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Validation of the Children's Hospital of Philadelphia Retinopathy of Prematurity (CHOP ROP) Model

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Key Points

Question

Can the CHOP ROP model be validated in a multicenter cohort large enough to obtain a precise estimate of the model's sensitivity for treatment-requiring retinopathy of prematurity?

Findings

In this secondary analysis of data from the Postnatal Growth and Retinopathy of Prematurity Study of 7483 premature infants at risk for retinopathy of prematurity, the original CHOP ROP model correctly predicted 452 of 459 infants with type 1 retinopathy of prematurity, reducing the number of infants requiring examinations by 34.3% if only high-risk infants received examinations.

Meaning

These results suggest that the CHOP ROP model has high but not 100% sensitivity and may be better used to reduce examination frequency.

Abstract

Importance

The Children's Hospital of Philadelphia Retinopathy of Prematurity (CHOP ROP) model uses birth weight (BW), gestational age at birth (GA), and weight gain rate to predict the risk of severe retinopathy of prematurity (ROP). In a model development study, it predicted all infants requiring treatment, while greatly reducing the number of examinations compared with current screening guidelines.

Objective

To validate the CHOP ROP model in a multicenter cohort that is large enough to obtain a precise estimate of the model's sensitivity for treatment-requiring ROP.

Design, Setting, and Participants

This investigation was a secondary analysis of data from the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study. The setting was 30 hospitals in the United States and Canada between January 1, 2006, and June 30, 2012. The dates of analysis were September 28 to October 5, 2015. Participants were premature infants at risk for ROP with a known ROP outcome.

Main Outcomes and Measures

Sensitivity for Early Treatment of Retinopathy of Prematurity type 1 ROP and potential reduction in the number of infants requiring examinations. In the primary analysis, the CHOP ROP model was applied weekly to predict the risk of ROP. If the risk was above a cut-point level (high risk), examinations were indicated, while low-risk infants received no examinations. In a secondary analysis, low-risk infants received fewer examinations rather than no examinations.

Results

Participants included 7483 premature infants at risk for ROP with a known ROP outcome. Their median BW was 1070 g (range, 310-3000 g), and their median GA was 28 weeks (range, 22-35 weeks). Among them, 3575 (47.8%) were female, and their race/ethnicity was 3615 white (48.3%), 2310 black (30.9%), 233 Asian (3.1%), 93 Pacific Islander (1.2%), and 40 American Indian/Alaskan native (0.5%). The original CHOP ROP model correctly predicted 452 of 459 infants who developed type 1 ROP (sensitivity, 98.5%; 95% CI, 96.9%-99.3%), reducing the number of infants requiring examinations by 34.3% if only high-risk infants received examinations. Lowering the cut point to capture all type 1 ROP cases (sensitivity, 100%; 95% CI, 99.2%-100%) resulted in only 6.8% of infants not requiring examinations. However, if low-risk infants were examined at 37 weeks' postmenstrual age and followed up only if ROP was present at that examination, all type 1 ROP cases would be captured, and the number of examinations performed among infants with GA exceeding 27 weeks would be reduced by 28.4%.

Conclusion and Relevance

The CHOP ROP model demonstrated high but not 100% sensitivity and may be better used to reduce examination frequency. The model might be used reliably to guide a modified ROP screening schedule and decrease the number of examinations performed.

