Biomarkers, Early Diagnosis, and Clinical Predictors of Bronchopulmonary Dysplasia

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KEYWORDS

• Bronchopulmonary dysplasia • Biomarkers • Prognosis • Early diagnosis • Infant • Premature • Systems biology • Pulmonary hypertension

KEY POINTS

- Bronchopulmonary dysplasia (BPD) is a disease with a clinical operational definition and multiple different clinical subphenotypes.
- Most clinical prediction models of BPD do not have a high predictive accuracy.
- Various biofluid biomarkers have been studied over the years, but none are currently used in routine clinical care.
- Newer omic strategies are promising for the discovery of novel biomarkers of BPD diagnosis, prognosis, and therapeutic response.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a common morbidity in extremely preterm infants. However, BPD defined by oxygen requirement even when more precisely assessed by the physiologic definition of BPD[1] is only an operational definition, which does not indicate the magnitude of lung disease or the underlying disease process. Lung disease process in BPD is variable, as certain infants with BPD have pulmonary hypertension (PH) as a major component of their pathophysiology,[2] whereas others have severe tracheobronchomalacia,[3] and many have patchy atelectasis or cystic

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lesions in their lung parenchyma.[4] It has increasingly become evident that severe BPD may be a different entity from mild or moderate BPD, both in terms of clinical operational definition as well as in terms of genetic predisposition.[5] This genetic predisposition is very different by race/ethnicity, indicating that biological pathways (and resulting biomarkers) contributing to BPD in different infants are probably dissimilar.[5] Therefore, it is likely that what is now termed *BPD* is not a single entity, or even a spectrum of disease resulting from a single pathophysiologic process, but a combination of several chronic lung diseases characterized by a common at-risk population of infants in the saccular or early alveolar stage of lung development with varying magnitudes of impairment of alveolar septation, lung fibrosis, and abnormal vascular development and remodeling. To modify Leo Tolstoy's quote on happy families from *Anna Karenina*, all normally developed preterm lungs are alike; each BPD lung is abnormal in its own way. The natural corollary is that the clinical predictors and biomarkers of each of these subphenotypes of BPD may be different, depending on the pathophysiology.

In this article, the authors first discuss the predictors and biomarkers starting from the clinical arena and then move on to progressively more sophisticated investigations and research esoterica (which may be at the bedside in the near future).

WHY DO WE NEED BIOMARKERS OR PREDICTORS?

Many interventions to reduce the risk of BPD have been tested in randomized clinical trials, but only a few have shown significant treatment effects.[6] Hence, earlier disease predictors are warranted to initiate preventive strategies in select patients. A biomarker has been defined as "a characteristic that is, measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[7,8] Biomarkers are any clinical features, radiological findings, or laboratory-based test markers that characterize disease activity, which are useful for early diagnosis, prediction of disease severity, and monitoring disease processes and response to therapy. Biomarkers are valuable for earlier diagnosis; it is possible that detection of BPD at an earlier stage may enable initiation of therapies when they may be more effective (a window of opportunity). It is also possible that nondetection of risk for BPD may enable the avoidance of therapies and their potential hazards.

Prognosis (risk prediction for the development of BPD or risk prediction for outcome of BPD in infants diagnosed with BPD) can also be evaluated using appropriate biomarkers. Similar to earlier diagnosis, the determination of a very high risk for BPD may enable the use of targeted therapy (eg, the use of vitamin A supplementation in extremely low-birth-weight [ELBW] infants[9]) and determination of a very low risk for BPD may enable the avoidance of therapies. As mentioned earlier, BPD has much heterogeneity with many subphenotypes in clinical presentation. The use of biomarkers may enable targeting specific therapies to specific subphenotypes (eg, use of inhaled nitric oxide in infants with biomarkers indicating early elevations in pulmonary arterial pressure).

Biomarkers may also be useful for following the efficacy of therapy as a surrogate measure. For example, the rate of the decrease of blood b-type natriuretic peptide (BNP) may possibly enable a clinician to determine the efficacy of a therapy for PH in BPD. The search for reliable biomarkers in BPD is ongoing and remains a challenge. Important issues to be addressed include the accuracy and reliability of biomarkers for the clinical state of interest, evaluation of clinical utility and cost-effectiveness, and real-world effectiveness compared with other biomarkers.[10]