Online clinical tool to estimate risk of bronchopulmonary dysplasia in extremely preterm infants

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ABSTRACT

Objective Develop an online estimator that accurately predicts bronchopulmonary dysplasia (BPD) severity or death using readily-available demographic and clinical data.

Design Retrospective analysis of data entered into a prospective registry.

Setting Infants cared for at centres of the United States Neonatal Research Network between 2011 and 2017.

Patients Infants 501–1250 g birth weight and 23 0/7–28 6/7 weeks' gestation.

Interventions None.

Main outcome measures Separate multinomial regression models for postnatal days 1, 3, 7, 14 and 28 were developed to estimate the individual probabilities of death or BPD severity (no BPD, grade 1 BPD, grade 2 BPD, grade 3 BPD) defined according to the mode of respiratory support administered at 36 weeks' postmenstrual age.

Results Among 9181 included infants, birth weight was most predictive of death or BPD severity on postnatal day 1, while mode of respiratory support was the most predictive factor on days 3, 7, 14 and 28. The predictive accuracy of the models increased at each time period from postnatal day 1 (C-statistic: 0.674) to postnatal day 28 (C-statistic 0.741). We used these results to develop a web-based model that provides predicted estimates for BPD by postnatal day.

Conclusion The probability of BPD or death in extremely preterm infants can be estimated with reasonable accuracy using a limited amount of readily available clinical information. This tool may aid clinical prognostication, future research, and center-specific quality improvement surrounding BPD prevention.

Trial registration number NCT00063063

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Bronchopulmonary dysplasia (BPD) is the most common chronic pulmonary morbidity associated with prematurity, affecting 30%–50% of infants who are born extremely preterm.
⇒ Preterm infants with BPD are more likely to die during early childhood or survive with severe developmental disability.
⇒ Surviving infants with BPD are more likely to experience impaired childhood health and quality of life, family stress and economic hardship, and increased healthcare costs.

WHAT THIS STUDY ADDS

⇒ Using respiratory and clinical data from a cohort of infants, we developed an updated BPD Outcome Estimator.
⇒ This tool estimates an infant's risk of developing the new outcome-driven definition of BPD or death at multiple time points in the first month post-birth.
⇒ This tool may aid clinical prognostication, future research and center-specific quality improvement surrounding BPD prevention.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Future externally validating studies would support clinicians using the new online tool to estimate the risk of BPD or death in extremely preterm infants.
⇒ The new online tool may guide treatment and inform discussions regarding prognosis.

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INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most common chronic pulmonary morbidity associated with prematurity, affecting 30%–50% of infants born extremely preterm.[1 2] Preterm infants with BPD are more likely to die during early childhood or survive with severe developmental disability.[3–6] While mortality and many other neonatal morbidities have decreased over time, BPD in large multicentre reports remains steady.[7] The prevalence of BPD varies widely across centres,[8] as do centre and individual clinician practices that may influence BPD risk over time.[9]

In 2011, the first web-based BPD Outcome Estimator was developed using infant data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal

Research Network (NRN) Benchmarking Trial.[10] This estimator accurately quantified probability of BPD (per the 2001 NIH consensus definition)[11] or death based on risk factors present on postnatal days 1 (day of birth), 3, 7, 14, 21 and 28 and has been used as a tool for epidemiologic research and clinical trials.[12–14] An updated estimator is needed for two main reasons: (1) respiratory care in very preterm infants continues to evolve as goal oxygen saturation targets, ventilator management strategies and medication use change over time[2 15–17]; and (2) the recent development of a new, outcome-informed definition of BPD.[18] This new definition is considered the best predictor of childhood respiratory and neurodevelopmental outcomes, categorising BPD severity into three grades based on mode of respiratory support at 36 weeks' postmenstrual age (PMA), regardless of prior or current oxygen therapy. We examined respiratory and clinical data from a cohort of infants born between 2011 and 2017 to develop an updated BPD Outcome Estimator that estimates an individual infant's risk of developing the new outcome-driven definition of BPD or death at multiple time points in the first month after birth.

