



Prediction of Late Death or Disability at Age 5 Years Using a Count of 3 Neonatal Morbidities in Very Low Birth Weight Infants

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Objective To evaluate bronchopulmonary dysplasia (BPD), serious brain injury, and severe retinopathy of prematurity (ROP) as predictors of poor long-term outcome in very low birth weight infants.

Study design We examined the associations between counts of the 3 morbidities and long-term outcomes in 1514 of 1791 (85%) infants with birth weights of 500-1250 g who were enrolled in the Caffeine for Apnea of Prematurity trial from October 1999, to October 2004, had complete morbidity data, and were alive at 36 weeks postmenstrual age (PMA). BPD was defined as use of supplemental oxygen at 36 weeks PMA. Serious brain injury on cranial ultrasound included grade 3 and 4 hemorrhage, cystic periventricular leucomalacia, porencephalic cysts, or ventriculomegaly of any cause. Poor long-term outcome was death after 36 weeks PMA or survival to 5 years with 1 or more of the following disabilities: motor impairment, cognitive impairment, behavior problems, poor general health, deafness, and blindness.

Results BPD, serious brain injury, and severe ROP occurred in 43%, 13%, and 6% of the infants, respectively. Each of the 3 morbidities was similarly and independently correlated with poor 5-year outcome. Rates of death or disability (95% CI) in children with none, any 1, any 2, and all 3 morbidities were 11.2% (9.0%-13.7%), 22.9% (19.6%-26.5%), 43.9% (35.5%-52.6%), and 61.5% (40.6%-79.8%), respectively.

Conclusions In very low birth weight infants who survive to 36 weeks PMA, a count of BPD, serious brain injury, and severe ROP predicts the risk of a late death or survival with disability at 5 years. (*J Pediatr* 2015;167:982-6).

Immature and very low birth weight infants have a higher risk of childhood disability than fullterm infants.¹ Adverse long-term outcomes such as motor and cognitive impairments or neurosensory deficits are increased in children with bronchopulmonary dysplasia (BPD),^{2,3} severe peri- and intraventricular hemorrhages and other types of brain injury,^{4,5} systemic infection,^{6,7} necrotizing enterocolitis,⁸ and severe retinopathy of prematurity (ROP).^{9,10}

We have previously shown in 910 extremely low birth weight infants who participated in the Trial of Indomethacin Prophylaxis in Preterms and survived to a postmenstrual age (PMA) of 36 weeks, that a count of BPD, brain injury, and severe ROP was a strong predictor of a late death or survival with impairment at 18 months.¹¹ This observation was subsequently confirmed in at least 1 other cohort.¹² Although neonatal infection and necrotizing enterocolitis increased the risk of a late death or survival with neurosensory impairment, infection and necrotizing enterocolitis were weaker predictors of poor outcome than BPD, brain injury, and severe ROP and thus were not added to the morbidity count.¹³

For the current study, we evaluated the count of BPD, brain injury, and severe ROP as a predictor of a late death or disability at 5 years in children who participated in the Caffeine for Apnea of Prematurity (CAP) trial.¹⁴ Confirmation of the validity of this simple predictive tool in a new cohort as a predictor of pre-school outcomes would justify its use in clinical practice, for example, to target especially high-risk infants for early intervention and long-term follow up.

Methods

Infants with birth weights of 500 to 1250 g were enrolled in the international CAP trial between 1999 and 2004 and followed to a corrected age of 5 years.¹⁴⁻¹⁶ The research ethics boards of all participating clinical centers approved the initial trial protocol and the additional 5-year follow-up. Written informed consent was

BPD	Bronchopulmonary dysplasia
CAP	Caffeine for Apnea of Prematurity
PMA	Postmenstrual age
ROP	Retinopathy of prematurity

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obtained from a parent or guardian of each infant prior to enrollment and again before the assessments at 5 years. Only infants who survived to 36 weeks PMA were eligible for the current study because infants who die early during their stay in the neonatal intensive care unit cannot develop BPD and severe ROP.

Neonatal Morbidities

BPD, brain injury, and severe ROP were pre-specified secondary outcomes in the CAP trial, and all data were collected prospectively in a standardized fashion. BPD was defined by the need for supplemental oxygen at 36 weeks PMA. Cranial ultrasonography to detect brain injury was recommended between days 14 and 28 of life and between 34 and 36 weeks PMA if the infant was still in the study center at that time. The following lesions were considered to indicate the presence of brain injury at any time throughout the neonatal course: intraparenchymal echodense lesions (grade 4 hemorrhage), cystic periventricular leucomalacia, porencephalic cysts, and ventriculomegaly with or without intraventricular hemorrhage (including grade 3 hemorrhage). Severe ROP was defined as unilateral or bilateral disease of stage 4 or 5, or receipt of retinal therapy in at least 1 eye. Infants were screened for ROP according to local nursery protocols.

