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Katherine C. Wai

Michael A. Kohn

Roberta A. Ballard

William E. Truog
Children's Mercy Hospital

Dennis M. Black

See next page for additional authors

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Early Cumulative Supplemental Oxygen Predicts Bronchopulmonary Dysplasia in High Risk Extremely Low Gestational Age Newborns

Katherine C. Wai, BS[1], **Michael A. Kohn, MD, MPP**[2], **Roberta A. Ballard, MD**[3], **William E. Truog, MD**[4], **Dennis M. Black, PhD**[2], **Jeanette M. Asselin, MS, RTT-NPS**[5], **Philip L. Ballard, MD, PhD**[3], **Elizabeth E. Rogers, MD**[3], and **Roberta L. Keller, MD**[3,*] **on behalf of the Trial of Late Surfactant (TOLSURF) Study Group**

[1]School of Medicine, University of California San Francisco

[2]Department of Epidemiology and Biostatistics, University of California San Francisco

[3]Department of Pediatrics, UCSF Benioff Children's hospital, San Francisco, CA

[4]Department of Pediatrics, Children's Mercy Hospital, Kansas City, MO

[5]Department of Pediatrics, UCSF Benioff Children's Hospital Oakland, Oakland, CA

Abstract

Objective—To assess the prognostic accuracy of early cumulative supplemental oxygen (CSO) exposure for prediction of BPD or death and to evaluate the independent association of CSO with BPD or death

Study design—We performed a secondary analysis of the Trial of Late Surfactant, which enrolled 511 infants ≤28 weeks' gestational age who were mechanically ventilated at 7–14 days. Our primary outcome was BPD or death at 36 weeks' post-menstrual age, determined by physiologic oxygen/flow challenge. Average daily supplemental oxygen (FiO_2−0.21) was calculated. CSO was calculated as the sum of the average daily supplemental oxygen over time periods of interest up to 28 days of age. We generated area under the receiver-operating-curve (AUROC) to evaluate the accuracy of CSO for prediction of BPD or death. We assessed the independent relationship between CSO and BPD or death in multivariate modeling, while adjusting for mean airway pressure.

Results—Infants were 25.2±1.2 weeks and 700±165g at birth. At 14 days, AUROC for CSO (0.70, 0.65–0.74) was significantly better than CSO at earlier time points for outcome prediction; it did not increase with addition of later data. In multivariate modeling, an increase of 1 in CSO at

Corresponding Author: Roberta L. Keller, Contact: kellerr@ucsf.edu | 550 16th St, Box: 0734, San Francisco, CA 94158 | 415-476-1888.

*List of additional members of TOLSURF Study Group is available at www.jpeds.com (Appendix).

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14 days increased the odds of BPD or death (OR=1.7, 1.3–2.2; p<0.0001), which corresponds to a 7% higher daily supplemental oxygen.

Conclusion—In high-risk ELGAN, the predictive accuracy of CSO plateaus at 14 days. CSO is independently associated with BPD or Death. This index may identify infants who could benefit from early intervention to prevent BPD.

Keywords

inhaled nitric oxide; mechanical ventilation; oxidative stress; prematurity; surfactant

Preterm infants are at high risk for bronchopulmonary dysplasia (BPD). There are up to 15,000 new cases of BPD annually nationwide, and more than 70% of extremely low gestational age newborns (ELGAN) who require ventilatory support after 7 days of age are affected.[1] BPD is associated with long-term pulmonary disability, neurodevelopmental abnormalities and death.[2–5]

The etiology of abnormal pulmonary development is complex and involves inflammation and volutrauma, as well as derangements in lung function, repair from injury, and ongoing growth and development.[6] Oxygen exposure contributes to injury; fetuses develop in a low oxygen environment and premature infants have reduced anti-oxidant systems, making them more susceptible to oxidant stress.[7] Additionally, biochemical markers of oxidative stress and clinical markers of oxygen exposure correlate with development of lung disease.[7–10]

Risk for respiratory disease has often been quantified by duration of supplemental oxygen.[11] But it is likely that both duration and concentration of supplemental oxygen contribute to oxygen toxicity and serve as a marker for severity of disease. To date, only Stevens *et al* have attempted to quantify total oxygen exposure, including duration and concentration of supplemental oxygen.[12] Among very low birth weight infants without BPD, they found that cumulative oxygen exposure at 72 hours of life independently predicted symptomatic airway disease at 1 year. These data suggest that differences in oxygen exposure can discriminate amongst infants early in their neonatal course, which may be beneficial as new therapies emerge.

