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Risk Factors for Retinopathy of Prematurity: Insights from Outlier Infants

Alexander D. Port, BA[1], **R.V. Paul Chan, MD**[1], **Susan Ostmo, MS**[2], **Dongseok Choi, PhD**[2,3], and **Michael F. Chiang, MD**[2,4]

[1]Department of Ophthalmology, Weill Cornell Medical College, New York, NY

[2]Department of Ophthalmology, Casey Eye Institute, Oregon Health and Science University, Portland, OR

[3]Dept. of Public Health and Preventive Medicine, Oregon Health and Science University, Portland, OR

[4]Department of Medical Informatics and Clinical Epidemiology, Oregon Health and Science University, Portland, OR

Abstract

Purpose—To investigate the characteristics of outlier infants for insights into ROP risk.

Methods—Chart data were collected from 1354 infants screened for ROP at Weill Cornell Medical Center and Columbia University Medical Center. ROP exam results and clinical risk factors were recorded. The cohort was stratified by weight, highest ROP stage, and need for ROP treatment. Descriptive and correlational statistics were performed.

Results—For the overall cohort, regression analysis found that birth weight (OR: 0.741 per 100g; 95% CI: 0.606, 0.905), gestational age at birth (OR: 0.563 per week; 95% CI: 0.454, 0.697), multiple gestation (OR 2.02, 95% CI: 1.15, 3.56), bronchopulmonary dysplasia (OR: 4.68, 95% CI: 1.93, 11.35), and necrotizing enterocolitis (OR 2.80, 95% CI: 1.40, 5.16) were independent risk factors for treatment-requiring ROP. Black race was found to be a protective factor for treatment-requiring ROP (OR 0.244, 95% CI: 0.095, 0.626).

Among 15 infants with BW <500g, there were no significant differences in any clinical risk factors between the 12 (80%) with ROP vs. the 3 (20%) without ROP. Similarly, among infants with BW >1500g, the 17 (9%) with ROP only differed from the 166 (91%) without ROP with respect to a higher incidence of necrotizing enterocolitis among those with ROP (11.8% vs 0%).

Conclusions—Although known clinical risk factors were predictive of ROP stage and need for laser treatment in this cohort, they were not significantly associated with ROP at extremes of birth

Correspondence to: Michael F. Chiang, MD, Knowles Professor of Ophthalmology & Medical Informatics and Clinical Epidemiology, Casey Eye Institute, Oregon Health & Science University, 3375 SW Terwilliger Boulevard, Portland, OR 97239, Tel: 503-494-7830 | Fax: 503-494-5347 | chiangm@ohsu.edu.

CONFLICTS OF INTEREST/DISCLOSURES

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weight. This suggests that other clinical, maternal, or genetic factors may protect from or predispose to ROP.

Keywords

Retinopathy of prematurity; retina; pediatric ophthalmology; risk analysis

INTRODUCTION

Retinopathy of prematurity (ROP) is a proliferative vitreoretinopathy that is a leading cause of childhood blindness in the United States and throughout the world. ROP is becoming an increasing clinical and public health problem worldwide because of improvements in neonatal care in developing economies, as well as increased survival among premature infants in developed economies. [1] Given the enormous societal impact of a lifetime of blindness caused by ROP, many researchers have studied ROP risk factors in order to improve disease screening and treatment. Findings from several large, multicenter trials of ROP interventions [2–5] have established low birth weight (BW) and gestational age (GA) as the most important clinical predictive factors. As a result, current screening guidelines in the United States stipulate that ROP examination should be performed on all infants born at ≤30 weeks or ≤1500g BW, and selected larger infants based on unstable clinical course.[6]

However, the current screening paradigm based primarily on GA and BW has limitations. Studies have shown that only 20–66% of infants screened for ROP will develop ROP [7–11] and an even smaller number (5–10%) will require treatment [7, 9, 10, 12], resulting in many infants being screened unnecessarily. Screening examinations are stressful for infants [13, 14], and are known to have adverse physiologic effects, including an increase in apnea events among screened infants.[15, 16] As such, there is a significant incentive to limit unnecessary screening examinations.[11, 15–17] At the same time, this must be balanced against the concern that some infants with birth weight >1500 grams are known to develop treatment-requiring ROP and might not be screened under the current guidelines.[18, 19]