Outcomes at a Corrected Age of 5 Years

The main outcome at 5 years was a composite of death before a corrected age of 5 years or survival with 1 or more of the following: motor impairment, cognitive impairment, behavior problems, poor general health, severe hearing loss, and bilateral blindness.¹⁴ Motor impairment in the current study was defined as level 2 through 5 using the Gross Motor Function Classification System.¹⁷ Severe cognitive impairment was defined as a full scale IQ of less than 70 (2 SD below the mean of 100) on the Wechsler Preschool and Primary Scale of Intelligence III.¹⁸ Site investigators used their respective national test norms. The full scale IQ was assumed to be less than 70 if the child could not complete the testing because of severe developmental delay or severe autism. A behavior problem was defined as a total problem T score (range 28-100) greater than 69 (2 SD above the mean of 50) on the Parent Form of the Child Behavior checklist.¹⁹ Poor general health included 1 or more of the following: need for supplemental oxygen, positive airway pressure, feeding through a tube or intravenously, seizures occurring more frequently than once per month, or a recent admission to an intensive care unit for complications resulting from a neonatal morbidity. Severe hearing loss was defined as the prescription of hearing aids or cochlear implants, and bilateral blindness as a corrected visual acuity less than 20/200 in the better eye.

Statistical Analyses

All 5-year outcomes in this analysis were dichotomous, and prevalence rates have been presented as percentages with exact 95% CI. Relationships between individual neonatal

morbidities and 5-year outcomes were expressed as OR with associated 95% CI based on the approximate SE for log OR. The Fisher exact test was used to assess the significance of an observed OR against the null hypothesis of no relationship (true OR = 1). Various logistic regression models were used to investigate the combined effect of the individual morbidities, the potential lack of additivity, and the gradient of outcome risk with morbidity count. Model-based estimates of OR were derived from the maximum likelihood regression coefficients and the corresponding 95% CI from the SE of these estimates.

Results

A total of 2006 infants with birth weights of 500-1250 g were enrolled in the original CAP trial. Four of 35 clinical centers did not participate in the 5-year follow-up. The remaining 31 centers had enrolled 1932 infants, of whom 1853 survived to 36 weeks PMA. All 3 neonatal morbidities—BPD, brain injury, and severe ROP—were known for 1791 CAP trial participants, of whom 1514 children had adequate data for the analysis of the composite outcome of death or disability at 5 years. The characteristics of the children and their families in this cohort were very similar to the characteristics reported previously for CAP trial participants at 5 years.¹⁴ Mean birth weight (SD) was 962 (180) g and mean gestational age (SD) 27.4 (1.8) weeks.

Univariate Relationships between Neonatal Morbidities and Poor Outcome at 5 Years

Of the 1514 study infants, 657 (43%) children had BPD, 196 (13%) had serious brain injury, and 93 (6.1%) had severe ROP. Each of these 3 neonatal morbidities was strongly associated with a late death after 36 weeks PMA or disability at 5 years. The OR ranged from 2.7 for BPD to 4.0 for severe ROP, with fairly narrow 95% CI (**Table I**). A logistic model was applied to the data that included a separate indicator variable for each morbidity to allow for inter-correlation between the 3 morbidities. The estimated independent prognostic contribution (labeled as the “Model estimated” OR in **Table I**) was similar for each of the 3 morbidities. An additional model that included interaction terms suggested that the 3 morbidities provided independent prognostic information, with little evidence of “non-additivity” ($P = .97$).

Combinations of Neonatal Morbidities and Poor Outcome at 5 Years

Table II gives the rates of death or disability at 5 years in infants with all possible combinations of the 3 neonatal morbidities, beginning with infants who survived without BPD, serious brain injury, or severe ROP, and ending with the group of 26 infants who developed all 3 morbidities. The observed rate of death or disability was 11.2% in children who remained free of BPD, brain injury, and severe ROP. This increased to 22.9% with any 1 of the

Table I. Univariate relationships between individual neonatal morbidities and poor outcome at 5 years

Neonatal morbidity	Death or disability at 5 y					
	No./total no. (%)		Observed OR (95% CI)	P value	Model estimated OR (95% CI)	P value
	Morbidity absent	Morbidity present				
BPD	110/857 (12.8)	187/657 (28.5)	2.7 (2.1-3.5)	<.001	2.3 (1.8-3.0)	<.001
Brain injury	222/1318 (16.8)	75/196 (38.3)	3.0 (2.2-4.2)	<.001	2.6 (1.9-3.6)	<.001
Severe ROP	254/1421 (17.9)	43/93 (46.2)	4.0 (2.6-6.1)	<.001	2.5 (1.6-3.9)	<.001

morbidities, 43.9% with any 2, and 61.5% with all 3. As already suggested by the fitted OR shown in **Table I**, the observed data confirm that each of the 3 neonatal morbidities was similarly and independently associated with poor outcome at 5 years. As the count of morbidities increased from 0 to 3, the OR increased multiplicatively by a nearly constant factor of 2-3 (**Table II**).