The aim of the current study was to determine the earliest time point at which cumulative supplemental oxygen exposure, which accounts for both duration and concentration of oxygen exposure, best predicts BPD or Death prior to 36 weeks' post-menstrual age (PMA) among high-risk infants. In addition, we evaluated the independent effect of this identified index of early cumulative supplemental oxygen exposure on BPD or Death.

Methods

This is a secondary analysis of infants enrolled in the randomized controlled Trial of Late Surfactant (TOLSURF), conducted under the original Institutional Review Board approval. The study protocol and initial outcomes have been described in detail.[13] In brief, 511 infants ≤28 0/7 weeks' gestational age, who required endotracheal intubation anytime between 7–14 days of life placing them at high risk for BPD or death, were randomized to late surfactant and inhaled nitric oxide (iNO) versus iNO alone.[1, 14] The primary outcome for the trial was

survival without BPD at 36 weeks' PMA, determined by physiologic oxygen/flow reduction challenge. No difference was seen between the treatment and control groups for the primary outcome, so the infants were treated as a single cohort for these analyses.

Neonatal clinical data were collected prospectively into the study database. Birth weight percentile was generated according to the Fenton 2013 growth curves.[15] Respiratory support measurements were recorded 3 times per day at approximately 0800, 1600 and 2400 hours per protocol. A daily average of supplemental oxygen (recorded fraction of inspired oxygen (FiO_2) – 0.21) was calculated for each 24-hour time period; this daily average was chosen to generate a overall estimate of an infant's supplemental oxygen exposure on a given day, as more frequent recordings were not collected. The recorded FiO_2 was converted to effective FiO_2 when the infant was on nasal cannula, under the STOP-ROP assumptions.[16] Cumulative supplemental oxygen (CSO) was the sum of the daily average over the time period of interest up to 28 days of age (i.e. CSO at 14 days = average supplemental oxygen day 1 + average supplemental oxygen day 2 + … + average supplemental oxygen day 14). For example, if the average FiO_2 was 0.3 on day 1, 0.5 on day 2, and 0.4 on day 3, then CSO at 3 days = (0.3 – 0.21) + (0.5 – 0.21) + (0.4 – 0.21) = 0.57. Cumulative mean airway pressure (MAP) was calculated similarly to CSO, in which a daily average for MAP was summed over various time periods, using data from both invasive and non-invasive ventilation. For the current study, infants missing a complete day of oxygenation data were excluded (n=16).

Although TOLSURF was largely conducted following dissemination of the results for oxygen saturation targets from the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)[17], we compared oxygen exposure and ventilation management for infants born before and after December 1, 2010, in order to evaluate consistency in the relationship of oxygen exposure to respiratory support needs. This date was chosen based on the timing of the SUPPORT publication and a pause in TOLSURF enrollment for an interim safety analysis.[13]

Primary outcome and statistical analyses

The primary outcome for the current study was BPD or Death prior to 36 weeks' PMA. Data were analyzed by chi squared or t-tests as appropriate (Stata 14.0, College Station, TX). Area under the receiver-operating-characteristic curve (AUROC) was used to assess the predictive value of CSO at day of life 1, 3, 7, 10, 14, 21 and 28. These days were chosen because previously published models have identified important predictors for BPD or Death in extremely premature infants at these time points.[18, 19] Published risk factors for BPD were considered *a priori* for inclusion into the multivariate model. Those variables selected for potential inclusion had a significant relationship ($p<0.05$) with BPD or Death on univariate analyses. Using backward selection, covariates were removed if $p>0.10$; gestational age was forced to stay in the model. Generalized estimating equations were employed to account for non-independence between siblings. Predictive performance of unadjusted and adjusted models was assessed by C-statistic, which corresponds to the AUROC. In unadjusted analyses, the covariate with the largest C-statistic was considered to contribute most to the predictive accuracy of the model.

