Physiologic Pulmonary Phenotyping of Infants Born Preterm and Post-Discharge Respiratory Morbidity

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Objective To determine whether airway and parenchymal function identifies subgroups of infants born preterm according to the predominant pulmonary pathophysiology, and whether these subgroups have different risks for respiratory disease during infancy.

Study design We prospectively enrolled a cohort of 125 infants born preterm with planned clinical follow-up after neonatal intensive care unit discharge. The study included monthly questionnaires for wheeze and visits to a physician or care provider for any respiratory illness. In addition, infant lung function testing near 5 months corrected-age included measures of airways and parenchymal function using forced expiratory flows, alveolar volume (V_A), and the carbon monoxide transfer constant (diffusion capacity of lung [D_L]/V_A). Phenotypes were defined using 2 approaches: an a priori defined phenotypes based on forced expiratory flow 75% and D_L/V_A z-scores, and an unbiased approach to classifying infants using k-means clustering.

Results We identified 4 pulmonary physiologic phenotypes that distinguished participants with predominantly decreased airway and/or parenchymal function. Although the worst physiologic phenotypes were associated with a lower gestational age at birth, these phenotypes had a better predictive value than gestational age, sex, and diagnosis of bronchopulmonary dysplasia for increased respiratory morbidity during infancy (area under the curve = 0.71 vs 0.63 for respiratory illness and 0.69 vs 0.63 for wheeze).

Conclusions Physiologic pulmonary phenotypes of infants born preterm were associated with differential risks for respiratory morbidities as infants, which may identify heterogeneous risks for long-term respiratory sequelae to individualize therapeutic strategies. *(J Pediatr 2025;279:114475)*.

Advances in perinatal care have led to dramatic improvements in the survival of infants born extremely preterm who have increased risk for bronchopulmonary dysplasia (BPD),[1-5] a condition leading to prolonged needs for respiratory support during the birth hospitalization. However, the clinical diagnosis of BPD is a poor surrogate for the subsequent risk for respiratory problems after preterm birth.[6-11] Most infants born preterm are not born at extremely low gestational ages (GAs), and most do not develop BPD[11]; however, infants without BPD often have impaired lung function and increased respiratory disease through childhood and into adulthood. The impaired lung function is not homogeneous, representing a spectrum of airway and parenchymal dysfunction,[12] which may contribute to differing late respiratory morbidities following preterm birth.[10,11]

Assessments of adult chronic lung disease have demonstrated pulmonary phenotypes with specific disease mechanisms.[13,14] Among infants born full-term, studies have demonstrated that the pulmonary physiologic phenotype of low airway function is associated with increased wheeze during infancy, as wells as an increased risk of respiratory morbidity into adulthood.[15-17] There is a growing literature on the impact of preterm birth on respiratory function throughout childhood beyond the standard definitions of BPD at 36 weeks PMA. Infants born preterm without a BPD diagnosis are often considered not to have significant respiratory problems at discharge; however, these infants may come to the attention of pediatric pulmonologists for recurrent respiratory illness following neonatal intensive care unit (NICU) discharge and are at risk for prematurity-associated lung disease throughout childhood. In contrast to studies of full-term birth, no studies have

A	Airway function
AUC	Area under the curve
BPD	Bronchopulmonary dysplasia
FEF	Forced expiratory flow
GA	Gestational age
NICU	Neonatal intensive care unit
P	Parenchymal function
VA	Alveolar volume

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evaluated whether there are pulmonary physiologic phenotypes (defined by airway and parenchymal function during infancy) which are associated with an increased risk for respiratory illness early in life following preterm birth. An National Institutes of Health Workshop on prematurity and lung disease concluded that improved characterization of respiratory phenotypes after preterm birth is necessary to better understand disease heterogeneity and variability in outcomes; to accurately identify at-risk infants for late respiratory disease; to improve specific therapeutic targets; and to enhance clinical trial design for early interventions.[9]

We hypothesized that infant respiratory illness after preterm birth is variable due to differential impairment of airway and parenchymal function, and that the relative contributions of impaired airway and parenchymal function can identify physiologic phenotypes that will be better than GA or sex for identifying risk for respiratory morbidity. To test this hypothesis, we measured forced expiratory flows (FEFs) and lung diffusion in a cohort of infants born preterm following discharge from the NICU and evaluated their relationships to respiratory illness.