Introduction

Retinopathy of prematurity (ROP) is a disease of the developing retinal vasculature that can lead to retinal detachment and vision loss. Treatment with laser retinal photocoagulation or intravitreous anti–vascular endothelial growth factor agent injection can reduce the risk of progression to retinal detachment, making timely diagnosis by ophthalmologists of treatment-requiring disease important. Current ROP screening guidelines are based on birth weight (BW) and gestational age at birth (GA). These criteria have high sensitivity but low specificity for identification of premature infants at risk for severe ROP, with less than 10% of examined infants requiring treatment. Insulin-like growth factor 1 (IGF-1) is a permissive factor in vascular endothelial growth factor–induced retinal vessel growth, which is inhibited by low serum IGF-1 levels. Both low serum IGF-1 levels and its surrogate measure slow postnatal weight gain are predictive of the development of severe ROP, and multiple statistical approaches have been applied to incorporate slow postnatal weight gain into the prediction of ROP to improve the specificity of screening. The resultant models have included WINROP (Weight, IGF, Neonatal ROP), PINT ROP (Premature Infants in Need of Transfusion ROP), ROPScore, CHOP ROP (Children's Hospital of Philadelphia ROP),[9] and CO-ROP (Colorado ROP).

The PINT ROP model was developed using data from a randomized trial of blood transfusion in 369 infants with BW less than 1000 g. It consists of a logistic regression equation, including BW, GA, and weight gain rate, calculated using weekly weight measurements. Numerous other risk factors, such as sepsis and necrotizing enterocolitis, were considered but were no longer statistically significant when weight gain was included in the model. The model equation was calculated on a weekly basis to predict the risk of Early Treatment of Retinopathy of Prematurity (ETROP) type 1 or 2 ROP, and if the risk was

greater than a predetermined alarm level, examinations were indicated. The PINT ROP model correctly predicted all 33 infants requiring laser treatment in a high-risk cohort of 369 infants, while reducing the number of infants requiring examinations by 30%. The CHOP ROP model was developed by applying the same approach to a broader risk group of 524 infants meeting current US ROP screening guidelines. The CHOP ROP model has a structure identical to that of the PINT ROP model, but the model coefficients and alarm risk level were changed. After updating the coefficients and alarm level to fit the new cohort, the CHOP ROP model correctly predicted all infants developing type 1 ROP (sensitivity, 100%; 95% CI, 84%-100%), while reducing the number of infants requiring examinations by 49%. Although promising, these studies were limited by sample sizes too small to provide precise estimates of sensitivity. Sufficient confidence to use the CHOP ROP model in clinical practice would require much narrower 95% CIs (eg, width <1%), with the width being driven by the number of type 1 ROP cases. In addition, it is important to validate a predictive model in a new cohort to determine its generalizability before clinical use. Recently, the CHOP ROP model correctly predicted all 44 infants with type 1 ROP in an Italian cohort of 445 infants. That study provided validation in a new cohort, but the sample size was again too small to provide a sufficiently precise estimate of sensitivity (sensitivity, 100%; 95% CI, 92.0%-100%).

We sought to validate the CHOP ROP model in a diverse, multicenter cohort large enough to obtain a precise estimate of the model's sensitivity for treatment-requiring ROP. Secondarily, we evaluated whether updating of the model improved its performance, and we considered alternative screening schedules in which examination timing and frequency are guided by the degree of risk predicted by the model.

Methods

Study Design

We performed a secondary analysis of data from the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study, the design of which has been reported previously in detail. Briefly, the G-ROP Study was a multicenter, retrospective cohort study of infants who underwent ROP screening at 30 hospitals in the United States and Canada between January 1, 2006, and June 30, 2012. The dates of analysis were September 28 to October 5, 2015. Institutional review board approval for the study was obtained, and waiver of informed consent was granted at the study headquarters (Children's Hospital of Philadelphia), the study data coordinating center (University of Pennsylvania), and at all study hospitals (listed in the Acknowledgments at the end of the article).

The study enrolled infants born between January 1, 2006, and December 31, 2011, who underwent ROP examinations and had a known ROP outcome. Infants received ROP examinations by meeting the screening guidelines being used during that time at each institution, typically BW less than 1501 g, GA less than 30 weeks, or larger-BW and older-GA infants with an unstable clinical course as determined by the neonatologist. A known ROP outcome included (1) type 1 ROP, type 2 ROP, or ROP treatment in either eye or (2) retinal vasculature maturity, immature vasculature extending into zone III without prior disease in zone I or II, or regression of ROP not reaching criteria for type 1 or 2 ROP in both eyes.