While the majority of ROP risk appears predictable based on low BW and low GA, there are “outliers” who continue to confound ophthalmologists and neonatologists. In particular, some high-risk infants with low BW and/or GA never develop clinically-significant ROP, whereas some low-risk infants with high BW and/or GA develop clinically-significant disease. A deeper knowledge of the determinants of ROP risk would enable fine-tuning of evidence-based screening guidelines and provide a better understanding of ROP pathophysiology.

Numerous clinical and demographic risk factors for ROP have been cited in the literature. These include supplemental oxygen exposure, prolonged mechanical ventilation, sepsis, necrotizing enterocolitis, and many other complications of prematurity.[9, 12, 20, 21] Some researchers have developed risk prediction models using various factors [22–24], but none have achieved widespread adoption. Therefore, these factors are not systematically incorporated into current ROP screening strategies.

This project aims to study the characteristics of “outlier” infants in terms of clinical and demographic risk factors. The premise of this study is that studying these “outlier” infants will provide insight about factors that protect against or predispose to ROP, beyond traditional clinical and demographic factors such as BW and GA. A cohort of infants screened for ROP at two major academic medical centers is reviewed, and clinical and demographic characteristics of “outlier” infants are compared with those of other infants in the cohort.

METHODS

Institutional Review Board approval was obtained at Columbia University Medical Center, Weill Cornell Medical College, and Oregon Health & Science University for data collection and analysis.

Setting

Medical records were retrospectively reviewed for all hospitalized infants who were screened for ROP between June 2002 and July 2010 at two large academic hospitals in New York City: Columbia University Medical Center and Weill Cornell Medical Center. In the neonatal intensive care unit of each hospital, all infants who met published criteria were screened for ROP. Since 2006, this has included infants with birth weight <1500g or gestational age at birth ≤30 weeks, and selected infants with birth weight 1500–2000 at discretion of the attending neonatologist.[6, 25, 26] Examinations were typically begun during inpatient hospitalization, and continued by the same ophthalmologists in outpatient offices after discharge. All inpatient examinations at the two medical centers were performed by one of four pediatric ophthalmologist or retina specialists, all of whom had either been certified as examiners in the Early Treatment for ROP (ETROP) study or published ≥5 peer-reviewed papers in ROP.

Data Collection

All ophthalmic examination data were recorded and collected from a database of ROP screening examination results maintained for routine care at each institution. Systemic and demographic data were obtained by chart review for 11 clinical factors: gender, BW, gestational age at birth, multiple gestation (i.e. twin, triplet), assisted conception, mechanical ventilation, bronchopulmonary dysplasia, neonatal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and maternal race/ethnicity. Race/ethnicity was self-reported in demographic data within the electronic health record and included five categories: White non-Hispanic, Black non-Hispanic, Hispanic, Asian, or Other/Not-Specified.

ROP examination findings were reviewed for each individual ophthalmoscopic examination, and were summarized based on highest stage in either eye, lowest zone in either eye, and need for ROP treatment in each infant. For purposes of data analysis, ROP exam results were classified using an ordinal scale based on the most severe exam findings in either eye. Definitions were adapted from the Cryotherapy for ROP (CRYO-ROP) and ETROP studies [2, 27] as follows: (1) no ROP; (2) mild-moderate ROP, defined as presence of ROP not requiring treatment; and (3) treatment-requiring ROP, defined as type 1 ROP (zone I, any

stage, with plus disease; zone I, stage 3, without plus disease; or zone II, stage 2 or 3, with plus disease) or worse.