Methods

Participants

The study was approved by the Institutional Review Board at the University of Indiana School of Medicine and registered (NCT03906708). Infants born preterm were recruited between 2019 and 2023, with written informed consent obtained from the parents or guardians prior to discharge from Indiana University Hospital NICU and from Saint Francis Hospital NICU in Indianapolis, Indiana. Participants were excluded if the infant had a congenital anomaly of the respiratory system, or clinical concerns for significantly impaired neurodevelopment that would preclude the use of sedation for the lung function testing as an outpatient. Clinical data for the infant and the mother were obtained from hospital charts and electronic medical records.

Infant Pulmonary Function

FEFs by the raised volume rapid compression technique, as well as alveolar lung volume and the rate constant for carbon monoxide diffusion using the induced respiratory pause technique, were measured following chloral hydrate sedation, as previously described.[18,19] Outcomes included forced vital capacity and FEFs at 75%, 50%, and between 25% and 75% expired volume (FEF_{75}, FEF_{50}, FEF_{25-75}), as well as alveolar volume (V_A) and diffusion capacity of lung (D_L)/V_A, adjusted for hemoglobin.

Respiratory Questionnaire

Parents or guardians were contacted to complete a monthly questionnaire that included information related to wheeze, visits to a physician or care provider for any respiratory illness, and hospitalization for a respiratory illness (**Appendix Table A1**; available at www.jpeds.com).

Statistical Analysis

Lung function z-scores were calculated using data collected from infants born full-term evaluated in our infant pulmonary function laboratory using the same equipment (**Appendix Table A2**; available at www.jpeds.com). Phenotypes were defined using FEF_{75} and D_L/V_A, which were preselected a priori based upon previous research studies of infants using these methodologies.[18,20-22] Clinical variables were compared across phenotypes using analysis of variance or chi-square tests. Fisher's exact tests were used when frequency counts were low. Respiratory survey outcomes were summarized as any reported outcome in participants with at least 6 of 12 questionnaires completed. Logistic regression analyses were used to assess the association between phenotypes and reported respiratory illness on survey after adjusting for GA and sex. Area under the receiver operating characteristic curve was used to compare the discriminative ability of the different approaches to calculating phenotypes. In addition to our a priori selected pulmonary function parameters, we also used an unbiased approach for selecting pulmonary function parameters to ensure that we had selected parameters that best defined physiologic phenotypes. Analyses were performed using R version 4.1.3[23] and SAS version 9.4 (The SAS Institute).

Results

Participants

The demographics of the 125 infants born preterm and evaluated with pulmonary function testing at a clinically stable outpatient visit are summarized in **Table I**. The average GA was 31 weeks (range: 24-36 weeks), 47% were male and 66% were White. Intrauterine growth restriction and maternal smoking were identified in 3% and 10% of this cohort, respectively. Thirty-seven infants (30%) were diagnosed with BPD based on established Jensen criteria.[24] The majority of infants with BPD had the lowest severity (grade-1: n = 23, grade-2: n = 12, grade-3: n = 2) at the time of the infant pulmonary function study, the mean corrected age was 6 months and the group had only mildly negative length and weight z-scores (**Table I**).

Group Pulmonary Function Parameters

The pulmonary function results for the group of infants born preterm expressed as z-scores are summarized in **Figure 1**A. All lung function measures of FEF and D_L/V_A had a negative mean z-score; only V_A had a positive mean z-score.

