The Diagnosis of Bronchopulmonary Dysplasia in Very Preterm Infants: An Evidence-Based Approach

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Online Data Supplement

Investigators for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Marie Gantz and Mr. Scott McDonald had full access to all study data and take responsibility for the integrity of the data and accuracy of the data analysis.

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Table E1. Modified* 2018 National Institute of Child Health and Human Development workshop definition for bronchopulmonary dysplasia

	Treatment with the following mode of respiratory support and FiO_2 at 36 weeks postmenstrual age or discharge home, if earlier:				
BPD severity	Breathing in room air	NC < 1L/min	NC 1 to < 3L/min	NC ≥ 3L/min, nCPAP, or NIPPV	Invasive PPV
No BPD	21%	21%	21%	-	-
Grade 1	-	22-70%	22-29%	21%	-
Grade 2	-	71-100%	30-100%	22-29%	21%
Grade 3	-	-	-	30-100%	22-100%

* The following modifications were made to the published criteria[1] to enable application to the study data: (1) no evaluation for radiographic evidence of parenchymal lung disease was performed, (2) respiratory support assessed only at 36 weeks PMA and not according to the supplemental oxygen level required to maintain arterial oxygen saturation of 90-95% for ≥3 consecutive days.

C-statistics for late death or serious respiratory morbidity and late death or moderate to severe neurodevelopmental impairment calculated for this definition using multivariable logistic regression: 0.768 and 0.738, respectively. Both values are significantly lower ($p \leq 0.002$) than those generated for the optimal definition of BPD.

Abbreviations: BPD, bronchopulmonary dysplasia; FiO_2, fraction of inspired oxygen; NC, nasal cannula; nCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; PPV, positive pressure ventilation

Table E2. Characteristics of the included and excluded infants

Characteristic	Infants included in the analysis n=2677	Infants lost to follow-up or missing data N=742	p-value*
Gestational age, weeks - mean (SD)	25.2 (1.3)	25.3 (1.2)	0.02
< 27 weeks, n (%)	2380 (89%)	666 (90%)	0.55
27-31$^{6/7}$ weeks, n (%)	297 (11%)	76 (10%)	
Birth weight, g - mean (SD)	765 (168)	789 (170)	<0.001
Male sex, n (%)	1356 (51%)	384 (52%)	0.53
Small for gestational age, n (%)	219 (8%)	42 (6%)	0.02
Race, n (%)			0.02
Black	1225 (46%)	274 (42%)	
White	1312 (49%)	327 (50%)	
Other	140 (5%)	51 (8%)	
Ethnicity, n (%)			<0.001
Hispanic	322 (12%)	129 (18%)	
Non-Hispanic	2355 (88%)	573 (82%)	
Antenatal corticosteroids, n (%)	2397 (90%)	667 (91%)	0.41
Antenatal magnesium, n (%)	2077 (78%)	558 (78%)	0.88
Maternal marital status - married n (%)	1126 (42%)	304 (41%)	0.64
Insurance type, n (%)			<0.001
Medicaid	1528 (57%)	463 (63%)	
Private	1012 (38%)	222 (30%)	
Self-pay/Uninsured	101 (4%)	38 (5%)	
Other	36 (1%)	17 (2%)	
Maternal level of education – less than high school, n (%)	499 (19%)	140 (22%)	0.04

Missing data: Male sex (n=4), SGA (n=4), Race (n=90), Ethnicity (n=40), Antenatal steroids (n=6), Antenatal magnesium (n=26), Marital status (n=2), Insurance type (n=2), Maternal education (n=118).

* P-values calculated using Fisher's exact test (categorical variables) or Wilcoxon two-sample tests (continuous variables).