Statistical Analysis

Demographic characteristics of the cohort and the frequency of each risk factor were analyzed. Subjects with and without ROP were compared, using the Student's t-test to compare means, and the chi-square test to compare the frequency of risk factors. In order to analyze "outlier" groups, the cohort was then divided into subgroups based upon birth weight in grams. Four subgroups were created, comprising infants <500g, 500–749g, 1251–1500g, and >1500g. "Outliers" were defined as infants with BW from 500–749g without any ROP, or with BW from 1251–1500g with any ROP. "Extreme outliers" were defined as those infants with BW <500g without any ROP, or with BW >1500g with any ROP. For each of the outlier groups, subjects with and without ROP were compared using the t-test or chi-square test, where appropriate.

Univariate analysis was performed to determine the association between individual risk factors and ROP or treatment-requiring ROP. Forward stepwise logistic regression was performed to identify independent risk factors for ROP or treatment-requiring ROP. Presence of treatment-requiring ROP was defined based on published guidelines at the time of management.[25, 26] Eleven predictors were entered into the regression model, including gender, race/ethnicity (White non-Hispanic, Black non-Hispanic, Hispanic, Asian, Other); BW; GA at birth; multiple gestation; use of assisted conception; need for prolonged mechanical ventilation; and the presence of neonatal sepsis, intraventricular hemorrhage, bronchopulmonary dysplasia, or necrotizing enterocolitis. Analyses were performed with the aid of statistical software (SAS Add-In 5.1 for Microsoft Office; SAS Institute, Cary, NC and SPSS Statistics for Mac, Version 21.0; IBM, Armonk, NY). For all analyses, a p-value <0.05 was considered significant.

RESULTS

Table 1 compares the characteristics of infants with and without ROP among the study cohort. In all, records were available for 1354 infants screened for ROP from January 2002 through December 2010, including 764 at Columbia University Medical Center and 590 at Weill Cornell Medical Center.

Overall, 526 (38.8%) developed any stage of ROP, whereas 828 infants (61.2%) never developed ROP during the screening process. Among infants who developed any level of ROP, 209 (15.4% of total, 39.7% of ROP cases) had stage 1, 174 (12.9% of total, 33.1% of ROP cases) had stage 2, 140 (10.3% of total, 26.6% of ROP cases) had stage 3, 3 (0.2% of total, 0.6% of ROP cases) developed stage 4, and no infants developed stage 5 ROP. Treatment-requiring ROP was present in 80 (5.9% of total, 15.2% of ROP cases) infants, and was managed with peripheral laser photocoagulation or incisional surgery, as clinically indicated.

Infants with ROP had lower birth weights ($p < 0.001$) and gestational age ($p < 0.001$), and were more likely to be female ($p = 0.008$) or the product of singleton pregnancy ($p = 0.026$).

Complications of prematurity, including prolonged mechanical ventilation ($p < 0.001$), neonatal sepsis ($p < 0.001$), intraventricular hemorrhage ($p < 0.001$), bronchopulmonary dysplasia ($p < 0.001$), and necrotizing enterocolitis ($p < 0.001$) were all more common among infants with ROP. Compared to White non-Hispanic infants, Asian and Hispanic infants were more likely to develop ROP, while Black non-Hispanic infants were less likely to develop ROP ($p = 0.002$).

Risk Factors Among Entire Cohort

Table 2 summarizes results from multivariate logistic regression analysis of clinical and demographic risk factors or presence of any ROP and treatment-requiring ROP in the entire study cohort. Forward stepwise regression for presence of any ROP showed that BW, GA, assisted conception, neonatal sepsis, bronchopulmonary dysplasia and race/ethnicity were all independent risk factors for ROP.

Regression analysis for presence of treatment-requiring ROP showed that BW, GA, multiple gestation, bronchopulmonary dysplasia, necrotizing enterocolitis, and race/ethnicity were all independent risk factors for treatment-requiring ROP.

Compared to White non-Hispanic neonates, Hispanic neonates were more likely to develop any ROP. Black non-Hispanic and Other race/ethnicity were found to be protective against both ROP and treatment-requiring ROP. Relative to White infants, Asian race/ethnicity was associated with an elevated risk of ROP and treatment-requiring ROP, but this relationship was not statistically significant.