SUBJECTS AND METHODS

Subjects

This was a retrospective analysis of data entered into a prospective registry of high-risk preterm infants maintained by the NRN.[19] Infants studied were born between 1 January 2011 and 31 December 2017 and were included if they had a birth weight of 501–1250 g and gestational age of 23 0/7–28 6/7 weeks. Infants with gestational age <23 weeks were not included, due to insufficient sample size to provide accurate risk assessment. Exclusion criteria were: death ≤12 hours after birth, major congenital anomalies, transferred prior to 36 weeks' PMA, remained hospitalised at 36 weeks' PMA but missing data to determine BPD status and admission to a neonatal intensive care unit (NICU) with <20 infants meeting inclusion criteria during the study period. While most NRN centres are comprised of multiple NICUs, each individual NICU was considered separately for study purposes. We excluded small NICUs so that the results would be generalisable to institutions routinely caring for these infants and to facilitate comparisons of outcomes' prevalence among NICUs.

Definitions

BPD severity was defined at 36 weeks' PMA according to the outcome-driven diagnostic criteria developed by NRN investigators. This definition categorises disease severity according to the mode of respiratory support utilised at 36 weeks' PMA, regardless of the use of supplemental oxygen.[18] No BPD was defined as breathing in room air at 36 weeks' PMA; grade 1 BPD as receipt of nasal cannula ≤2 L/min (or hood O2); grade 2 BPD as nasal cannula >2 L/min, nasal continuous positive airway pressure (CPAP), or nasal intermittent positive pressure ventilation; and grade 3 BPD as invasive mechanical ventilation. For infants discharged home prior to 36 weeks' PMA, respiratory status at discharge was used to determine BPD. Surgical necrotising enterocolitis (NEC) was defined as modified Bell's stage IIIB.[20] Sepsis was defined as a blood and/or cerebrospinal fluid culture growing a recognised bacterial or fungal pathogen if the infant was administered antibiotics for ≥5 days or until death.

Statistical analysis

We compared demographic and clinical characteristics among infants with no BPD, grade 1 BPD, grade 2 BPD, grade 3 BPD and death prior to 36 weeks using χ^2 tests for categorical variables and Wilcoxon tests for continuous variables. Analyses were conducted using SAS V.9.4 (SAS Institute).

We performed a multistage approach to select covariates for inclusion into the final multinomial regression models used to estimate the individual probabilities of death or BPD severity level at the following five time points: postnatal day 1 (day of birth), 3, 7, 14 and 28. Candidate covariates determined a priori were gestational age, birth weight, race, ethnicity, sex, receipt of antenatal steroids, receipt of postnatal steroids, highest mode of respiratory support on the day of interest (high-frequency ventilation, conventional ventilation, non-invasive positive pressure ventilation, CPAP, nasal cannula or hood oxygen), maximum fraction of inspired oxygen on the day of interest, sepsis and surgical NEC. Sepsis was only considered for models estimating BPD risk on days 7, 14 and 28. We excluded race as a covariate from the models because it is a social construct (not a biological risk factor) and did not materially improve model prediction. We excluded receipt of postnatal steroids because of variable use across centres and because postnatal steroids are more often considered as treatment for developing BPD rather than a risk factor. Sepsis and surgical NEC were coded as 'yes' if occurring prior to or on the day of interest. Site was not included because we hoped to develop a model that would be broadly applicable to any NICU. We performed stepwise forward selection of covariates using $p<0.2$ for entry into separate multinomial regression models for each day of interest to generate preliminary models for a five-level outcome: no BPD, grade 1 BPD, grade 2 BPD, grade 3 BPD and death. Final models were selected after exclusion of covariates with a p value>0.01.

Predictive performance of our multinomial outcome models was assessed using a C-statistic, which corresponds to the area under the receiver-operating characteristic curve. C-statistics were calculated after adding each covariate to the models. To estimate the optimism of the overall C-statistic from each of the models, the regression models were repeated on 100 bootstrap samples drawn with replacement from the corresponding cohort of infants who survived to the day of the model; the sample size for the bootstrap samples matched the sample size of the corresponding regression model. The difference between the full cohort and bootstrap C-statistic is an estimate of the optimism of the model performance.[21] The average optimism over the 100 samples was subtracted from the full cohort C-statistic to obtain the internally-validated C-statistic.[22]

The institutional review board at each site approved this study (online supplemental table 1).