Neonatal Morbidity Count as Predictor of 5-Year Outcomes

The final step in the analysis was to fit a logistic model that included the morbidity count as the sole predictor variable. This model yielded a highly significant ($P < .001$) gradient of risk of death or impairment at 5-years with an incremental OR of 2.4 per morbidity. The **Figure** confirms the excellent fit between the predictions that are based on the morbidity count model and the observed rates of poor 5-year outcome in children with none, 1, 2, and all 3 morbidities. To explore whether sex had any influence on the prognostic value of the morbidity count, we added a term for sex and an interaction term for morbidity count X sex to the logistic model already containing a term for the morbidity count. The interaction term was non-significant ($P = .90$). Thus, the morbidity count predicts the risk of poor outcome at 5 years equally well in boys and girls.

Table III shows observed rates of poor outcome by morbidity count for the composite outcome of death or disability at 5 years and for each of the 7 components that made up this composite outcome. There was a strong

relationship between the gradient of risk (incremental OR) and the morbidity count for every single outcome—death after 36 weeks PMA, cognitive impairment, motor impairment, behavior problems, poor general health, deafness, and blindness.

Effect of Neonatal Caffeine Therapy

The presence or absence of caffeine treatment could have affected the intercept and/or slope of the relationship between morbidity count and outcome. We investigated this possibility by including an indicator variable for caffeine, and an interaction term (product of caffeine X morbidity count), in addition to morbidity count alone, in the logistic model for each outcome. This approach allowed for different intercepts and slopes when caffeine therapy was present compared with absent. We examined whether caffeine therapy modulated the relationship between morbidity count and outcome by applying significance tests to the estimated coefficients that were associated with the caffeine and interaction terms in the logistic models. These tests were nonsignificant (smallest P value .39) for all outcomes in **Table III**.

Table II. Relationships between combinations of neonatal morbidities and poor outcome at 5 years

Neonatal morbidities	Death or disability at 5 y		
	No./total no.	% (95% CI)	OR (95% CI)
None	85/759	11.2 (9.0-13.7)	1.0
Any single morbidity	135/590	22.9 (19.6-26.5)	2.4 (1.7-3.2)
BPD	112/494	22.7	
Brain injury	20/84	23.8	
Severe ROP	3/12	25.0	
Any 2 morbidities	61/139	43.9 (35.5-52.6)	6.2 (4.1-9.3)
BPD + brain injury	37/84	44.0	
BPD + Severe ROP	22/53	41.5	
Brain injury + severe ROP	2/2	100.0	
All 3 Morbidities	16/26	61.5 (40.6-79.8)	12.7 (5.6-28.9)

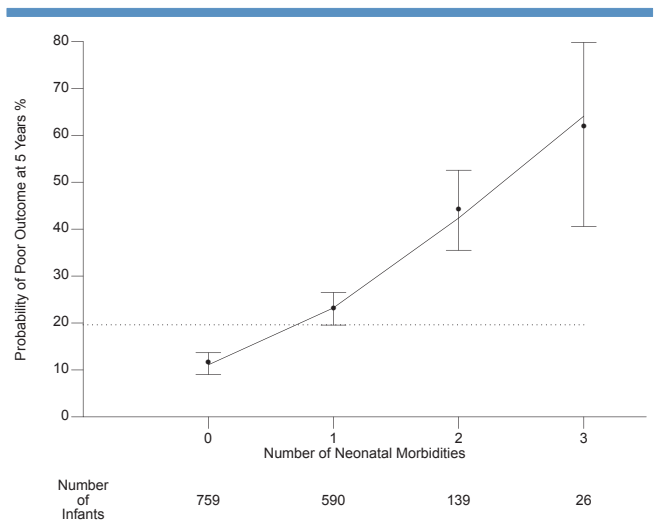


Figure. Probability of poor 5-year outcome in study infants (N = 1514) with none, 1, 2, and all 3 neonatal morbidities; 95% CI (error bars). Sloping solid line indicates predictions based on the fitted morbidity count model; horizontal dotted line indicates the overall probability of a poor 5-year outcome.