Risk Factors among “Outlier” and “Extreme Outlier” Infants

Table 3 summarizes results from multivariate logistic regression analysis for presence of any ROP, after dividing the entire study cohort into weight subgroups (BW <500g, 500–749g, 1251–1500g, >1500g), and Table 4 summarizes results from a similar analysis for presence of treatment-requiring ROP. Among 223 infants in the study cohort with BW 500–749g, 63/223 (28%) were small “outliers” who did not develop any ROP. For infants with BW 500–749g, assisted conception, mechanical ventilation, and neonatal sepsis were independent risk factors for any ROP (Table 3). Among this same group of infants, only GA and white non-Hispanic race/ethnicity were independent risk factors for treatment-requiring ROP (Table 4).

Among 293 infants with BW 1251–1500g, 48/293 (16%) were large “outliers” who developed any ROP. For infants with BW 1251–1500g, only gestational age and race/ethnicity were independent risk factors for ROP (Table 3). Of note, there were no infants with BW >1250g in the study cohort that developed treatment-requiring ROP. The largest infant that was treated for ROP was 1075g at birth and was born at 28 weeks and 6 days gestation.

Among the 15 infants in the study cohort with BW <500g, 3/15 (20%) were small “extreme outliers” who did not develop any ROP, 10/15 (66.6%) developed mild-moderate ROP, and 2/15 (13.3%) developed treatment-requiring ROP. Among the 183 infants in the study cohort with BW >1500 g, 17/183 (9.3%) were large “extreme outliers” who developed any

ROP, while the remaining 166 (90.7%) did not develop any ROP, and no large extreme outlier infants developed treatment-requiring ROP.

Table 5 compares clinical and demographic risk factors among infants with BW <500g. Among these 15 infants, there were no statistically-significant differences in any clinical risk factors between the 12 (80%) with ROP vs. the 3 (20%) “extreme outliers” without any ROP (Table 5). On multivariate logistic regression analysis, there were no independent risk factors for ROP or treatment-requiring ROP among infants with BW <500g (Tables 3 and 4).

Table 6 summarizes clinical and demographic risk factors among infants with BW >1500g. Among these 183 infants, the only statistically-significant difference between those “extreme outliers” with any ROP vs. without ROP was a higher prevalence of necrotizing enterocolitis among infants with any ROP (p=.0001). On multivariate logistic regression, there were no independent risk factors for ROP among infants with BW >1500g (Table 3).

DISCUSSION

This study was designed to examine demographic and clinical risk factors for ROP, with an emphasis on studying “outliers”: infants with low birth weight who did not develop ROP and infants with high birth weight who did develop ROP. The principal findings are as follows: (1) Risk factors associated with presence of ROP or treatment-requiring ROP include birth weight, gestational age, multiple gestation, bronchopulmonary dysplasia, necrotizing enterocolitis, and race/ethnicity. (2) Among “outlier” infants, there were few or no clinical or demographic risk factors associated with ROP or treatment-requiring ROP. These findings raise the possibility that there may be underlying protective or risk factors for ROP beyond these traditional demographic and clinical factors.

The first key finding is that clinical and demographic risk factors in this study cohort are largely consistent with previously-published research involving ROP risk factors. Birth weight and gestational age are consistently the most important risk factors for ROP in published studies, but several other significant risk factors were also identified, including demographic features, and systemic complications of prematurity such as necrotizing enterocolitis.[9, 12, 20, 21]

In prior studies [21, 28–32], race and ethnicity have also been identified as significant risk factors, with Whites [30, 32], Asians [31], and Alaskan Natives [28] found to be at increased risk of developing severe ROP. In the present study, we found that race/ethnicity was an independent predictor of any ROP and treatment-requiring ROP. Relative to White non-Hispanic infants, Hispanic ethnicity was associated with increased risk of any ROP (odds ratio 2.88), but not treatment-requiring ROP among infants with BW 500–1500g.. The multi-center CRYO-ROP trial, and other major studies, found Black non-Hispanic race/ethnicity to be protective against development of severe ROP.[9, 32] In this study, Black non-Hispanic race/ethnicity was found to be protective against any ROP (odds ratio 0.484) and treatment-requiring ROP (odds ratio 0.244). Additionally, in this study “other” race/ethnicity, which includes infants of mixed racial heritage, was found to be independently

associated with a decreased risk of ROP (odds ratio 0.501) and treatment-requiring ROP (odds ratio 0.473).