RESULTS

Sample description

A total of 9181 infants from 38 NICUs met all inclusion and exclusion criteria (figure 1). The mean (SD) birth weight and gestational age overall were 850 g (192) and 25.9 weeks (1.57), respectively. Among the entire cohort, 11% died prior to 36 weeks' PMA, 35% survived without BPD, 30% developed grade 1 BPD, 17% developed grade 2 BPD and 6% developed grade 3 BPD (table 1). Multiple clinical factors were significantly associated with grade of BPD (table 1). Centre differences in outcomes were substantial; for example, the combined prevalence of grade 2 or 3 BPD or death ranged from 6% to 67% among the NICUs included in the study. Infants with more invasive respiratory support and those with higher fraction of inspired oxygen were more likely to die or have higher grades of BPD (figure 2, online supplemental table 2). Over time, there

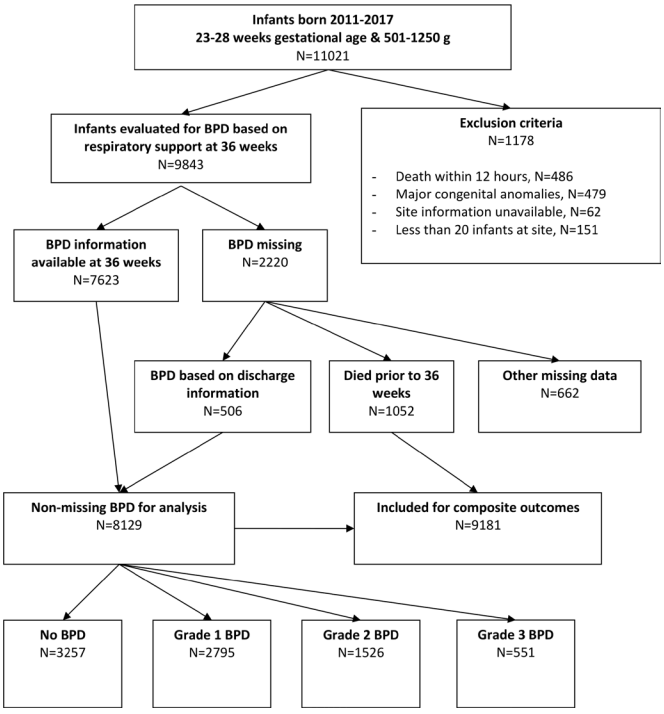

Figure 1 Study flow diagram. This figure displays the study population, from initial cohort, through exclusions, to the final study population. BPD, bronchopulmonary dysplasia.

were trends toward increased use of high-frequency ventilation and nasal ventilation or CPAP (online supplemental figure 1).

Prediction models

Five risk factors were identified for inclusion in the final multinomial models at each time point: birth weight, gestational age, sex, mode of respiratory support and fraction of inspired oxygen. Treatment with antenatal steroids was included in the day 1 model only; surgical NEC was included on days 14 and 28 (table 2). Birth weight was the covariate that explained the most variation in outcome risk on day 1. For all subsequent days, mode of respiratory support was the most predictive. Validated C-statistics produced via bootstrap analysis differed from the full-model C-statistics by 0.005 or less. Using the final regression models, we developed a web-based BPD Outcome Estimator that provides individual predicted estimates for the probabilities of death or BPD by severity grade at postnatal days 1, 3, 7, 14 and 28[23] (online supplemental tables 3–7 show model ORs and p values).

DISCUSSION

We examined >9000 hospitalised very preterm infants from 38 NICUs, more than twice the number included in the development of the original NRN BPD risk estimator. Our models accurately estimated BPD and death grades at multiple time points in the first 28 postnatal days, with reasonable accuracy after the first postnatal week. Accurately predicting BPD is critical to help inform parents and the neonatal care team about an individual infant's risk and prognosis. Furthermore, knowledge of risk advances BPD research and clinical care by contributing to a deeper understanding of factors influencing prevalence.