Detailed demographic, ophthalmologic, and medical data, including BW, GA, and weight gain rate measurements, were collected from the medical record by certified data abstractors and entered into a web-based database. Data quality was ensured through data entry validation rules, data audits, and discrepancy check algorithms, with investigation and resolution of all flagged values. The details of these algorithms have been previously published.

Statistical Analysis

The CHOP ROP model consists of a logistic regression–based equation, which has terms for BW, GA, and

weight gain rate. Rate of weight gain is calculated by taking the difference between the mean of the immediately preceding week's daily weights and the mean of the penultimate week's daily weights. Alternatively, weekly weight measurement values can be used in lieu of weekly averages. For this validation analysis, daily weights with weekly averages were used because in the model development study there was a small (3%) advantage to using daily vs weekly weight measurements with regard to the number of infants that would not need examinations. Weights during the first week after birth are excluded from the analysis owing to the common weight loss that occurs in very low-BW infants during this period.

The probability of severe ROP is calculated using the CHOP ROP model equation on a weekly basis to predict the risk of developing ETROP type 1 or 2 ROP. Diagnostic examinations are indicated if the predicted risk for any single weekly calculation is greater than a threshold level, and no further weekly calculations are necessary. The model can also be represented as a nomogram (Figure).

In the primary analysis of this CHOP ROP model validation study, the same model terms (BW, GA, and weight gain rate), coefficients, and risk threshold level of 0.0140 as the original description of the model were used to make all-or-none ROP screening decisions (ie, infants with a predicted risk above the threshold level received examinations; the remaining infants did not receive examinations). The study outcomes were sensitivity for type 1 or 2 ROP (the proportion of infants who developed type 1 or 2 ROP for whom examinations would be indicated by the model), sensitivity for type 1 ROP, and the reduction in the number of infants receiving examinations, which is a more intuitive measure of the specificity of the model. The 95% CIs for the measures of sensitivity were calculated using the Clopper-Pearson exact method.

In a secondary analysis of this validation study, model updating and a modified screening schedule were considered. In the validation of a predictive model, the initial step is to simply evaluate the model using the original structure (terms, coefficients, etc); however, if the performance is not as high as in the model development study, the model should be updated. Model updating may involve adjusting the model coefficients or even adding new variables if necessary. Therefore, an a priori plan was made to update the CHOP ROP model if the sensitivity of the original model was not 100% by lowering the risk threshold level to capture all type 1 ROP cases and by keeping the same model structure but refitting the coefficients using multivariable logistic regression. In addition, a modified screening schedule was considered in which high-risk infants (infants with a predicted risk above the threshold level using the original model and threshold level) received examinations per routine clinical care, and the remaining low-risk infants (infants whose predicted risk never surpassed the threshold level) received a single examination and were followed up further only if ROP of any stage was present at that examination. The timing of the examination was based on postmenstrual age (PMA) and was determined by identifying the latest PMA week at which an infant with type 1 ROP who had been identified by the model incorrectly as low risk could be examined before the development of type 1 ROP (ie, the latest possible developmental age at which implementation of the modified screening schedule still would result in the diagnosis of ROP on clinical examination before the need for treatment). The reduction in the number of examinations was calculated instead of the reduction in the number of infants receiving any examinations because all infants would receive at least one examination using the modified screening schedule.

All analyses were performed using statistical software. SAS (version 9.3; SAS Institute Inc) was used.

Results

The G-ROP Study cohort included 7483 infants, all of whom were included in this validation study (Table 1). The median BW was 1070 g (range, 310-3000 g). The median GA was 28 weeks (range, 22-35 weeks). Retinopathy of prematurity developed in 3224 infants (43.1%); 459 infants (6.1%) developed type 1 ROP, 472 infants (6.3%) developed type 2 ROP, and 524 infants (7.0%) were treated.