Within the traditional ROP framework, it would be expected that very-low birth weight infants who did not develop ROP would have fewer complications of prematurity than their peers who did develop ROP (i.e. they would be small but “healthy”). From this perspective, it is striking that in this study cohort the smallest “outlier” infants who never developed any ROP did not differ significantly from similarly-small infants who developed ROP with respect to clinical and demographic risk factors (Tables 3–5). Conversely, it would be expected that relatively large babies who did develop ROP would be “sicker” than their peers. Again, it is striking that among larger infants in this study cohort, the only difference between the “outliers” who developed ROP and similarly-large infants who never developed any ROP was a higher incidence of necrotizing enterocolitis (Tables 3, 6). However, it is important to note that this study was limited by sample size among outlier infants, especially those with BW <500g, and may have been underpowered to detect differences between those with and without ROP. Furthermore, it should be noted that none of the larger outlier infants (BW >1250g) developed treatment-requiring ROP. In this study cohort, all of the clinically-significant cases of ROP would have been detected under current screening guidelines, even among the outlier infants.

Given the relative lack of clinical and demographic risk factors among the “outlier” and “extreme outlier” groups in this study, it is possible that other factors may be involved in ROP pathogenesis. In particular, genetic factors may explain some heterogeneity of ROP risk for similar weight infants. FEVR (familial exudative vitreo-retinopathy) and Norrie disease are heritable diseases that mimic the pathology observed in ROP, and causative genes for these disorders such as FZD4 (frizzled-4), NDP (Norrie disease protein), and LRP5 (low density lipoprotein receptor protein-5) have been implicated in ROP.[33] However, in recent case-control studies of these genes in ROP, mutations only accounted for 3–11% of ROP cases.[33–36] Additional studies of the molecular and genetic basis of ROP will help improve our understanding of disease pathophysiology and our ability to identify infants at risk for disease.

Limitations

There are several limitations of this study design: (1) Sample size was limited. In particular, our subgroup analysis of infants with BW <500g (n= 15) may have been underpowered to detect all but very large differences between those with and without ROP. Nevertheless, we note that this was a large study (n=1354 infants over 8 years) at two major academic medical centers with a large range of systemic and ophthalmic disease pathology, and we are not aware of previous studies that have examined risk factors in “outlier” infants in this manner. We hope that this study will stimulate further research involving outlier infants in ROP. (2) We did not perform a separate subgroup analysis of infants with BW 751–1250g, but did include these infants in the whole-cohort analysis. This decision was made to ensure that the “outlier” groups remained at the extremes of birth weight. To our knowledge, this is the first study to assess ROP risk in this manner. (3) This was a retrospective study in which ROP examinations were performed by 4 different examiners, and it is possible that some data on

clinical and demographic risk factors were incomplete or were recorded inconsistently in patient charts. However, we note that ophthalmologic exam results were available for all study patients throughout the duration of inpatient hospitalization, and for all outpatient exams. Furthermore, we note that all exams were performed by ophthalmologists who were considered ROP experts based on national academic and leadership roles. (4) The number of clinical and demographic risk factors included in this study was limited. Many ROP risk factors have been cited in the literature, and it is possible that the "outlier" groups differed with respect to clinical or demographic risk factors that were not included in our analysis. However, risk factors chosen for analysis were frequently cited in the literature, and we believe it is relevant that there were no statistically significant differences with respect to these variables. Future research involving additional risk factors may be informative. (5) Maternal race was recorded with a limited menu of descriptors. Our hospitals treat extremely diverse, multiracial and multiethnic populations. For example, the limited number of options may have resulted in subjects from different backgrounds being grouped together under the "other" category. (6) This study did not investigate the role of postnatal weight gain in the development of ROP among outlier infants. In recent years, algorithms based upon postnatal weight gain, such as the WINROP (weight, IGF, neonatal ROP) and CHOP-ROP (Children's Hospital of Philadelphia ROP) algorithms have been shown to have a high sensitivity for detecting ROP among at-risk infants.[22, 24] In this study, it was not possible to evaluate the role of postnatal weight gain because these algorithms were not in use at the time of initial screening, and data on longitudinal weight gain were not readily available.