Results

Of 511 infants enrolled in TOLSURF, 16 (3%) were excluded for missing ≥1 day of oxygenation data. Among those included, 283/495 (57%) had BPD and 53/495 (11%) died. Infants were predominantly male, with mean gestational age and birth weight similar to those enrolled in the trial (25.2±1.2 weeks and 700 ±165 grams, respectively; Table I).[13] Although 143 infants were products of multiple gestation, only 105 (21%) had a sibling enrolled in TOLSURF.

To evaluate the value of CSO in prediction of BPD or Death, we assessed AUROC at various time points up to 28 days of life. The AUROC increased from day of life 1 to 14, and then plateaued at ~0.70 through 28 days (Table II). We compared the AUROC for CSO at each individual time point to the CSO at 14 days. We found that CSO at 14 days was significantly better than earlier time points, and did not improve with additional days of data (Table II).

After identifying CSO at 14 days as the earliest and most accurate predictor for oxygen exposure in the first 28 days, other respiratory support measurements at 14 days were evaluated for their association with the outcome, BPD or Death. The average CSO at 14 days was higher in the BPD or Death group compared to the survivors without BPD (2.4±1.4 vs. 1.5±0.98, p <0.0001), which corresponded to a daily average of 17% supplemental oxygen over 14 days in the BPD or Death group compared to 11% supplemental oxygen over 14 days in the survivors without BPD.

Similarly, cumulative MAP was higher in the BPD or Death group compared to survivors without BPD (131±26 vs. 115±23 cm H_2O, p <0.0001), corresponding to an daily average MAP of 9.4 cm H_2O over 14 days in the BPD or Death group compared to 8.2 cm H_2O over 14 days in the survivors without BPD. Infants who were not previously extubated prior to 14 days were more likely to have the outcome BPD or Death compared to infants who had been extubated (44% vs. 32%, p <0.0001). Furthermore, the number of days of invasive mechanical ventilation at 14 days of age was greater in infants with BPD or Death (13.3±2.7 vs. 12.5±1.6 days, p<0.0001). The respiratory management of infants born before (n=76) and after (n=398) December 1, 2010 did not appear to differ, with a similar relationship of CSO to Cumulative MAP (Figure 1; available at www.jpeds.com). The average CSO at 14 days for those born before December 1, 2010 was similar to the CSO for those born after (2.0±1.2 vs. 2.2±1.4, p=0.27). We identified additional non-respiratory covariates with a statistically significant relationship by univariate analysis (Table I).

After backward selection, 474 infants were included in the final model; 21 infants were excluded due to incomplete data (7 deaths prior to 14 days, 14 missing ≥1 day of MAP recordings). After adjustment for other risk factors, CSO at 14 days remained strongly associated with BPD or Death (Table III). The odds ratio of 1.7 for each CSO increase of 1 corresponds to an average of 7% higher supplemental oxygen per day over 14 days for an infant with the outcome BPD or Death. Cumulative MAP was retained in the model as an independent risk factor. For every 10 cm H_2O increase in Cumulative MAP, the odds of BPD or Death increased by 1.2; this corresponds to an average of 0.7 cm H_2O greater per day for 14 days.

We tested the model for prediction of BPD among survivors only in a sensitivity analysis, and found the model predicted BPD well. Notably, CSO remained an independent risk factor with its effect size unchanged, supporting the importance of oxygen exposure in the development of BPD. Further, the effect sizes of other included variables were minimally altered (Table III).

To assess the contribution of CSO at 14 days to the predictive accuracy of the full model, we generated C-statistics for each covariate. In this analysis, CSO provided the greatest contribution of any variable [AUROC 0.69 (95% CI 0.64 – 0.74)] (Table IV; available at www.jpeds.com). The predictive accuracy for the full adjusted model demonstrated improvement with inclusion of the other important risk factors (AUROC 0.76 [95% CI 0.72 – 0.81], p=0.0003; Figure 2).