Pulmonary Phenotypes

Using our a priori selected airway and parenchymal parameters, 4 pulmonary phenotypes were characterized by FEF_{75} and D_L/V_A z-scores above (+) and below (−) zero. The distribution of infants among these 4 phenotypes is illustrated in **Figure 1**B. Most [71 (57%)] had airway function and parenchymal z-scores < zero (**A**−**P**−; lower left quadrant). Compared with this most frequent

Table I. Participant Demographics (n = 125)

Prenatal	
Gestational age (weeks), mean (std)	31 (3)
Female sex	66 (53%)
Race	
Black or African American	35 (28%)
Multiple or not reported	8 (7%)
White	82 (66%)
Hispanic or Latino ethnicity	8 (6%)
Caesarean delivery	94 (75%)
Pre-eclampsia	44 (35%)
Gestational diabetes	13 (10%)
Antenatal steroids	110 (88%)
Chorioamnionitis	9 (7%)
Maternal smoking	12 (10%)
Maternal alcohol use	7 (6%)
Maternal illicit drug use	11 (9%)
Birth weight (kg), mean (std)	1.7 (0.6)
Intrauterine growth restriction	3 (3%)
Postnatal	
Administered surfactant	59 (47%)
Pulmonary hypertension	11 (9%)
Necrotizing enterocolitis	3 (2%)
Patent ductus arteriosus	16 (13%)
Intraventricular hemorrhage	6 (5%)
Retinopathy of prematurity	17 (14%)
BPD classification (1: n = 23; 2: n = 12; 3: n = 2)	37 (30%)
Days of high flow nasal cannula or CPAP, median (IQR)	13.5 (3.5, 31)
Days on Sipap or NiPPV, median (IQR)	1 (0, 5.5)
Days of mechanical ventilation, median (IQR)	0 (0, 2)
At time of PFT	
Nasal oxygen	6 (5%)
Asthma meds (inhaled bronchodilator +/or corticosteroid)	16 (13%)
Hypertension meds	0 (0%)
Corrected age (months), mean (std)	6 (2)
Length z-score, mean (std)	−0.6 (1.1)
Weight z-score, mean (std)	−0.1 (1.2)

IQR, interquartile range; *CPAP*, continuous positive airway pressure; *PFT*, pulmonary function tests.

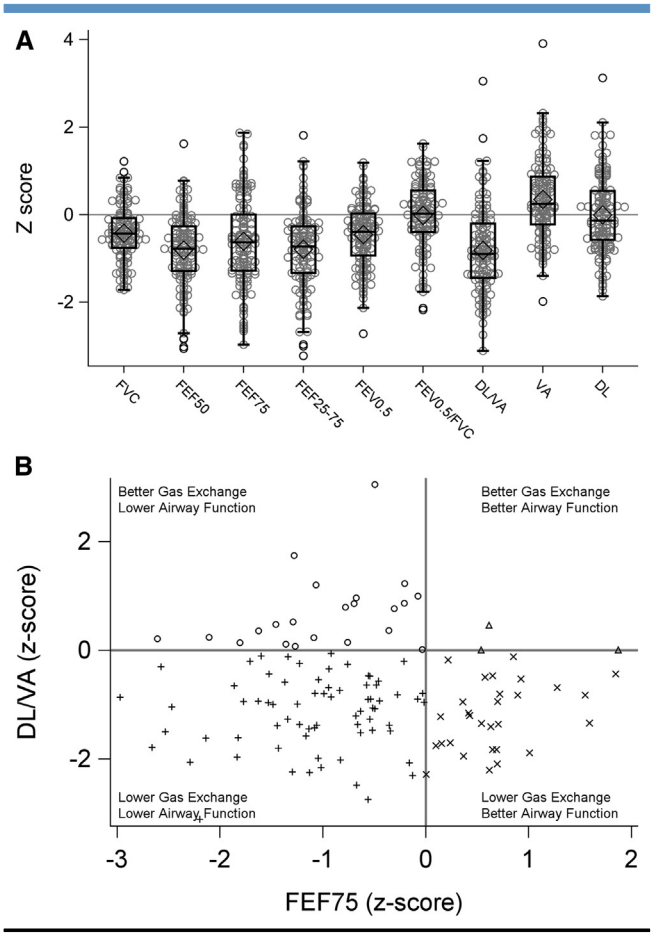

Figure 1. A, Distribution of participants' airway and parenchyma z-scores based on our laboratory standards from healthy full-term participants. **B,** Distribution of participants among the 4 a priori pulmonary physiologic phenotypes defined by airway (FEF_{75}) and parenchymal (D_L/V_A) z-score values above (+) and below (−) zero. Most infants had **A** and **P** function with z-scores < zero (**A**−**P**−; lower left quadrant), with fewer participants in the **A**−**P**+ (upper left quadrant) and **A**+**P**− (lower right quadrant) groups. Three participants had A and P function with z-scores > zero [**A**+**P**+; upper right quadrant].