Within this entire study cohort, nine known clinical risk factors (female sex, BW, GA, multiple gestation, sepsis, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, and race/ethnicity) were found to be significantly associated with ROP (Table 1). On multivariate regression analysis, six factors (BW, GA, assisted conception, sepsis, bronchopulmonary dysplasia and race/ethnicity) were independently associated with ROP. Similarly, six known risk factors (BW, GA, multiple gestation, bronchopulmonary dysplasia, necrotizing enterocolitis and race/ethnicity) were independently associated with treatment-requiring ROP by multivariate regression (Table 2). However, upon subgroup analysis of "outlier" and "extreme outlier" infants, clinical and demographic factors were not significantly associated with ROP among infants at either extreme of birth weight. Taken together, these trends suggest that other factors may explain the heterogeneity of ROP risk. Additional research examining molecular and genetic risk factors may provide insight for better understanding ROP pathogenesis, prediction, and treatment.

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Table 1

Clinical and demographic characteristics of entire study cohort.

	Any ROP (N= 526)	No ROP (N =828)	P-value
Female (N, %)	279 (53.0 %)	378 (45.7%)	0.008
Birth Weight (Mean ± SD)	904.6 ± 279.5g	1250.7 ± 342.1 g	<0.001
Gestational Age (Mean ± SD)	27.2 ± 2.1 wks	29.7 ± 2.3 wks	<0.001
Multiple gestation (N, %)	226 (43.0%)	407 (49.2%)	0.026
Assisted conception (N, %)	107 (20.3%)	171 (20.7%)	0.891
Mechanical ventilation (N, %)	289 (54.9%)	207 (25.0%)	<0.001
Sepsis (N, %)	79 (15.0%)	36 (4.3%)	<0.001
Intraventricular hemorrhage (N, %)	92 (17.5%)	69 (8.3%)	<0.001
Bronchopulmonary dysplasia (N, %)	34 (6.5%)	14 (1.7%)	<0.001
Necrotizing enterocolitis (N, %)	56 (10.6 %)	28 (3.4%)	<0.001
Race/Ethnicity			0.002
White non-Hispanic (N, %)	239 (45.4%)	369 (44.6%)	
Black non-Hispanic (N, %)	73 (13.9%)	128 (15.5%)	
Hispanic (N, %)	46 (8.7%)	34 (4.1%)	
Asian (N, %)	40 (7.6%)	49 (5.9%)	
Other race/ethnicity (N, %)	128 (24.3%)	248 (30.0%)	

Data regarding clinical and demographic risk factors are shown for infants with vs. without retinopathy of prematurity (ROP). P-values are calculated using two-tailed t-test for continuous variables and chi-square test for categorical variables.

Table 2

Odds ratios from multivariate logistic regression analysis of clinical and demographic risk factors for presence of any retinopathy of prematurity (ROP) and treatment-requiring ROP in entire study cohort (N=1354 infants).

