Editorial

Predicting bronchopulmonary dysplasia in premature infants: has the research come of age?

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Since first described by Northway [1967], bronchopulmonary dysplasia (BPD) in premature infants has been the most debated topic in the field of neonatal medicine (1). A PubMed search for "bronchopulmonary dysplasia preterm" brings up more than 4,500 hits, with "patent ductus arteriosus preterm" a distant second at 2,000+ articles. With the increased survival of extremely premature infants, the rate of BPD has been growing worldwide (2). Experts in the field of neonatology agree on some basic facts. First, BPD is associated with poor long-term outcomes, not only respiratory but also neuro-developmental (3). Second, BPD rates have been stable or increasing in most recent reports despite a vast body of research over the last two decades (2).

Once BPD has developed, it can only be managed to reduce its complications. There is no magic cure for it. So, the focus of the stakeholders shifted towards the prevention of BPD. The experts realized that prediction models are needed to identify infants with a higher likelihood of developing severe disease to target them for early intervention to prevent BPD. The challenging issue for the researchers trying to put a prediction model together in BPD has been defining the appropriate outcome. While the need for oxygen supplementation at 28 days of life has been an acceptable definition for any BPD, the definition of the levels of severity of BPD has been a matter of debate (4).

The earliest attempts at predicting BPD started in the mid-80s when Lifschitz [1987] demonstrated that infants with intracranial hemorrhage, pulmonary air leaks and increased length of hospital stay had a higher chance of developing BPD (5). Since then, multiple research studies have tried to predict BPD. Peng [2022] published a systematic review of eighteen studies with BPD prediction models (6). Recently, a narrative review by Verder [2023] sheds light on the early prediction and newer therapies of BPD (7). In this article, we will discuss the currently available risk prediction models for BPD prediction and the challenges faced to create a perfect one.

Most of the studies (71%) used oxygen requirement at 36 weeks for their outcome while the rest used oxygen requirement at 28 days of life. Interestingly, some of the studies used oxygen requirement at 36 weeks or death as a composite outcome creating bias in modeling as these are competing variables (8,9). Birth weight and gestational age were the most frequently used predictors which also included multiple other antenatal, perinatal, postnatal, laboratory tests and complications as variables (8). Very few studies have used biomarkers to predict BPD. Almost half of these studies have tried to establish their models to be used early in life, within the first 3 days, while the other half have developed predictive models at 7 or 14 days of life. A recent systematic review involving 64 studies showed that the five most used predictors were gestational age (GA), birthweight, the fraction of inspired oxygen (FiO_2), sex and invasive ventilation requirement. In the same review, 33% of the studies used predictors available within the first 24 hours, another 33% between 2–7 days while the rest used predictors at different points in time (10).

Verder *et al.* [2023] in their detailed narrative review,

laid out an outline of the available contemporary prediction models using mathematical models based in clinical factors and biomarkers such as N-terminal-pro-brain natriuretic peptide (NT-Pro BNP), sphingolipid metabolites, ceramides in tracheal aspirates, and changes in plasma proteome concentrations related to infections and to BPD (7). They also discuss their own study where they were able to predict BPD at birth using artificial intelligence (AI) combining clinical data and infrared spectroscopy of gastric aspirate. While most other biomarkers required complex costly laboratory techniques, the authors state that this bedside technique taking about 10–15 minutes along with the need for surfactant treatment (a clinical factor) has a sensitivity of 88% and specificity of 91% in predicting BPD (11). Although this method has a potential for utilization as a rapid bedside predictor of BPD, the authors acknowledge that further studies are needed to validate this considering the study included a small sample size of 61 infants. The review also goes on to discuss the promising early treatment of BPD including surfactant with budesonide or other additives, inositol, vitamins, recombinant human Clara cell 10 protein, azithromycin, and stem cells. Most of these therapies are in different stages of clinical testing and it remains to be seen whether any of them will make an impact on the outcome.

The review also describes some of the currently available tools to predict BPD such as the model created by Faleh [2021], using receiver operating characteristic (ROC) curves, used gestational age, birth weight, antenatal corticosteroids, surfactant administration, proven infection, patent ductus arteriosus and duration of mechanical ventilation were found to have a large area under the curve (AUC) of close to 0.9 (12). Leon Joseph [2010] and other authors have utilized NT-ProBNP at 4 weeks of life to predict BPD in 34 premature infants (13,14). Recently airway microbiome signature has been studied as a predictor of BPD. Although novel and still premature, studies involving airway lactobacilli and Ureaplasma urealyticum have been associated with the severity of lung disease (15,16). Early lung ultrasound (<32 weeks) in the first 2 weeks of life has also been utilized as a predictor of moderate to severe BPD (17). It is known that intrauterine infection/inflammation is associated with increased severity of BPD (18) while surfactant administration itself has not been associated with severity of BPD but may lead to decrease in mechanical ventilation with an indirect positive effect on it (19).

The review points out the major issue with smaller studies predicting BPD which has been the lack of external validation. Due to substantial variation in management of respiratory problems in premature infants between neonatal intensive care units (NICUs), and considerable variation of BPD rates, it is imperative to externally validate these models which unfortunately most of these studies lack.

The proponents of developing a tool to predict the severity of BPD argue that there are two main reasons to do so: the first is to empower the provider with the ability to discuss the prognosis of the infant with the family as early as possible and secondly to institute early measures to reduce the severity of BPD. In most cases, the questions regarding the outcome of the infant of the treatment team and the parents differ significantly. Parents have simple questions such as: whether their baby is going to survive? Whether he/she will go home on oxygen? How long will be the stay? And if the baby is going to lead a good quality life? Unfortunately, the current array of BPD prediction tools at our disposal are not able to accurately answer those questions. While there are interventions such as the use of non-invasive ventilation, surfactant administration, early initiation of nutrition, avoidance of hyperoxia that can reduce the severity of BPD, there are several others which may or may not have an impact, such as use of corticosteroids and treatment of patent ductus arteriosus. The newer interventions as described by Verder *et al.*, although promising, have not been validated to be generalized (7).

The current standard of care is to maximize our efforts to reduce the severity of BPD with interventions in during pregnancy, at the time of birth and postnatally. I have a considerable apprehension about the impact, if any, of the knowledge of BPD prediction score to the provider. Although every individual infant is different in terms of how they respond to stimuli, treatment can be individualized to a certain extent using AI and precision medicine. Electrical impedance tomography and electromyography of the diaphragm, understanding of the genomic variation in caffeine metabolism and adjusting the dosing individually and breath volatile organic compound analysis are a few examples of precision medicine that could work in neonatology (20). A far more practical approach is to establish formalized standard protocols for every unit with specifically targeted lung sparing strategies. For example, individual preterm infants could be categorized into two groups—high- or low-risk and protocols tailored to the specific group. This would lead to heightened awareness among team members about the possibility of poor outcome leading to closer attention to adjustable therapies (like

fractional inspiration of oxygen) and decreased variability of management among the provider teams. Until we have accurate means to predict the severity of BPD and a good grip on the risks and benefits of the newer therapies, this is the minimum we can do to improve outcome of our tiny babies.

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