Identification of which care practices and therapies have the most impact on BPD remains elusive. Over the past 20 years, many studies have investigated the impact of multiple interventions on BPD, such as less invasive respiratory support,[24] high-frequency ventilation,[25 26] inhaled nitric oxide,[27] hydrocortisone,[28] patent ductus arteriosus management[29] and minimally invasive surfactant therapy.[30] Most of these studies have shown mixed results, with minimal to no effect on BPD or the composite outcome of death or BPD. One recent trial of furosemide used the previous NRN BPD Outcome Estimator to calculate BPD risk at multiple time points as a secondary outcome.[13] Such use of our new estimator in future trials could detect differences in BPD risk that occur over the course of an intervention during the first 28 days of the NICU hospitalisation, allowing researchers to estimate impact of potential therapies throughout the hospital course.

Our estimator can also quantitatively stratify prospective trial participants into risk groups. For several therapies that have proven effective in the prevention of BPD, underlying BPD risk has been shown to be critical for effectiveness.[31 32] For example, multiple clinical trials have demonstrated that postnatal corticosteroids improve lung function, but are associated with increased risk of cerebral palsy. A 2014 meta-analysis of 20 randomised clinical trials showed that when the risk of chronic lung disease was <33%, postnatal corticosteroids increased the chance of death or cerebral palsy, while when the risk of BPD was >60%, postnatal corticosteroids decreased the chance of both adverse outcomes.[32] Likewise, risk of BPD appears to influence the

Table 1 Demographics and clinical characteristics

	No BPD	Grade 1 BPD	Grade 2 BPD	Grade 3 BPD	Death prior to 36 weeks	P value*
N	3257	2795	1526	551	1052	
Birth weight, g, mean±SD	951±173	838±176	778±173	752±168	722±161	<0.0001
Gestational age, weeks, mean±SD	26.7±1.24	25.8±1.49	25.5±1.51	25.1±1.52	24.7±1.49	<0.0001
Male, n (%)	1480 (45)	1420 (51)	896 (59)	315 (57)	613 (58)	<0.0001
Race						
Black, n (%)	1576 (50)	973 (36)	511 (35)	237 (44)	415 (41)	
White, n (%)	1399 (44)	1531 (57)	870 (59)	267 (50)	533 (52)	
Other, n (%)	198 (6)	196 (7)	100 (7)	32 (6)	73 (7)	<0.0001
Hispanic ethnicity, n (%)	447 (14)	439 (16)	228 (15)	48 (9)	142 (14)	0.0004
Patent ductus arteriosus, n (%)	971 (30)	1445 (52)	950 (62)	356 (65)	419 (40)	<0.0001
Sepsis, n (%)	378 (12)	624 (22)	444 (29)	253 (46)	339 (41)	<0.0001
Surgical necrotising enterocolitis, n (%)	46 (1)	61 (2)	51 (3)	63 (11)	156 (15)	<0.0001
Antenatal corticosteroids, n (%)	2990 (92)	2543 (91)	1379 (90)	515 (93)	904 (86)	<0.0001

BPD, bronchopulmonary dysplasia.