	Any ROP (N=526)	Treatment-Requiring ROP (N=828)
Risk Factor	**Odds ratio and (95% confidence interval)**	
Female sex	*	*
Birth Weight (100g)	0.819 (0.740, 0.905)†	0.741 (0.606, 0.905)†
Gestational Age (weeks)	0.738 (0.676, 0.805)†	0.563 (0.454, 0.697)†
Multiple Gestation	*	2.021 (1.147, 3.562)†
Assisted conception	1.72 (1.207, 2.453)†	*
Mechanical ventilation	*	*
Sepsis	2.466 (1.498, 4.060)†	*
Intraventricular hemorrhage	*	*
Bronchopulmonary dysplasia	3.301 (1.534, 7.103)†	4.676 (1.925, 11.354)†
Necrotizing Enterocolitis	*	2.804 (1.400, 5.615)†
Race/Ethnicity‡:		
Black, non-Hispanic	0.484 (0.321, 0.729)†	0.244 (0.095, 0.626)†
Hispanic	2.883 (1.639, 5.072)†	0.641 (0.157, 2.607)
Asian	1.255 (0.738, 2.136)	1.170 (0.403, 3.399)
Other race/ethnicity	0.501 (0.353, 0.712)†	0.473 (0.252, 0.887)†

*Variable entered in the model but excluded from final regression equation.

†Statistically significant at the $p < 0.05$ level.

‡Odds ratios for race/ethnicity are compared to reference category White, non-Hispanic.

Eleven clinical and demographic risk factors were modeled as discrete variables (presence or absence) except for gestational age (GA, continuous variable with odds ratio calculated per 1-week increase), birth weight (BW, continuous variable with odds ratio calculated per 100-gram increase), and race/ethnicity (categorical variable).

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Table 3

Odds ratios from multivariate logistic regression analysis for presence of any retinopathy of prematurity (ROP) based on weight subgroups (birth weight <500g, 500–749g, 1251–1500g, >1500g).

	Whole cohort (N= 1354)	**<500g (N= 15)**	**500–749g (N= 223)**	**1251–1500g (N= 293)**	**>1500g (N= 183)**
Risk Factor	**Odds ratios and (95% Confidence interval)**				
Female	*	*	*	*	*
Birth Weight (100g)	0.819 (.740, .905)†	*	*	*	*
Gestational age	0.738 (0.676, 0.805)†	*	*	0.660 (0.571, 0.843)†	*
Multiple gestation	*	*	*	*	*
Assisted conception	1.720 (1.207, 2.453)†	*	8.957 (1.154, 69.543)†	*	*
Mechanical ventilation	*	*	1.996 (1.024, 3.891)†	*	*
Sepsis	2.466 (1.498, 4.060)†	*	5.015 (1.118, 22.505)†	*	*
Intraventricular hemorrhage	*	*	*	*	*
Bronchopulmonary dysplasia	3.301 (1.534, 7.103)†	*	*	*	*
Necrotizing enterocolitis	*	*	*	*	*
Race/Ethnicity‡:					
Black non-Hispanic	0.484 (0.321, 0.729)†	*	*	0.394 (0.128, 1.214)	*
Hispanic	2.883 (1.639, 5.072)†	*	*	1.688 (0.520, 5.476)	*
Asian	1.255 (0.738, 2.136)	*	*	0.347 (0.073, 1.643)	*
Other race/ethnicity	0.501 (0.353, 0.712)†	*	*	0.362 (0.141, 0.930)†	*

*Variable entered in the model but excluded from final regression equation.

†Statistically significant at the $p < 0.05$ level.

‡Odds ratios for race/ethnicity are compared to reference category White, non-Hispanic.

Eleven clinical and demographic risk factors were modeled as discrete variables (presence or absence) except for gestational age (GA, continuous variable with odds ratio calculated per 1-week increase), birth weight (BW, continuous variable with odds ratio calculated per 100-gram increase), and race/ethnicity (categorical variable).