phenotype, there were fewer and similar numbers of infants in **A**−**P**+ (upper left quadrant, n = 22) and **A**+**P**− (lower right quadrant, n = 29); 3 infants had airway function and parenchymal parameters with z-scores > zero [**A**+**P**+; upper right quadrant]. Z-scores for D_L/V_A and FEF_{75} were not significantly correlated (P = .81). The demographic comparisons for the phenotypes are summarized in **Table II**. The infants in the **A**−**P**− phenotype had lower GA, and there was a greater percentage of females in quadrant 4 (**A**−**P**+); however, the 3 groups did not differ at the time of pulmonary function tests evaluation for corrected-age, as well as weight and length z-scores. The selection of unbiased phenotypes is summarized in the Appendix (**Figures 1**, A and B, **Appendix Tables A3** and **A4**; available at www.jpeds.com).

Pulmonary Function Phenotype and Respiratory Outcomes

Ninety-five percent of parents completed >6 monthly surveys. The completion rate of the survey was the same for the different phenotypes and clusters. At least one respiratory illness was reported for 79 (66%) infants, including 16 requiring hospitalization. Wheeze was reported at least once for 56 (47%) infants. The respiratory illness outcomes are summarized by phenotype in **Figure 2**A. Those in the lower airway function groups (**A**−**P**−; **A**−**P**+) were more likely to report wheeze compared with **A**+**P**− phenotype (54%, 55%, and 27%; $P < .05$). Those with low airway function (**A**−**P**−; **A**−**P**+) were also more likely to report respiratory illness compared with **A**+**P**− phenotype (71%, 77%, and 31%, respectively; $P < .01$).

The associations between respiratory survey outcomes and pulmonary phenotypes are summarized in **Table III**. The odds ratios illustrate that the phenotypes added to the discrimination between respiratory outcomes over that provided by GA and sex. In addition, for the 16 infants

Table II. Participant Characteristics Defined by Physiologic Pulmonary Phenotypes

Birth	A+P− (n = 29)	A−P− (n = 71)	A−P+ (n = 22)	*P* value
GA (weeks), mean (std)	32.6 (2.8)	30.5 (3.3)	31.8 (2.8)	.01
Female sex	14 (48%)	31 (44%)	19 (86%)	<.01
Jensen BPD classification				.06*
1	3 (75%)	15 (60%)	5 (62%)	
2	1 (25%)	8 (32%)	3 (38%)	
3	0	2 (8%)	0	
At time of PFT				
Corrected age (months.), mean (std)	5.0 (0.9)	5.8 (2.2)	5.2 (1.7)	.13
Weight z-score, mean (std)	−0.3 (1.1)	−0.1 (1.2)	0.1 (1.1)	.42
Length z-score, mean (std)	−0.5 (1.0)	−0.6 (1.3)	−0.5 (0.9)	.92

PFT, pulmonary function tests.
*Fisher's exact test; phenotype **A+P+** is not included in the Table, as there were only 3 subjects.

that were hospitalized for a respiratory illness, all 16 were in had the **A−P−** phenotype. Of the 69 infants with **A−P−** phenotype, 59 had GA <32 weeks, and 32 had a BPD diagnosis. Among this group, those hospitalized compared with those not-hospitalized had significantly lower z-FEF_{75} (−1.73 vs −0.86; $P < .01$) and significantly lower z-D_L/V_A (−1.45 vs −0.83; $P < .05$); however, they did not differ in the frequency of BPD diagnosis (51% vs 70%; $P = .27$).

