Retinopathy of Prematurity Risk Prediction for Infants with Birth Weight Less than 1251 Grams

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Objective To predict retinopathy of prematurity (ROP) exam findings among infants with birth weight <1251 g from 32-40 weeks postmenstrual age (PMA).

Study design Secondary analysis of 3714 eye exams from 1239 infants.

Results The likelihood of developing type 1 ROP by 40 weeks PMA varied by gestational age (GA) ($P < .001$), from 33% for ≤25 weeks, 10% for 26 or 27 weeks, 4% for 28 or 29 weeks, and none for ≥30 weeks. By 40 weeks PMA, 51% with GA ≤27 weeks still needed subsequent exams. Previous exam findings, GA, and PMA were predictive of the development of type 1 ROP (area under the curve, 0.78) or mature retina (area under the curve, 0.85).

Conclusions This analysis provides the opportunity for development of an ROP approach to estimate resource needs in the neonatal intensive care unit and to facilitate communication with families when planning discharge or transfer. *(J Pediatr 2015;166:257-61)*.

Decreasing the incidence of blindness from retinopathy of prematurity (ROP) relies upon repeated ophthalmologic examination of infants based on gestational age (GA), birth weight (BW), and postmenstrual age (PMA), with subsequent treatment for those who develop specific retinal findings.[1] Most infants at risk will not develop significant ROP; however, even short delays in diagnosis can lead to blindness. In high-income countries such as the US, fewer than 5% of infants born with GA less than 32 weeks require treatment for ROP (ie, type 1 ROP).[2] The need for repeated timely eye exams is a challenge for many neonatal intensive care units (NICUs) because of the shortage of ophthalmologists who examine and treat ROP.[3] In addition, families may become frustrated because of the inability to transfer infants to NICUs closer to home because of the inability to assure subsequent eye exams.[3] Understanding the risk of developing significant ROP or the likelihood of no longer requiring eye exams for ROP detection could allow revision of management guidelines for efficient strategies for the detection of ROP and to inform families about the benefits of receiving timely eye exams.

Our goal was to develop a clinically useful model to predict the likelihood that the findings from an eye exam would lead to a treatment (ie, type 1 ROP), lead to subsequent eye exams (ie, immature retinae, mild ROP, type 2 ROP), or suggest that the infant is no longer at risk for developing ROP (ie, mature retinae). Many risk factors are associated with the development of ROP, including infant characteristics (eg, race, multiparity) and markers of severe illness (eg, use of supplemental oxygen therapy, prolonged mechanical ventilation, treatment with inhaled nitric oxide, sepsis, rate of early postnatal growth, prolonged NICU stay).[4,5]

Not surprisingly, information about the status of the retinae can help predict the likelihood of developing ROP. A risk model, based on data published in 1991, used a wide array of infant characteristics, including previous eye exam findings, to predict the risk of progression from prethreshold ROP to unfavorable outcome at 3 months post-term for individual eyes.[6] However, more recent risk-prediction models have focused on other clinical factors and did not include information about the previous status of the retina. For example, 2 studies found that BW, GA, and daily weight gain were sensitive risk predictors of significant ROP; however, the specificity was low.[7,8] A more recent analysis from The Netherlands found that clinical characteristics could be used to decrease the number of infants with GA from 30-32 weeks by 29% without missing any cases of type 1 ROP.[9]

We took advantage of recent longitudinal exam data from the Telemedicine Approaches to Evaluating Acute-Phase ROP (e-ROP) study, a prospective cohort study to compare eye examinations with remote evaluation of digital images. We

AUC	Area under the curve
BW	Birth weight
e-ROP	Telemedicine Approaches to Evaluating Acute-Phase ROP
GA	Gestational age
NICU	Neonatal intensive care unit
PMA	Postmenstrual age
ROP	Retinopathy of prematurity
SGA	Small for gestational age

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used a subset of the data for those from 32-40 weeks PMA. Unlike earlier risk-prediction models, we considered the degree to which knowledge of the previous retinal exam findings predicted the subsequent development of ROP.