Table E3. Comparison of c-statistics calculated using the full cohort and 100 bootstrap cohorts

BPD definition	Late death or serious respiratory morbidity		Late death or moderate to severe neurodevelopmental impairment	
	Full cohort c-statistic	Internally-validated c-statistic	Full cohort c-statistic	Internally-validated C-statistic
1	0.741	0.731	0.727	0.719
2	0.763	0.755	0.736	0.728
3	0.741	0.732	0.725	0.717
4	0.780	0.771	0.743	0.735
5	0.776	0.767	0.740	0.732
6	0.784	0.776	0.745	0.738
7	0.782	0.774	0.743	0.736
8	0.779	0.770	0.741	0.733
9	0.775	0.766	0.738	0.730
10	0.741	0.732	0.730	0.722
11	0.764	0.756	0.739	0.731
12	0.742	0.733	0.728	0.720
13	0.781	0.773	0.745	0.738
14	0.776	0.767	0.742	0.734
15*	0.785	0.777	0.747	0.740
16	0.783	0.775	0.746	0.739
17	0.780	0.772	0.744	0.737
18	0.776	0.768	0.741	0.734

* Definition 15 produced the highest c-statistics for both study outcomes in the full cohort and through bootstrap internal validation

Abbreviations: BPD, bronchopulmonary dysplasia; NDI, neurodevelopmental impairment

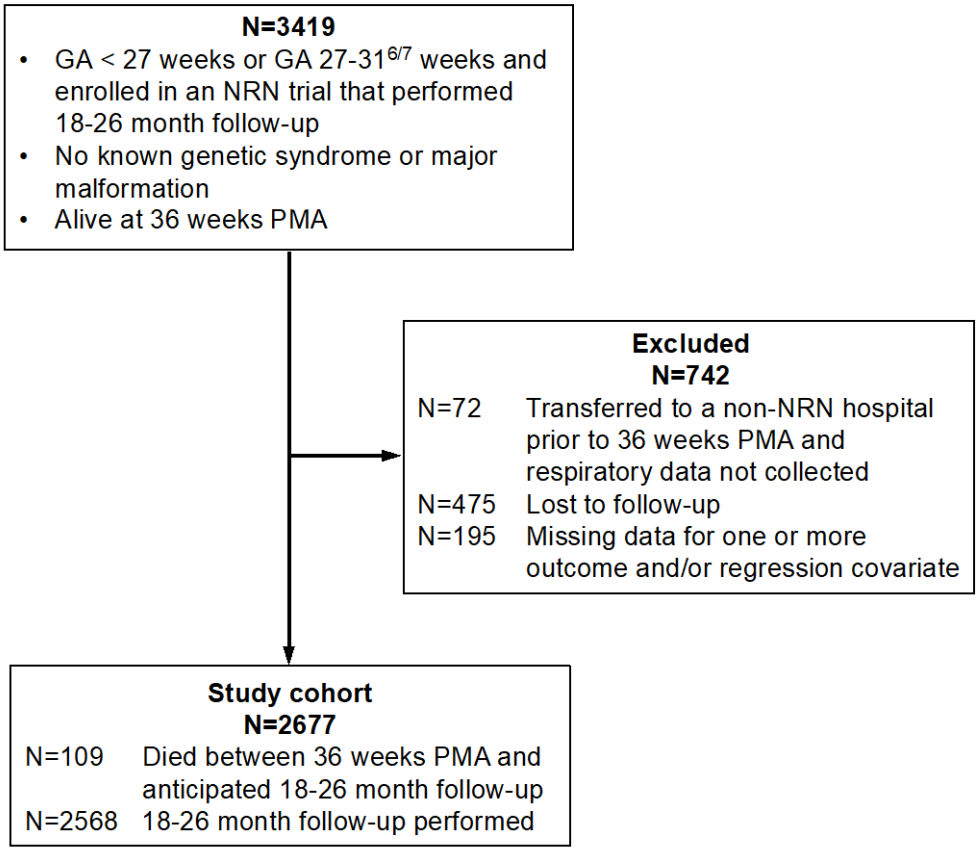
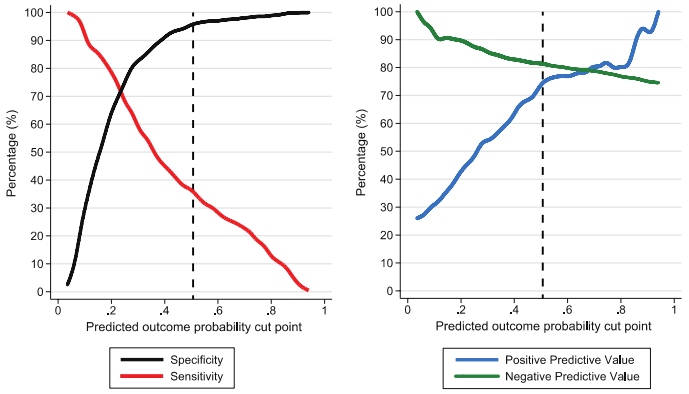