Table 4

Odds ratios from multivariate logistic regression analysis for presence of treatment-requiring retinopathy of prematurity (ROP) based on weight subgroups (birth weight <500g, 500–749g)

	Whole Cohort (N= 1354)	<500g (N= 15)	500–749g (N= 223)
Risk Factor	**Odds ratios and (95% Confidence interval)**		
Female	*	*	*
Birth Weight (100g)	0.741 (.606, .905)†	*	*
Gestational Age	0.563 (0.454, 0.697)†	*	0.621 (0.464, 0.830)†
Multiple Gestation	2.021 (1.147, 3.562)	*	*
Assisted conception	*	*	*
Mechanical ventilation	*	*	*
Sepsis	*	*	*
Intraventricular hemorrhage	*	*	*
Bronchopulmonary dysplasia	4.676 (1.925, 11.354)†	*	*
Necrotizing enterocolitis	2.804 (1.400, 5.615)†	*	*
Race/Ethnicity‡:			
Black, non-Hispanic	0.244 (0.095, 0.626)†	*	0.263 (0.093, 0.739)
Hispanic	0.641 (0.157, 2.607)	*	0.933 (0.077, 11.273)
Asian	1.170 (0.403, 3.399)	*	1.278 (0.289, 5.650)
Other race/ethnicity	0.473 (0.252, 0.887)†	*	0.303 (0.132, 0.697)†

*Variable entered in the model but excluded from final regression equation.

†Statistically significant at the $p < 0.05$ level.

‡Odds ratios for race/ethnicity are compared to reference category White, non-Hispanic

Eleven clinical and demographic risk factors were modeled as discrete variables (presence or absence) except for gestational age (GA, continuous variable with odds ratio calculated per 1-week increase), birth weight (BW, continuous variable with odds ratio calculated per 100-gram increase), and race/ethnicity (categorical variable). There were no cases of treatment-requiring ROP in infants with BW >1250g.

Table 5

Clinical and demographic risk factors among infants with birth weight <500g.

	<500g, No ROP N = 3	<500g, Any ROP N = 12	p-value
Female (N, %)	1	7	0.438
Birth weight (Mean ± SD)	425.3 ± 57.3 g	443.9 ± 31.9 g	0.450
Gestational age (Mean ± SD)	26.9 ± 3.0 weeks	25.3 ± 1.6 weeks	0.208
Multiple gestation (N, %)	2	2	0.080
Assisted conception (N, %)	0	1	0.605
Mechanical ventilation (N, %)	3	8	0.333
Sepsis (N, %)	0	2	0.448
Intraventricular hemorrhage (N, %)	1	1	0.255
Bronchopulmonary dysplasia (N, %)	0	3	0.333
Necrotizing enterocolitis (N, %)	0	2	0.448
Race/Ethnicity			0.567
White non-Hispanic (N, %)	1	1	
Black non-Hispanic (N, %)	0	2	
Hispanic (N, %)	0	1	
Asian (N, %)	0	3	
Other (N, %)	2	5	

Data are compared for infants who developed retinopathy of prematurity (ROP) vs. “extreme outliers” in this weight group who never developed any ROP. P-values are calculated using two-tailed t-test for continuous variables and chi-square test for categorical variables.

Table 6

Clinical and demographic risk factors among infants with birth weight <1500g.

	>1500g, No ROP N = 166	>1500g, Any ROP N = 17	p-value
Female (N, %)	66	9	0.293
Birth Weight (Mean ± SD)	1730.6 ± 203.0g	1663.7 ± 166.2g	0.191
Gestational Age (Mean ± SD)	31.3 ± 1.2 weeks	30.8 ± 1.0 weeks	0.100
Multiple Gestation (N, %)	114	9	0.188
Assisted conception (N, %)	15	3	0.518
Mechanical ventilation (N, %)	6	1	0.256
Sepsis (N, %)	62	5	0.642
Intraventricular Hemorrhage (N, %)	9	2	0.295
Bronchopulmonary dysplasia (N, %)	4	0	0.518
Necrotizing enterocolitis (N, %)	0	2	<0.001
Race/Ethnicity			0.706
White non-Hispanic (N, %)	94	10	
Black non-Hispanic (N, %)	11	1	
Hispanic (N, %)	12	2	
Asian (N, %)	10	2	
Other (N, %)	39	2	

Data are compared for “extreme outlier” infants in this weight group who developed retinopathy of prematurity (ROP) vs. those who never developed any ROP. P-values are calculated using two-tailed t-test for continuous variables and chi-square test for categorical variables.