Methods

This is a secondary analysis of data from the e-ROP study. The e-ROP study was designed to enroll subjects with an increased likelihood of developing ROP. The study enrolled infants with BW <1251 g from 11 clinical centers in the US and 1 in Canada from 2011 through 2013. Subjects included those born within each center or transferred from other NICUs for clinical management (eg, chronic lung disease, necrotizing enterocolitis, posthemorrhagic hydrocephalus, progressive ROP). The exclusion criteria included PMA >39 weeks at the first opportunity for an eye exam within an e-ROP clinical center, admission to an e-ROP clinical center with treated or known regressing ROP, the presence of a significant media opacity precluding visualization of the retina, or major ocular or systemic congenital abnormality. Infants were included if their parents or guardians provided informed consent. Overall, 60% of eligible subjects were enrolled. The e-ROP study did not specify the timing of eye exams; instead, exams were conducted as indicated by the neonatologists and the study-certified ophthalmologists.

For this analysis, we included only those exams conducted from 32-40 weeks PMA or NICU discharge/transfer if that occurred first. We only evaluated the first exam in any particular week of PMA for infants who received more than one exam. We also excluded exams after infants were found to have type 1 ROP because these infants would usually receive treatment, and we excluded infants with mature retinae bilaterally because these infants would no longer need routine eye exams for the detection of clinically significant ROP. The Duke University School of Medicine institutional review board and the institutional review boards from each of the clinical centers approved this study.

Classification of Eye Exams

Infants were classified as having mild, type 2, or type 1 ROP based on classification of the more severely affected eye.[10] As previously described, we assumed that infants identified with type 1 ROP would be treated and infants with mature retina would no longer require subsequent exams for ROP. We also assumed that infants with type 2 ROP (ie, zone 1, stage 1 or 2 ROP without plus disease or zone II, stage 3 ROP without plus disease), mild ROP (ie, any degree of ROP that does not meet the criteria for type 2 ROP), or immature retinae bilaterally would continue to need subsequent eye exams.

Predictor Variables

Potential predictor variables for ROP status included GA, classified as ≤25 weeks, 26 or 27 weeks, 28 or 29 weeks, or ≥30 weeks; PMA in weeks; BW, classified as small for GA (SGA) or appropriate for GA[11]; multiparity, classified as singleton or multiple; sex; race/ethnicity, classified as non-Hispanic white, non-Hispanic black, Hispanic, other, and unknown; and relative average daily weight gain. The weight of all subjects within 24 hours of each eye exam was recorded. For the first examination, the relative average daily weight gain (g/kg/d) was based on the difference between the weight recorded at time of the eye exam and the BW normalized to the average of the 2 weights. For subsequent eye exams, the relative average daily weight gain (g/kg/d) was based on the difference between the weight at the current eye exam and the weight at the previous exam normalized to the average of the 2 weights.[12]

In addition to these variables, we also considered whether knowledge of ROP status from previous exams was a predictor of current eye exam findings. To do this, we evaluated the eye exam from the previous week, classified as immature, mild or type 2, or unknown if the infant did not have an exam in the study center in the previous week. We assumed that prior to 32 weeks PMA, all subjects would have immature retina. In clinical management, infants with immature retina or mild ROP often wait for 2 weeks before the next exam. Therefore, we imputed the exam from the previous week with the results from 2 weeks earlier if the eyes were immature or had mild ROP.

Statistical Analyses

The χ^2 tests were used to assess for differences across categorical variables. The Spearman correlation coefficient was used to test the justification of categorizing infants at each exam based on the most severely affected eye. For these comparisons, we considered $P < .05$ to be statistically significant. Kaplan-Meier curves stratified by GA were constructed to determine the cumulative probability over time, based on PMA, that subjects would develop type 1 ROP and thus, need treatment, or mature retina and thus, not require subsequent exams. Next, we developed separate logistic regression models to predict the odds of having type 1 ROP and the odds of having mature retinae. For these models, we separately assessed the association between each predictor variable and outcome adjusted to GA and PMA and the clustering of infants within each clinical site. We included those variables associated with $P < .20$ in univariate analyses. To assess the performance of the prediction models, goodness of fit was evaluated by measuring the area under the receiver operating characteristic curve (area under the curve [AUC]). To simplify the model, predictors were then iteratively removed starting with the least strongly associated variable. The AUC between models was compared to evaluate whether further simplification was possible. We then combined these 2 models into a multinomial logistic regression model with robust variance estimates to predict the likelihood and 95% CIs of the following 3 outcomes from an exam: type 1 ROP, mature retina, or the need for future exams (ie, immature retina, mild ROP, or type 2 ROP). Stata 12 statistical software (StataCorp LP, College Station, Texas) was used for all analyses.