Discussion

In this cohort of high-risk ELGAN, we demonstrated that the predictive value of cumulative supplemental oxygen increased until 14 days of life and then plateaued. Further, this measure of supplemental oxygen exposure at 14 days was independently associated with BPD or Death. Thus, CSO provides early identification of infants at highest risk for BPD or Death.

ELGAN are born in the late canalicular/early saccular phases of lung development prior to alveolarization.[20] Experimental models demonstrate that short-term hyperoxia disrupts alveolar and microvascular development, leading to alveolar simplification.[21–23] Similarly, short-term exposure to higher oxygen concentrations at birth increases the risk of BPD; preterm infants randomized to initial resuscitation with high vs. low FiO_2 were more likely to develop BPD.[10, 24] Further, these short-term exposures were associated with increases in markers of oxidative stress at 1–7 days of age. Consistent with these findings, elevated markers of oxidative stress in the first week of life are strongly associated with BPD, supporting the importance of early life events, and reinforcing the need for prompt recognition of those at highest risk for poor outcome.[8–10, 25] Our findings are consistent with this prior work, suggesting that the degree of supplemental oxygen is important in the pathogenesis of BPD with an early, critical window during which the developing lung is most susceptible to oxidative stress. In addition, preliminary studies of mesenchymal stem cell transplantation in a rat hyperoxia model demonstrate that early therapy (3 versus 10 days of age) more effectively interrupts oxygen-induced inflammation and attenuates structural abnormalities. These data suggest that early identification of high-risk infants for intervention may be more effective in preventing BPD, before hyperoxia-induced lung injury peaks.[26] Thus, interventions that improve lung function (thereby decreasing the degree of respiratory support and reducing early supplemental oxygen exposure) or those directly focused on mitigating oxidative stress (such as recombinant human superoxide dismutase) are most likely to decrease the risk of BPD and its repercussions.[26–28]

Studies focused on oxygen exposure have shown that higher oxygen exposure early in life increases the risk of BPD, consistent with our results; studies focused on oxygen saturation targets throughout neonatal hospitalization have demonstrated less conclusive results

regarding BPD.[10, 17, 24, 29, 30] Studies targeting oxygen saturation have shown a non-significant trend towards a decreased risk of BPD in lower target saturation groups. This inconsistency may be due to heterogeneity of the populations studied and/or differences in respiratory support strategies. Regardless of these differences, oxygen exposure is an important contributor and risk factor for BPD in preterm populations.

Multiple studies that developed prediction models for BPD have included some measure of oxygen exposure; however the approach to quantifying this varies widely.[31] Early prediction models often focus on FiO_2 recorded on a particular day.[18, 32, 33] The variability from this approach is demonstrated by Laughon *et al*, who found that the relative importance of FiO_2 for prediction of BPD or death changed based on day of life; mean FiO_2 was the fourth most important factor on postnatal day 14, but the second greatest contributing factor on day 21.[18] In contrast, we found that oxygen exposure was the most important contributor to BPD or Death. This difference may be due to multiple factors, including the fact that we evaluated a higher-risk, selected cohort, and we quantified oxygen exposure as a cumulative measure, using both concentration and duration.

To date, few studies have analyzed the cumulative effect of oxygen exposure over time. Laughon et al found that the trend in supplemental oxygen exposure in the first 2 weeks of life (increasing FiO_2 requirement vs. consistently low FiO_2) was associated with BPD in a cohort of infants <28 weeks' GA; however, they did not record daily data through this time period, and did not evaluate oxygen exposure as an independent risk factor for BPD.[34] In a low risk preterm population, Stevens *et al* found that among infants without BPD (n=75), cumulative oxygen exposure at 72 hours of life independently predicted symptomatic airway disease at 1 year of life.[12] This study is consistent with our findings. Together, these data provide strong support for the application of early, cumulative supplemental oxygen indices to identification of infants at high risk for adverse pulmonary outcomes.