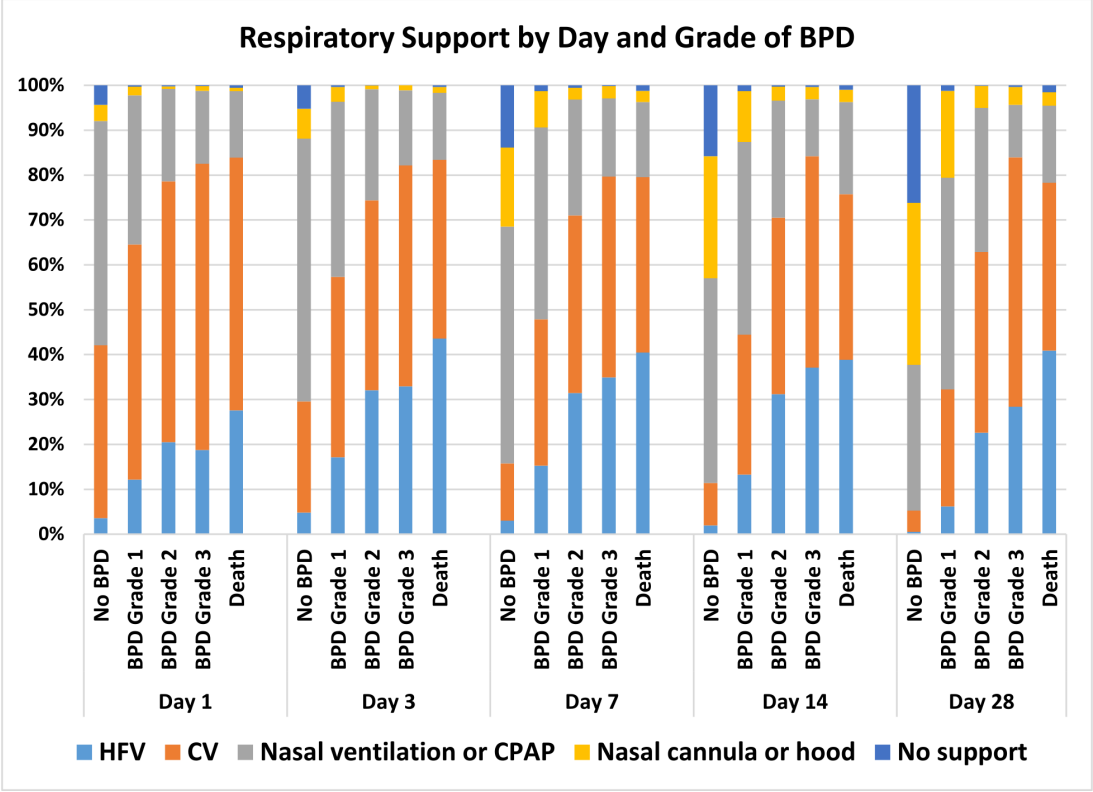

Figure 2 Respiratory support by day and grade of BPD. Infants who were more likely to die or have a higher grade of BPD had more invasive respiratory support and a higher fraction of inspired oxygen. BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; CV, conventional ventilation; HFV, high-frequency ventilation.

impact of vitamin A on the outcomes of BPD or death, with infants at lower risk showing a greater positive effect of vitamin A therapy.[31] Such examples demonstrate that using therapies without consideration for an individual's outcomes risk may result in a potentially useful therapy at a quantifiable risk level being deemed ineffective or even harmful in clinical trial results. Centre variation in outcomes remains a persistent finding in the field of neonatology. In our study, prevalence of grade 2/3 BPD or death was quite variable (6%–67%). Our study was not designed to investigate the influence of population differences or treatment and care practices associated with these differences. However, these results underscore the importance of focusing on centre care differences while trying to improve the overall BPD prevalence.

We found that risk factors for BPD or death were similar to those found for the previous estimator; in particular, birth weight is the most important risk factor on postnatal day 1, while respiratory support becomes the most important factor as time progresses after the first postnatal day. For example, at postnatal day 7, a male 500 g 24-week gestational age infant on 50% fraction of inspired oxygen on the high-frequency ventilator would have a 16% probability of grade 3 BPD, a 23% probability of death and a 2% probability of no BPD or death, while the same infant administered the identical oxygen concentration on CPAP would have a 9% probability of grade 3 BPD, 18% probability of death and 10% probability of no BPD or death, thereby demonstrating how postnatal management choices affecting respiratory support could have substantial impact on infant outcomes.