Table III. Relationships between neonatal morbidity count and components of poor outcome at 5 years

Death after 36 wk PMA and individual impairments in survivors	Morbidity count				OR (95% CI) (per morbidity)	P value
	0	1	2	3		
Death or impairment (n = 1514), %	11.2	22.9	43.9	61.5	2.4 (2.0-2.9)	<.001
Death* (n = 1575), %	0.8	3.4	4.1	15.4	2.5 (1.7-3.6)	<.001
Cognitive impairment* (n = 1471), %	2.2	6.0	14.4	33.3	2.7 (2.1-3.6)	<.001
Motor impairment* (n = 1527), %	1.0	2.9	10.9	31.8	3.6 (2.6-5.1)	<.001
Behavior problem* (n = 1474), %	4.6	6.7	11.7	13.6	1.6 (1.2-2.1)	<.001
Poor health* (n = 1531), %	2.2	5.4	10.1	4.6	1.9 (1.4-2.6)	<.001
Deafness* (n = 1522), %	1.3	3.6	9.6	9.5	2.4 (1.7-3.4)	<.001
Blindness* (n = 1506), %	0.0	0.3	5.4	25.0	10.2 (5.1-20.7)	<.001

*For the analyses of individual impairments, all available follow-up data were included, not just the data for those infants with a known composite outcome of death or disability at 5 years.

Discussion

This ancillary analysis of CAP trial data for infants with birth weights of 500-1250 g confirmed the independent prognostic effect of BPD, serious brain injury, and severe ROP we previously observed in the Trial of Indomethacin Prophylaxis in Preterms cohort.¹¹ Counting whether infants developed none, any 1, any 2, or all 3 of these neonatal morbidities strongly predicted a late death after 36 weeks PMA or disability at a corrected age of 5 years. Each additional morbidity multiplies the odds of poor outcome by a constant amount: the incremental OR per morbidity in the current analysis was 2.4 (95% CI; 2.0-2.9) compared with an incremental OR of 2.9 (95% CI; 2.4-3.5) in participants of the Trial of Indomethacin Prophylaxis in Preterms who were followed to a corrected age of 18 months.¹¹ Despite the differences between the 2 studies, which included different populations of preterm infants, different prevalence rates for the 3 morbidities, different ages at follow-up, and different definitions and prevalence rates of disability, the incremental OR per morbidity were remarkably similar in these analyses of the predictive count of BPD, serious brain injury, and severe ROP. Caffeine therapy reduced the risks of BPD and severe ROP^{15,16} and, therefore, the morbidity count, but the subsequent prognosis was dictated by the morbidity count, with no additional influence of caffeine therapy.

The value of the morbidity count has been confirmed in a small Korean cohort of extremely low birth weight infants who were followed to 18-24 months.¹² Farooqi et al examined the impact of the 3 neonatal morbidities on outcomes at age 11 years in 97 Swedish children and concluded that severe ROP and brain injury, but not BPD, predicted poor childhood outcomes.²⁰ The authors speculated that the low power of their study may be one possible reason for the apparent lack of prognostic value of BPD. The strengths of both our initial study and our present study include the relatively large size of both cohorts (910 and 1514 infants, respectively), the geographically diverse origin of the children, and the prospective, rigorous, and standardized neonatal and follow-up study protocols.^{11,14} Limitations of the present study include the fact that the inception cohort is not population-

based and further, that complete data for all 3 neonatal morbidities and for the composite outcome of death or disability at age 5 years were not available for 339 of 1853 children (18%).

We anticipate 2 main applications of the neonatal morbidity count to predict long-term outcome. First, parents of very preterm infants who are discharged home after their initial hospitalization free of BPD, brain injury, and severe ROP can be reassured that their children have a lower risk of a future disability than children who were born equally small and immature but who acquired 1 or more of these morbidities during their stay in the neonatal intensive care unit. However, the risk of future disability in the absence of the 3 morbidities is not negligible: in the present cohort, 85 of 759 (11.2%) children with a morbidity count of "0" had an adverse long-term outcome. Second, very high-risk infants who are discharged with 2 or all 3 of these neonatal morbidities deserve close and prolonged neurodevelopmental follow-up. Moreover, such infants should be referred to effective early developmental intervention programs.²¹

The morbidity count prediction model cannot be used for early considerations of withdrawal of care in very sick infants. We included only infants who survived to 36 weeks PMA because infants who die earlier cannot develop all 3 morbidities of interest. BPD is typically diagnosed at 36 weeks and severe ROP at or beyond this PMA. However, a small minority of very immature infants receive protracted ventilation.²² If such children with severe BPD have also acquired brain injury, and if they are still ventilator-dependent when they are diagnosed with severe ROP, their parents should be made aware of the additive and adverse prognostic effect of these 3 morbidities.

We conclude that in very low birth weight infants who survive to 36 weeks PMA, a simple count of BPD, serious brain injury, and severe ROP strongly predicts the risk of survival with disability at 5 years. ■

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Appendix

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