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Brief Report

Title

Bronchopulmonary Dysplasia Outcome Estimator in Current Neonatal Practice

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Ethics

This study was granted ethical approval by The Royal Women's Hospital Human Research Ethics Committee on the 23rd of October 2018 and by the Monash Health Human Research Ethics Committee on the 13th of August 2019.

A subset of this data was presented in poster format at the 2019 Annual Congress of the Perinatal Society of Australia and New Zealand.

Predicting an infant's risk of bronchopulmonary dysplasia (BPD) is challenging, particularly during the first weeks after birth. However, strategies to prevent BPD may have most benefit if delivered during this period. A tool assessing BPD risk would prove valuable to clinicians and researchers – aiding clinical decisions and developing eligibility criteria to evaluate preventative BPD therapies.

The NICHD 'BPD Outcome Estimator' (BPD estimator) uses clinical and demographic data to estimate, on postnatal days one, three, seven, 14, 21 and 28, an infant's risk of mild, moderate and severe BPD, and the competing outcome of death before 36 weeks' post menstrual age (PMA) (1). NICHD 2001 consensus definition(2) and physiological challenge(3) defined BPD. The validity of the BPD estimator outside the United States has not been evaluated.

This retrospective cohort study assessed the BPD estimator's accuracy in predicting risk of severe BPD (sBPD) or death in infants admitted to two perinatal centres in Victoria, Australia. Infants admitted to Royal Women's Hospital or Monash Children's Hospital born

≥23 weeks' and ≤28 weeks' gestational age (GA), between October 2016 and September 2017, birthweight >500g and <1251g were included.

Infant characteristics (GA, birthweight, sex, race, postnatal day, respiratory support mode and fraction of inspired oxygen (FiO_2)) were entered into the BPD estimator to generate risk estimates for death and sBPD on postnatal days one, three, seven, 14, 21, and 28. The binary outcome of sBPD or death before 36 weeks' PMA, chosen for its importance in both clinical practice and research, was generated based on infants' outcomes. Receiver operator characteristics (ROC) curves evaluated the BPD estimator's accuracy at distinguishing infants with this outcome from those without. To compare estimated risk with observed incidence of sBPD or death, infants were stratified into risk groups; <10%, 10-19%, 20-29%, 30-39%, 40-49% and ≥50%.

On the day of interest FiO_2 was defined as the mean FiO_2 of four time points and respiratory support as the 'highest' level received on that day. Nasal high flow therapy (nHF) and non-invasive positive pressure ventilation were classified as continuous positive airway pressure (CPAP). NICHD BPD definitions(2) were applied at 36 weeks' PMA. Infants receiving nHF at 36 weeks' PMA were classified as having sBPD if they required an FiO_2 >0.21. If infants' ethnicity was unknown or not available on the BPD estimator (options 'White', 'Black' or 'Hispanic'), they were assigned 'White'.

During the study period 215 eligible infants were admitted. Twenty-six infants with birthweight <501g or >1250g and two infants with unknown BPD outcomes were excluded; 187 infants were included. Their mean (SD) GA was 26.6 (1.5) weeks' and mean (SD) birthweight 872g (178). Fifty-two percent of infants were male, 91% exposed to antenatal corticosteroids, 73% received surfactant and 31% received postnatal corticosteroids for BPD treatment.

The incidence of death before 36 weeks' PMA or sBPD was 48.1%. Eighteen infants (9.6%) died before 36 weeks' PMA and 72 infants (38.5%) were diagnosed with sBPD.

In this population, the BPD estimator accurately distinguishes infants who die before 36 weeks' PMA or have sBPD from those who do not, as evidenced by AUC of 0.81-0.84 at all postnatal time points (figure S1). The accuracy reported here is comparable to that reported in the population used to model the estimator(1).

However, predicted risk underestimates the observed incidence of sBPD or death. The observed incidence of sBPD or death was higher than the estimated risk in all risk strata except estimated risk group <10% (table 1). This underestimation may reflect practice changes and population differences.

The BPD estimator, modelled on infants born between 2000 and 2004, uses mode of respiratory support to predict outcome. The use of non-invasive respiratory support has evolved. Modes available in the estimator no longer reflect practice and their influence on predicting outcome may have changed. Variation in the use of invasive support modes, such as high frequency oscillatory ventilation, may erroneously influence risk estimates.

The use of postnatal corticosteroids has changed. Use declined in very low birthweight infants from 20% in 1997-2000 to 8% in 2004(4). The BPD estimator was modelled on infants born during this period. Thirty-one percent of infants in our cohort received postnatal corticosteroids. The BPD estimator does not use postnatal corticosteroid exposure to estimate outcome, though differences in use may modify BPD evolution.

Multiple factors may contribute to the high incidence of sBPD or death (48.1%) observed in our population. Intensive care is provided to infants born at 23 weeks' GA. Of the ten infants born at 23 weeks' GA included in this cohort, five died prior to 36 weeks' PMA and the five survivors had sBPD. The lack of a physiological test of BPD severity and nHF use at 36 weeks' PMA may have increased the diagnosis of sBPD. Sixty-two infants received nHF at 36 weeks' PMA; how these infants' BPD is best categorised is currently unknown. Finally, clinical practices in our nurseries may increase BPD rates.

The BPD estimator has limited ethnicity options. Those available; White, Black or Hispanic, don't reflect our community with a substantial Asian population.

In the original population, equal numbers of infants died before 36 weeks' PMA or had sBPD (13% for each outcome). In our population, sBPD incidence was four-fold higher than that of death. This differential may reflect recent increases in preterm infant survival rates and an associated BPD increase(5).

Infants ≤28 weeks' GA were included in our cohort, whereas the estimator was based on a population of infants <30 weeks' GA. Whilst limiting comparison at population level, this difference should not influence individuals' estimated risk.

Despite limitations, the BPD estimator distinguishes infants with sBPD/death from those without in our population. However, the BPD estimator needs recalibrating for local populations.

Conflict of Interest

The authors have no conflicts of interest to declare.

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TABLE

Observed incidence of sBPD or death before 36 weeks PMA	NICHD estimated risk of sBPD or death 36 before weeks' PMA					
	<10%	**10 - <20%**	**20 - <30%**	**30 - <40%**	**40 - <50%**	**≥50%**
Day 1	7% (3/45)	45% (22/49)	54% (21/39)	80% (16/20)	69% (9/13)	93% (14/15)
Day 3	5% (2/43)	32% (14/44)	69% (25/36)	64% (16/25)	71% (12/17)	100% (14/14)
Day 7	12% (5/41)	27% (14/51)	55% (17/31)	78% (18/23)	73% (11/15)	100% (13/13)
Day 14	12% (3/25)	26% (19/72)	44% (12/27)	80% (16/20)	79% (11/14)	100% (16/16)
Day 21	7% (2/30)	32% (24/76)	62% (8/13)	74% (17/23)	87% (20/23)	100% (2/2)
Day 28	5% (1/21)	27% (21/77)	63% (17/27)	73% (16/22)	77% (10/13)	100% (6/6)

Table 1: Observed incidence of severe BPD (sBPD) or death before 36 weeks' post menstrual age (PMA) stratified by estimated risk group. Data displayed as the percentage of infants within the risk group who had severe BPD or died before 36 weeks' PMA.