In our high-risk population, the use of the respiratory severity score (MAP × FiO_2) might be considered for prediction models, to mitigate concerns regarding variable respiratory support strategies. However, the strength of the current model is that it isolates the effect of oxygen exposure while controlling for MAP, demonstrating that effects of both positive pressure and supplemental oxygen exposure require ongoing attention. Importantly, the effect of oxygen is similar in unadjusted and adjusted models, in which previously identified risks for BPD were retained, namely birth weight and male sex.[19, 31, 32]

There were potential limitations to our study. Clinical guidelines for TOLSURF specified target oxygen saturations of 85–94%, but the actual oxygen saturations achieved were not recorded.[13] However, if there were inconsistencies in oxygen saturation targets, this would bias our analysis toward a decreased effect of oxygen exposure as a marker of illness. Regardless, any inconsistencies would not change the effect of increased supplemental oxygen exposure as a cause of BPD or Death. Thus, it is reassuring that respiratory support strategies appeared to be consistent across the duration of the study with respect to the relationship of MAP and FiO_2. Further, the potential beneficial effects of lower oxygen saturation targets in randomized studies were offset by increases in mortality, yet we demonstrated similar effects of CSO in models of BPD or Death and models of BPD in

survivors, suggesting that the effect of oxygen is not due to inconsistency in oxygen saturation targets.[14, 23, 31, 35] In addition, our study analyzed only a select group of high-risk ELGAN from tertiary care neonatal intensive care units who received iNO beginning at 7–14 days. Therefore, our results may not generalize to broader preterm populations. However, for ELGAN intubated at 7–14 days, who were primarily supported with invasive mechanical ventilation, our results suggest that quantification of cumulative oxygen exposure can provide additive information toward recognition of infants at highest risk for poor outcomes.

In conclusion, we identified a new quantitative index of supplemental oxygen exposure. In our high-risk cohort, cumulative supplemental oxygen, assessed early in the neonatal hospitalization, was independently associated with BPD or Death, and BPD among survivors. Cumulative supplemental oxygen thus provides early recognition of high-risk infants. This could identify the highest risk ELGAN who may benefit from intervention in investigational clinical trials, or serve as a marker of beneficial response to trials of very early interventions.

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Abbreviations

AUROC	area under the receiver-operating-curve
BPD	bronchopulmonary dysplasia
CSO	cumulative supplemental oxygen
ELGAN	extremely low gestational age newborns
FiO_2	fraction of inspired oxygen
GA	gestational age
iNO	inhaled nitric oxide
MAP	mean airway pressure
PMA	post-menstrual age
STOP-ROP	Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity
SUPPORT	Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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APPENDIX

Additional members of the TOLSURF Study Group include:

