nutrition are typical; enteral feeds are often halted due to concerns about feeding intolerance and coexisting diseases [62]. Nutrition is an important part of how lungs grow and mature. Malnutrition has big negative effects on how well the lungs work.

6. Conclusion

BPD is different from other respiratory illnesses because it has respiratory symptoms and histological findings like simple alveoli, less pulmonary vascularization, parenchymal fibrosis, and edema. In a nutshell, the pathogenesis of bronchopulmonary is multifactorial. A combination of mechanical ventilation, intrauterine factors, inflammation, genetic predispositions, insufficient surfactants, docosahexaenoic Acid, and nutrition, among other minor risk factors, is all required in one way or another to influence BPD development. Evidence to support these factors as independent predictors is weak. GA was shown to be a constant independent risk factor for BPD. This suggests that prematurity has a significant independent impact on the development of BPD and that this effect is unaffected by preeclampsia. It is unknown if preeclampsia is a positive or negative predictor of BPD. Animal models used to study the etiology of BPD should discover distinct sub-pathophysiological processes resulting from various prenatal and postnatal stressors (such as preeclampsia). As the etiology changes, so will the presentation and definition of cases. Thus, studies must keep up with the changing pattern of the disease and continuously update findings to ensure a consensus on the generally agreeable etiology and evidence of their connection to the disease. Furthermore, explicit knowledge of etiology will promote a clear case definition that encourages the collection of credible and useful data to assist the frontline healthcare workers managing these very preterm neonates and the research community in designing better clinical trials for new therapeutics.

Conflicts of Interest

All the authors declare no conflict of interest.

Authors' Contribution

Shukri Omar Yusuf conducted the literature search, data extraction and manuscript drafting. Dr. Chen Peng conceived the study and supervised the entire process of the study. All authors have read and agreed to the published version of the manuscript.

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Abbreviations

BPD:	Bronchopulmonary Dysplasia
GA:	Gestational Age
BW:	Birth Weight
EPT:	Extremely Preterm
VPT:	Very Preterm
IVM:	Invasive mechanical Ventilation
DHA:	Docosahexaenoic Acid
VLBW:	Very low Birth Weight
MV:	Mechanical Ventilation
VILI:	Ventilator-Induced Lung Injury
CA:	Chorioamnionitis
IL:	Interleukin
TNF-α:	Tumor Necrosis Factor-alpha
MCP-1:	Monocyte Chemoattractant Protein-1
PMN:	Polymorphonuclear Leukocytes
RDS:	Respiratory Distress Syndrome
SP-D:	Surfactant Protein D