The areas under the curve (AUCs) increased only slightly when including the interaction between z-FEF_{75} and z-D_L/V_A, both as continuous measures, compared with the binary classification; from 0.69 to 0.71 for wheeze, and from 0.71 to 0.72 for respiratory illness. The interaction was significant for the respiratory illness variable indicating that the association with both airway and parenchymal measurements were relevant. We also evaluated all other possible combinations of airway and parenchymal variables; however, none outperformed FEF_{75} and D_L/V_A (**Figure 2**B).

The inclusion of BPD did not improve the ability to discriminate between those with and without wheeze or any respiratory morbidity (**Figure 3**A). This contrasted to the inclusion of the pulmonary physiologic phenotype variable, which resulted in higher AUC values compared with only including GA and sex. We also evaluated whether including the pulmonary function parameters as continuous, rather than dichotomous variables, as well as including BPD, made a difference. The addition of FEF_{75} to GA and sex improved the prediction of wheeze but not any respiratory morbidity. The addition of D_L/V_A and/or BPD did not improve the prediction (**Figure 3**B).

The preselected a priori phenotypes performed equal or better (higher AUC) than the unbiased phenotypes at discriminating those who reported a respiratory event (**Appendix Table A5**; available at www.jpeds.com).

Lastly, we evaluated the impact of z-scores <0 as our selection of the phenotypes using 2 different approaches: varying z-score cut-offs ranging from −1.75 to 0, with 0.25 increments, or using a decision tree analysis. Both approaches yielded similar cut-offs, which differed for each respiratory outcome and each lung function parameter. Z-FEF_{75} cut-offs for wheeze and respiratory illness were −0.55 and −0.11, respectively, and z-D_L/V_A cut-offs were −1.75 and 0, respectively. However, the AUC values were not significantly different for these cut-offs compared with our original a priori z-scores <0 for wheeze ($P = .18$) or respiratory illness ($P = .62$).

Discussion

Evaluating infants born preterm over a wide spectrum of GA (23-37 weeks) using measures of airway and parenchymal lung function, our study identified physiologic phenotypes that predicted the increased risk for respiratory illness for preterm birth during the first year following NICU discharge. These physiologic phenotypes performed better than GA, sex, and the diagnosis of BPD. Our findings also suggest that at this very young age, impaired airway function was relatively more important than impaired parenchymal function as a predictor. Overall, our findings support our hypothesis that infant respiratory morbidities after preterm birth are variable due to differential impairment of airway and parenchymal function, which can be characterized as distinct physiologic phenotypes.

In our study, the mean GA was 31 weeks. Infants born at <29 weeks GA have higher risks for the development of BPD and <35% of our cohort had BPD. Most of the infants with BPD in this study were in the least severe classification, which is also the situation for most preterm infants. Although most studies of preterm birth focus upon the outcome of BPD to define severity of respiratory disease, the clinical diagnosis of BPD made at 36 weeks of postmenstrual age provides limited insight into the underlying pulmonary pathophysiology or subsequent risk for respiratory morbidity. Our cohort had a high incidence (66%) of respiratory illnesses, and 45% had at least one episode of wheeze. In addition, 13% were hospitalized for a respiratory illness. This degree of respiratory morbidity is consistent with previously published studies of infants born preterm but lower than prospective studies of infants born at lower GAs.[25-27]

Our cohort was evaluated in the first year following discharge and had impaired airway and parenchymal