UCSF Benioff Children's Hospital, San Francisco, CA: Suzanne Hamilton Strong, RN, Jill Immamura-Ching, RN, Margaret Orfanos-Villalobos, RN, Cassandra Williams, RN, Lisa Palermo, MS; Alta Bates Summit Medical Center, Berkeley, CA, and UCSF Benioff Children's Hospital Oakland, Oakland, CA: David Durand, MD, Dolia Horton, RRT, Jeffrey Merrill, MD, Loretta Pacello, RCP, April Willard, RN; UC Davis Children's Hospital, Sacramento, CA: Robin Steinhorn, MD; Children's Mercy Hospital, Kansas City, MO: Cheryl Gauldin, RN, Anne Holmes, RN, Patrice Johnson, RRT, Kerrie Meinert, RRT; Women and Children's Hospital of Buffalo, Buffalo, NY: Anne Marie Reynolds, MD, Janine Lucie, NNP, Patrick Conway, Michael Sacilowski, Michael Leadersdorff, RRT, Pam Orbank, RRT, Karen Wynn, NNP; Anne and Robert H. Lurie Children's Hospital/Northwestern University, Chicago, IL: Maria deUngria, MD, Nicolas Porta, MD, Janine Yasmin Khan, MD, Karin Hamann, RN, Molly Schau, RN, Brad Hopkins, RRT, James Jenson, RRT; Texas Children's Hospital, Houston, TX: Carmen Garcia, RN; Stony Brook University Hospital, Stony Brook, NY: Aruna Parekh, MD, Jila Shariff, MD, Rose McGovern, RN, Jeff Adelman, RRT, Adrienne Combs, RN, Mary Tjersland, RRT; University of Washington, Seattle, WA: Dennis Mayock, MD, Elizabeth Howland, Susan Walker, RN, Jim Longoria, RRT, Holly Meo, RRT; University of Texas Health Science Center, Houston, TX: Eric Eichenwald, MD, Amir Khan, MD, Georgia McDavid, RN, Katrina Burson, RN, BSN, Richard Hinojosa, BSRT, RRT, Christopher Johnson, MBA, RRT, Karen Martin, RN, BSN, Sarah Martin, RN, BSN, Shawna Rogers, RN, BSN, Sharon Wright, MT; University of Florida College of Medicine, Jacksonville, UF Health Shands Hospital, and Wolfson Children's Hospital, Jacksonville, FL: Mark Hudak, MD, Kimberly Barnette, RRT, Amanda Kellum, RRT, Michelle Burcke, RN, Christie Hayes, RRT, Stephanie Chadwick, RN, Danielle Howard, RN, Carla Kennedy, RRT, Renee Prince, RN; Wake Forest School of Medicine and Forsyth Medical Center, Winston Salem, NC: T. Michael O'Shea, MD, Beatrice Stefanescu, MD, Jennifer Helderman, MD, Kelly Warden, RN, Patty Brown, RN, Jennifer Griffin, RRT, Laura Conley, RRT; University of Minnesota Amplatz Children's Hospital, Minneapolis, MN: Catherine Bendel, MD, Michael Georgieff, MD, Bridget Davern, Marla Mills, RN, Sharon Ritter, RRT; Medical University of South Carolina, Charleston, SC: Carol Wagner, MD, Deanna Fanning, RN, Jimmy Roberson, RRT; Children's Hospitals and Clinics of Minnesota, St. Paul, MN: Andrea Lampland, MD, Mark Mammel, MD, Pat Meyers, RRT, Angela Brey, RRT; Children's Hospitals and Clinics of Minnesota, Minneapolis, MN: Ellen Bendel-Stenzel, MD, Neil Mulrooney MD, Cathy Worwa, RRT, Pam Dixon, RN, ANM, Gerald Ebert, RRT-NPS, Cathy Hejl, RRT, Molly Maxwell, RT, Kristin McCullough, RN; University of Tennessee Health Science Center, Memphis, TN: Mohammed T. El Abiad, MD, Ramasubbareddy Dhanireddy, MD, Ajay Talati, MD, Sheila Dempsey, RN, Kathy Gammage, RRT, MBA, Gayle Gower, RN, Kathy James, RRT, Pam LeNoue, RN; All Children's Hospital, St. Petersburg, FL: Victor McKay, MD, Suzi Bell, DNP, Dawn Bruton, RN, BSN, CCRP, Michelle Beaulieu, DNP, Richard Williams, RRT; Florida Hospital for Children, Orlando, FL: Rajan Wadhawan, MD, Robin Barron-Nelson, RN, Shane Taylor, RRT; Arkansas Children's Hospital and University of Arkansas Medical Sciences, Little

Rock, AK: Sherry Courtney, MD, Carol Sikes, RN, Gary Lowe, RRT, Betty Proffitt, RRT; University of South Carolina, Charleston, SC: Frances Koch, MD, Rita Ryan, MD.

Figure 1.

Respiratory support settings at 14 days before and after December 1, 2010. Cumulative mean airway pressure versus cumulative supplemental oxygen at 14 days of life, in infants born before (n=76) (A) and after (n=389) (B) December 1, 2010.

Figure 2.

C-statistic for cumulative supplemental oxygen exposure at 14 days alone compared to the multivariate model for prediction of BPD or death (p=0.0003).