Figure E1. Flow diagram of study infants.

Abbreviations: GA, gestational age; NRN, neonatal research network; PMA, postmenstrual age.

A Late death or serious respiratory morbidity

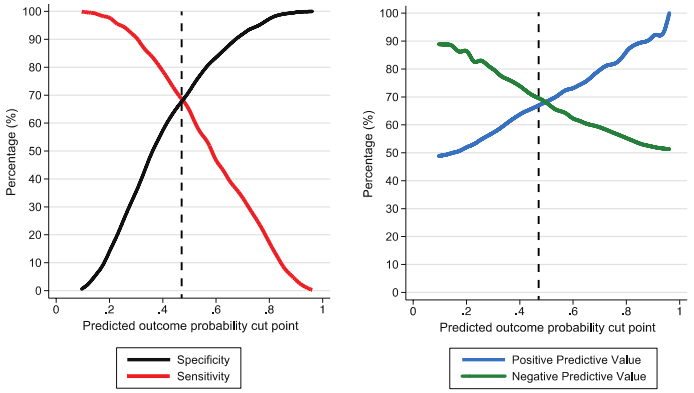


Diagnostic performance of the optimal BPD definition for predicting late death or serious respiratory morbidity

	Predicted outcome probability cutpoint		
Performance measure	**25%**	**51%***	**75%**
Sensitivity	69%	36%	18%
Specificity	75%	96%	99%
Positive predictive value	48%	75%	81%
Negative predictive value	87%	81%	78%
Likelihood ratio +	2.7	8.6	12.7
Likelihood ratio -	0.42	0.67	0.83
Percent correctly classified	73%	81%	78%

*Probability cut point resulting in the highest proportion of infants classified correctly for the study outcome

B Late death or moderate to severe NDI



Diagnostic performance of the optimal BPD definition for predicting late death or moderate to severe NDI

	Predicted outcome probability cutpoint		
Performance measure	**25%**	**47%***	**75%**
Sensitivity	95%	69%	26%
Specificity	24%	68%	94%
Positive predictive value	54%	67%	82%
Negative predictive value	83%	70%	57%
Likelihood ratio +	1.3	2.2	4.7
Likelihood ratio -	0.21	0.45	0.79
Percent correctly classified	59%	69%	61%

*Probability cut point resulting in the highest proportion of infants classified correctly for the study outcome

Figure E2. Diagnostic performance of the optimal definition of bronchopulmonary dysplasia for (A) predicting for late death or serious respiratory morbidity and (B) late death or moderate to severe neurodevelopmental impairment (NDI).

The outcome probability values were calculated using logistic regression, adjusting for gestational age, birth weight, sex, small for gestational age, race/ethnicity, treatment with antenatal corticosteroids, treatment with antenatal magnesium, maternal level of education, insurance type, primary caretaker marital status, and study center. The adjusted outcome probability cut point (x-axis) indicates the point at which all infants with a calculated probability equal to or above that threshold were assumed to develop the outcome of interest. The data shown in the figures were generated by comparing this dichotomous predicted outcome at each cut point with each infant's actual outcome using receiver operating characteristic curves. The dashed lines indicate the predicted outcome probability cut point resulting in the highest proportion of infants classified correctly for the presence or absence of the study outcome. Curves smoothed using a median band-line function.

REFERENCES

1. Higgins RD, Jobe AH, Koso-Thomas M, et al. Bronchopulmonary dysplasia: executive summary of a workshop. J Pediatr 2018;197:300-08.