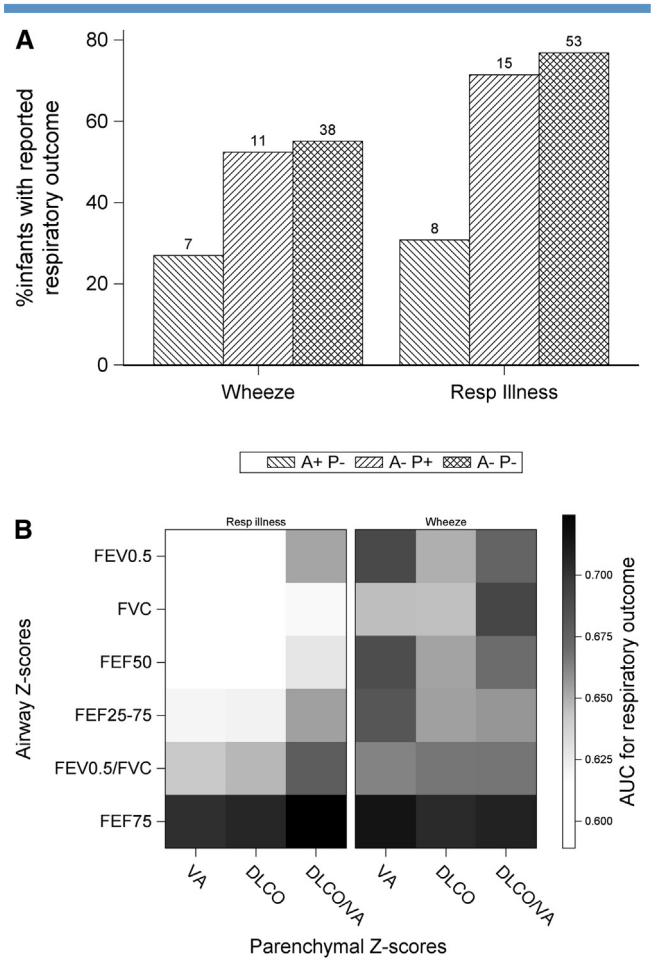

Figure 2. **A,** Frequency of respiratory outcomes of wheeze and respiratory illness by pulmonary physiologic phenotypes. **B,** Pulmonary function parameter combinations as predictors of respiratory outcomes. The heatmap displays the area under curves (AUCs) values from the logistic regression models with wheeze or respiratory illness as the outcomes and the different pairwise combinations of each airway and parenchymal z-score. The 2 parameters included in the a priori phenotype (FEF_{75} and D_L/V_A) had the highest AUC as predictors of respiratory outcomes.

Table III. Association of Respiratory Outcomes With Pulmonary Physiologic Phenotypes Based Upon Negative (−) or Positive (+) z-Score for Airway (A) and Parenchymal (P) Function

Outcome	AUC	Variable	OR (95% CI)
Respiratory illness	0.71	GA	0.95 (0.83-1.09)
		Female	1.10 (0.45-2.72)
		A−P+ vs **A+P−**	5.22 (1.40-19.40)
		A−P− vs **A+P−**	6.67 (2.36-18.83)
Wheeze	0.69	GA	0.88 (0.78-1.00)
		Female	1.23 (0.54-2.81)
		A−P+ vs **A+P−**	2.54 (0.71-9.08)
		A−P− vs **A+P−**	2.58 (0.92-7.20)

CI, confidence interval; *OR*, odds ratio.

function. These infants had mean z-scores for airway and parenchymal function that were <0 and only 3 of 125 participants had values > 0. These findings are consistent with previous studies for participants evaluated as infants, and also for those evaluated as older children.[7,20-22,28] Our selection of FEF_{75} and D_L/V_A to define physiologic phenotyping based upon airway and parenchymal function was based upon our previous infant research. FEF_{75} is reduced in infants born preterm, both those with BPD, as well as late preterm infants.[20,21] D_L/V_A is also reduced following preterm birth, and results equally from the membrane and pulmonary capillary volume components, thus consistent with impaired alveolarization.[18,22] Our combined assessments of FEF_{75} and D_L/V_A identified 4 pulmonary phenotypes that distinguished infants with predominantly airway and/or parenchymal function. Those infants with low airway phenotypes, whether they had z-score for D_L/V_A above or below zero, were more likely to report wheeze compared with those with better airway function. This finding among infants born preterm is consistent with prior studies of infants born full-term; lower FEFs during infancy was associated with an increased risk of wheeze during infancy.[15,16] We also verified that the 2 parameters we used to define our pulmonary physiologic phenotype (FEF_{75} and D_L/V_A) were the best combination of airway and parenchymal factors regarding their association with respiratory outcomes.