Table 1

Cohort characteristics and comorbidites from the first 14 days of life

		Infant status at 36 weeks' PMA		
	Total cohort (N=495)	**No BPD (N=159)**	**BPD/death (N=336)**	**p-value**
Neonatal characteristics				
Gestational age (weeks)	25.2 ± 1.2	25.4 ± 1.1	25.2 ± 1.3	0.03
Birth weight (grams)	700 ± 165	735 ± 156	683 ± 166	0.0009
Birth weight percentile *	40.2 ± 27.4	44.7 ± 26.2	38.1 ± 27.4	0.01
Male sex	54% (269)	46% (73)	58% (196)	0.01
Antenatal steroids	87% (427)	87% (138)	87% (289)	0.87
Cesarean delivery	73% (360)	75% (120)	71% (240)	0.35
Product of multiple gestation	29% (148)	32% (51)	28% (97)	0.38
Neonatal comorbidities †				
Severe IVH	17% (86)	13% (21)	19% (65)	0.09
Sepsis	30% (149)	30% (47)	30% (102)	0.86
Pulmonary hypertension	7% (33)	3% (5)	8% (28)	0.03
Maternal characteristics				
Maternal age	28.6 ± 6.4	28.8 ± 6.8	28.6 ± 6.3	0.71
Maternal race				
White Non-Hispanic	48% (237)	39% (62)	52% (175)	0.03
White Hispanic	10% (51)	11% (17)	10% (34)	
African American	37% (184)	44% (70)	34% (114)	
Other	5% (23)	6% (10)	4% (13)	

BPD, bronchopulmonary dysplasia; PMA, post-menstrual age; IVH, intraventricular hemorrhage

Data reported as mean±SD or % (N)

* Using Fenton growth curve standard (2013)

† Co-morbidities assesed in first 14 days of life only

Table 2

Comparison of predictive value of cumulative supplemental oxygen exposure at 14 days vs. other time points up to 28 days

Time point*	Day of life	AUROC (95% CI)	P-value
1d vs. 14d	1d	0.58 (0.52–0.63)	0.0001
	14d	0.70 (0.65–0.74)	
3d vs. 14d	3d	0.60 (0.55–0.65)	0.0002
	14d	0.70 (0.65–0.74)	
7d vs. 14d	7d	0.65 (0.60–0.70)	0.006
	14d	0.70 (0.65–0.74)	
10d vs. 14d	10d	0.67 (0.62–0.72)	0.04
	14d	0.70 (0.65–0.74)	
21d vs. 14d	21d	0.69 (0.64–0.74)	0.9
	14d	0.69 (0.64–0.74)	
28d vs. 14d	28d	0.70 (0.65–0.75)	0.38
	14d	0.69 (0.64–0.74)	

AUROC, area under the receiving-operating-curve; CI, confidence interval; d, day

*n varies from 475–488 as infants drop out due to death

Table 3

Multivariate modeling with adjusted odds ratio for BPD or Death, and for BPD among survivors only

	BPD/death (N=474)			BPD among survivors (N=441)		
Variable	**OR**	**95%CI**	**P value**	**OR**	**95% CI**	**P-value**
Gestational age (weeks)	1.1	0.88–1.4	0.40	1.1	0.89–1.4	0.33
Birth weight (grams)	0.80	0.68–0.94	0.007	0.81	0.68–0.96	0.01
Maternal race						
White, Non-Hispanic	Reference			Reference		
White, Hispanic	0.97	0.46–2.0	0.93	0.87	0.41–1.8	0.72
African American	0.38	0.24–0.63	<0.001	0.37	0.23–0.61	<0.001
Other	0.58	0.22–1.5	0.26	0.55	0.21–1.5	0.23
Male	2.1	1.3–3.3	0.002	2.1	1.3–3.3	0.003
CSO at 14 days	1.7	1.3–2.2	<0.001	1.7	1.3–2.2	<0.001
Cumulative MAP at 14 days*	1.2	1.1–1.3	0.001	1.2	1.1–1.3	0.001

BPD, bronchopulmonary dysplasia; CI, confidence interval; CSO, cumulative supplemental oxygen; MAP, mean airway pressure; OR, odds ratio

*Cumulative MAP divided by 10

Table 4

Comparison of C-statistic for cumulative supplemental oxygen exposure at 14 days vs. other variables selected for inclusion in multivariate modeling for prediction of BPD or Death, ordered from most to least important

Variable	C-statistic	P-value
CSO at 14 days	0.691	Reference
Cumulative MAP at 14 days	0.688	0.92
Maternal race	0.588	0.007
Birth weight (grams)	0.584	0.001
Male	0.563	0.0003
Gestational age	0.545	<0.0001

CSO, cumulative supplemental oxygen; MAP, mean airway pressure