Our C-statistics were slightly lower than those for the previous estimator (maximum C-statistic 0.741 vs 0.854 for the previous estimator, both on day 28).[10] Hypothetically, the lower C-statistics in the current study are likely due to a combination of the following factors: (1) different methods used to estimate C-statistics; (2) different definitions of BPD; (3) inclusion of a larger

Table 2 Multinomial regression model prediction C-statistics with the addition of individual variables for postnatal days 1, 3, 7, 14 and 28*

Day 1		Day 3		Day 7		Day 14		Day 28	
Variable	**C-statistic**	**Variable**	**C-statistic**	**Variable**	**C-statistic**	**Variable**	**C-statistic**	**Variable**	**C-statistic**
Birth weight	0.629	Respiratory support	0.629	Respiratory support	0.654	Respiratory support	0.669	Respiratory support	0.709
Respiratory support	0.655	Birth weight	0.664	Birth weight	0.674	FiO_2	0.688	FiO_2	0.728
Gestational age	0.660	FiO_2	0.678	FiO_2	0.686	Birth weight	0.694	Birth weight	0.731
FiO_2	0.668	Gestational age	0.682	Male	0.690	Male	0.696	Surgical NEC	0.737
Male	0.672	Male	0.686	Gestational age	0.692	Surgical NEC	0.699	Male	0.738
Antenatal steroids	0.674					Gestational age	0.702	Gestational age	0.741

*The C-statistic for each row corresponds to the model with the variable on that row and the variables above that row.
FiO_2, fraction of inspired oxygen; NEC, necrotising enterocolitis.

number of centres (therefore introducing more variability) and (4) changes in patient population and care practices over time.

Our study has multiple strengths. We created a BPD Outcome Estimator with an online application, allowing widespread use for both clinical and research purposes. We validated our Estimator internally using a bootstrap method, which is more robust than a simple division of the cohort into development and validation cohorts. While we did not conduct external validation as a part of this study, the online availability of the estimator will allow (and we encourage) any interested investigator to perform external validation using local or other multicentre cohorts. This external validation will be critical to understand the broader applicability of the estimator. The use of the outcome-driven definition of BPD,[18] which is pragmatic in its application because of its sole reliance on respiratory support (without the need for radiographs or inspired oxygen concentrations), will facilitate retrospective use of this estimator for existing databases. Yet, like any study of BPD using a clinical definition, the 'BPD' predicted by our estimator almost certainly represents multiple clinical phenotypes lumped together into one diagnosis, so any individual result should be interpreted with caution, especially when using individual results for prognostication. Centre differences in BPD and death were marked. Centres that utilise substantially different care practices from NRN centres may find the estimator to be less reliable. For example, different centres may have unique protocols for using high-frequency ventilation; for some, this might represent an escalation of care, but for others, it may be standard for infants of certain size and gestation. Individual centre was intentionally not included as a covariate in our models since we hoped to create a tool usable at any centre; however, a reasonable amount of variation remains that is unexplained by our model. The substantial centre variation, although typical of BPD rates reported in previous multicentre studies,[33 34] likely affected our model's performance. Other factors not included in our model, such as condition at birth, medical interventions and therapeutic management, could also account for such variation. Practice changes in respiratory support over time could reflect population changes and perhaps affected the model's performance. In the future, new practice changes may influence the estimator's validity.

In conclusion, birth weight was the most important risk factor for BPD or death on postnatal day 1, while respiratory support was most important on days 3, 7, 14 and 28. Future externally validating studies would support clinicians using the new online tool to estimate risk of BPD or death in extremely preterm infants to guide treatment and inform discussions regarding prognosis.

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Contributors RG conceptualised and designed the study, drafted the initial manuscript, interpreted the data analyses, and reviewed and revised the manuscript. RG accepts full responsibility for the work, had access to the data, and controlled the decision to publish. SAM and ADas carried out the data analysis, assisted with interpretation of the data analyses and reviewed and revised the manuscript for important intellectual content. CMC assisted with acquisition of the data, interpreted the data analyses, reviewed and revised the manuscript for important intellectual content and obtained funding to support the study. ML assisted with acquisition of data and critical revision of the manuscript for important intellectual content. DT, EJ, KVM, ECE, JEB, ADuncan, and MW provided analysis and interpretation of the data and critical revision of the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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