When we used continuous variables of FEF_{75} and D_L/V_A, rather than dichotomous variables, we found that impaired airway function, not impaired parenchymal function, was the significant predictor of increased wheeze and any respiratory morbidity in the year following NICU discharge. Although this might suggest that impaired parenchymal function was not clinically important during infancy, all infants hospitalized for respiratory illness had the worst physiologic phenotype, which included impaired airway and parenchymal function. As wheezing is the most frequent respiratory symptom in this age group and only a small percentage of our cohort were hospitalized for a respiratory illness, we are not able to discern the relative importance of impaired parenchymal function at this young age. As the airways are embedded within the lung parenchyma, maldevelopment of the lung parenchyma may also contribute to impaired airway function, as well as impaired gas exchange. In addition, follow-up of asymptomatic young adults who were born preterm exhibit not only lower D_L/V_A, but also early pulmonary vascular disease.[29] The impaired lung function in adults born preterm has become well-recognized as an important risk factor for the development of chronic obstructive pulmonary disease.[7,28,30-34] Therefore, life-long impairment of distal lung parenchymal growth may become more clinically apparent at an older age and contribute to the development of chronic obstructive pulmonary disease in adulthood.

The use of an unbiased approach to identifying phenotypes partitions participants into groups based on similarity of their lung function parameters. This technique is not guaranteed to be associated with any meaningful clinical

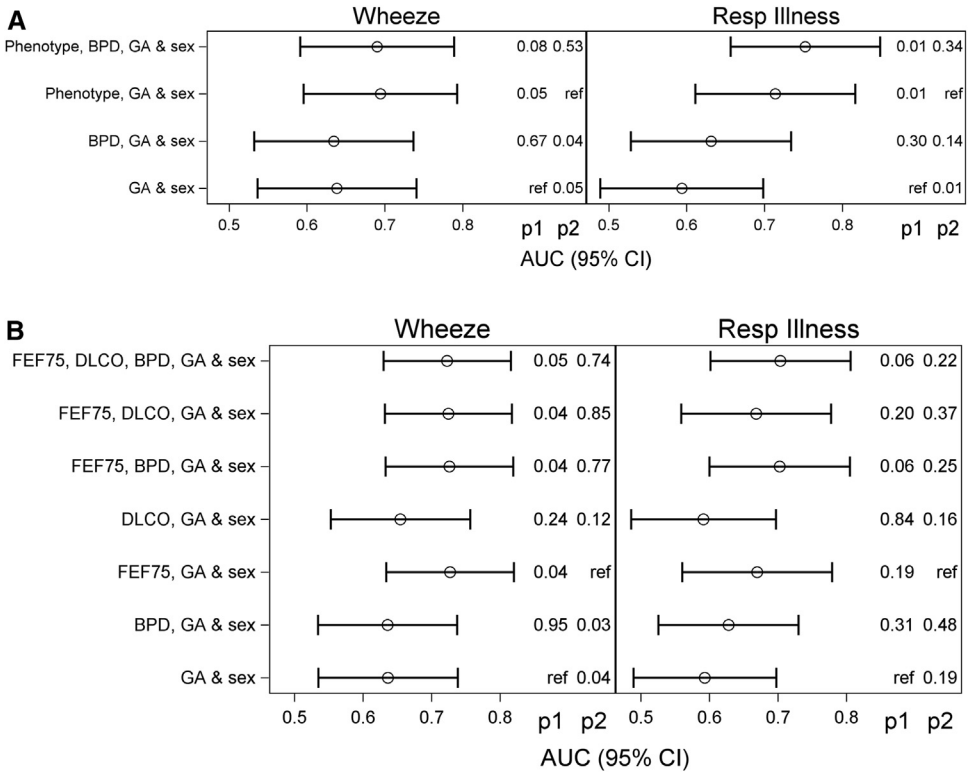

Figure 3. The area under curve (AUC) values and corresponding 95% confidence intervals from the logistic regression models with wheeze and respiratory illness as the outcomes and different combinations of variables are displayed with z-FEF_{75} and z-$D_LV/_A$ expressed as **(A)** phenotypes, and **(B)** continuous variables. Each plot includes 2 *P* values; p1 is the comparison between that model and the model with only GA and sex as the referent. The p2 *P* value uses a separate model that includes either the a priori phenotype **(A)** or FEF_{75} **(B)** as the referent group.

