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Original Article

Application of CHOP ROP model in predicting risk of severe retinopathy of prematurity (ROP) in Chinese premature infants

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Abstract: *Objective*: To evaluate the application value of the CHOP (Children's Hospital of Philadelphia) retinopathy of prematurity (ROP) model in predicting the risk of severe ROP in Chinese premature infants. *Methods*: Totally, 480 premature infants born between January, 2009 and December, 2015, at the Army Bayi Children's Hospital Affiliated to General Hospital, with a gestational age (GA) of 26-34 weeks were enrolled as eligible subjects. In the model, body weight (BW), GA, and daily weight gain rate were used repeatedly each week to predict risk. The probability of severe ROP was calculated on a weekly basis for each child, and when the calculated risk was greater than 0.014, the child was flagged as needing examinations. *Results*: Of the 480 premature infants, 178 cases (34.2%) were type I ROP, 51 cases (65.4%) were type II ROP, and 251 cases were required no additional intervention treatment. Among the infants with type I and type II ROP, a total of 109 premature infants had a GA≥29 weeks (22%) and 140 premature infants had a BW≥1000 g (30%). CHOP ROP model was used to predict the risk of the patients with low risk (210 cases) and high risk (270 cases). According to this model, the premature infants who need repeated screening were reduced by 41.6%. The sensitivity, specificity, positive predictive value and negative predictive value for predicting type I ROP was 97.7%, 80%, 64.4%, and 95.2%. *Conclusion*: According to this retrospective study, CHOP ROP prediction model provides an early identification for severe ROP in Chinese premature infants, but it may also result in omission and over-screening and this model could not completely replace the retinal screening.

Keywords: CHOP ROP model, retinopathy of prematurity (ROP), Chinese premature infants

Introduction

Retinopathy of Prematurity (ROP) is a kind of ocular diseases, characterized by pathologic retinal vascular proliferation. It occurs commonly in premature infants and infants with low-birth weight and is the main cause of blindness in children worldwide, even leading to retinal detachment in some severe cases [1, 2]. Thus, early screening is of great importance for the intervention of ROP. The clinical approaches include serial fundus examinations by an ophthalmologist with expertise in ROP and diagnosis and treatment of disease, if indicated, to prevent progression to retinal detachment [3]. However, a previous study indicated that, of all of the early-detected, visually impaired children, 16% had not been treated for ROP and were considered screening failures [4]. A previous study found several changes occur during the course of ROP screening, including the induced heart-eye reflex, the fluctuations of pulse rate, oxygen saturation and blood pressure, leading to more pain and irritation [5]. Therefore, a predictable ROP risk model that is simple, transparent and clinically easy-to-use is developed in the previous studies.

Binenbaum *et al.* developed a birth weight (BW), gestational age (GA), and postnatal-weight gain ROP prediction model in a cohort of infants meeting current screening guidelines. The results indicated that this model demonstrates accurate ROP risk assessment and a large reduction in the number of ROP examinations compared with current screening guide-

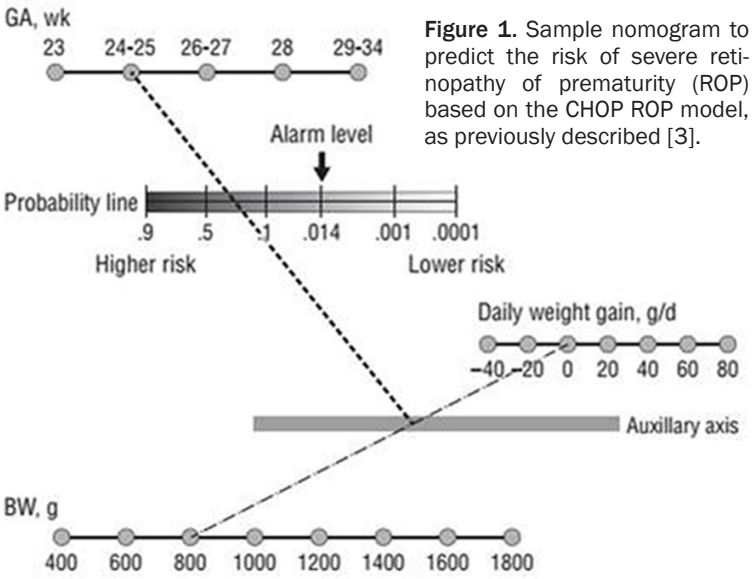

Figure 1. Sample nomogram to predict the risk of severe retinopathy of prematurity (ROP) based on the CHOP ROP model, as previously described [3].