outcomes. Although we found some overlap of participants for the *a priori* and the unbiased phenotyping, *a priori* selection performed as well or better than the unbiased selection in their associations with respiratory outcomes (**Appendix**; available at www.jpeds.com). Furthermore, we verified that the set of 2 parameters included in the a priori phenotype (FEF_{75} and D_L/V_A) were the best combination of airway and parenchymal factors regarding their association with respiratory outcomes. Importantly, both approaches to pulmonary phenotyping using airway and parenchymal function provided a better assessment than GA and sex as predictors of increased risk for respiratory illness.

Our study had several strengths and limitations. The strengths include our unique assessment of airway and parenchymal function in infants using techniques we developed for this very young age.[18,19] In addition, our z-scores were based upon body length and sex using values from healthy infants born full-term evaluated in the same laboratory, which minimizes potential problems using reference values from other laboratories. Lastly, the incidence of respiratory illness was obtained from monthly questionnaires, which minimized parental recall bias.

Potential limitations of our study include that our group of infants born preterm did not represent those with the most severe respiratory disease, a group that often have neurological complications and more severe lung disease that would have excluded them from sedation at follow-up for lung function evaluation. The exclusion of these most severe participants may make our findings less generalizable; however, we believe that our cohort reflects the wide spectrum of preterm birth, including infants born preterm who are often misperceived as not having any significant respiratory problems at discharge. Our study demonstrated and characterized altered lung function in this group of infants who often experience recurrent respiratory illness after discharge and constitute high risk participants for prematurity-associated lung disease.

Another limitation is the evaluation of only 125 infants. Although this is a small sample size, this is large study for a single center, particularly with infant follow-up requiring outpatient lung function using mild sedation. Our assessment of respiratory illness following discharge was obtained by questionnaires. As the infants were not examined by a medical practitioner during the reported respiratory illness, we are not able to distinguish upper and/or lower respiratory illness, as well as the accuracy of wheeze identified by the parent. In addition, the time-period for our study included the onset of Covid pandemic, which may have resulted in greater respiratory precautions and isolation than usual, thus potentially underestimating the frequency and severity of respiratory illness.

Our use of airway and parenchymal measurements of these infants is a strength; however, these research measurements are not commercially available, thus limiting the generalizability of our pulmonary phenotyping. However, the development of other methodologies may provide equivalent phenotyping, particularly an assessment of airway function, which appears to be the more important phenotyping at this young age.

In summary, we characterized pulmonary physiologic phenotypes in infants born preterm based upon the assessment of airway and parenchymal function. The physiologic phenotypes were associated with a greater risk for respiratory morbidity during infancy, following NICU discharge. The phenotype with lower values for both airway and parenchymal function was associated with a lower GA; however, among our cohort, the risk for increased respiratory morbidity was best predicted by pulmonary physiologic phenotypes, rather than GA, sex, and BPD. Our findings address some of the limitations identified by the National Institutes of Health Workshop on prematurity and lung disease.[9] Better pulmonary phenotyping of infants born preterm has the potential to improve our understanding of the determinants of the heterogeneous pulmonary pathology in these participants, the identification of specific endotypes, and provide specific therapeutic interventions to minimize the long-term respiratory sequelae that may need to be differentially directed at airway and parenchymal function in this population. ■

CRediT authorship contribution statement

Robert S. Tepper: Writing – original draft, Formal analysis, Conceptualization. **Brandie D. Wagner:** Writing – original draft, Formal analysis, Data curation. **Jeffrey Bjerregaard:** Data curation. **Christina Tiller:** Data curation. **Laura Amos:** Data curation. **Greg Sokol:** Data curation. **Dominic Adducci:** Formal analysis. **Steven H. Abman:** Writing – original draft, Formal analysis, Conceptualization.

Declaration of Competing Interest

This study received funding from NHLBI RO1 HD095067. The authors declare no conflict of interest.

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