lines. As a simple logistic equation, it can be calculated by hand or represented as a nomogram for easy clinical use [3]. Thus, this study was designed to evaluate the application value of the CHOP ROP model in predicting the risk of severe ROP in Chinese premature infants.

Subjects

Eligible subjects were premature infants born between January, 2009 and December, 2015, at the Army Bayi Children's Hospital Affiliated to General Hospital, with a GA of 26-34 weeks and with a known ROP outcome, defined as diagnosis in either eye of type 1 or 2 ROP (defined below) or diagnosis in each eye with one of the following: regressing or regressed ROP that had not met type I or II ROP criteria, immature retinal vasculature in zone III without prior ROP in zones I or II, or mature retinal vasculature. There were no further medical or surgical exclusion criteria. Type I ROP and Type II ROP were determined as previously described [6].

Data collection

Medical data, including BW, GA, and all available weight measurements, which were typically taken daily, were retrospectively collected from the medical records of infants meeting the inclusion criteria. ROP data included stage (1-5) of disease, zone (I, II, or III) of disease, and presence or absence of plus disease for each eye at each examination and any laser or other treatments performed. Medical data considering the differences in the treatment of premature infants, numerous additional covariates were collected, including infant sex, the presence of bronchopulmonary dysplasia (BPD), the diagnosis and operation of patent ductus arteriosus (PDA), prenatal use of drugs (dexamethasone), pregnancy health conditions (pregnancy hypertension, diabetes), red blood cell transfusion volume, intracranial hemorrhage, diagnosis and surgery of necrotizing enterocolitis, sepsis, postnatal oxygen use method and time, invasive ventilation or other clinical treatments. Premature infants with unclear data and informal born, or diagnosed with genetic metabolic diseases or congenital malformations were excluded in our study.

Statistical analysis

Analyses were performed using SPSS statistical software (version 19.0). Multivariate logistic regression was used to analyze the probability of type I or II ROP based on the CHOP ROP model.

Daily weight gain and the probability of severe ROP was calculated on a weekly basis for each infants according to the previous method [3], and when the calculated risk was greater than 0.014, the child was flagged as needing examinations. Once the high-risk was changed into low-risk, the assessment should be interrupted and will continue to follow the retinal screening criteria to complete clinical fundus screening until a clear fundus lesions and treatment. At last, the sensitivity of children with type 1 ROP was calculated, and the number of screening children was decreased to assess whether this prediction model was applied to Chinese premature infants.

Results

The sample nomogram, plotting BW, GA, and weight gain on a weekly basis to determine the

Table 1. Characteristics of the 480 premature infants

Gestational Age (weeks)	Type 1	Type 2	Other	*P*
Mean (SD)	27.5 (0.13)	30.5 (0.22)	29.2 (0.12)	<0.01
Median (range)	28 (24-30)	30 (27-34)	29 (25-34)	
24	16	0	0	
25	13	0	1	
26	16	0	18	
27	36	1	28	
28	38	3	50	
29	32	11	50	
30-34	27	36	14	
Weight (g)				
Mean (SD)	1068.5 (15.52)	1261.9 (37.68)	1373.6 (18.81)	<0.01
Median (range)	1100 (620-1800)	1250 (750-1800)	1345 (620-2600)	
≤750	8	0	1	
>750 and <1000	65	12	16	
>1000 and <1200	66	10	75	
≥1200	39	29	159	
No ROP				
Stage 1	8	4	78	<0.01
Stage 2	62	10	173	
Stage 3	102	37	0	
Stage 4	5	0	0	
Stage 5	1	0	0	
Plus disease				
Yes	166	0	0	<0.01
No	12	51	251	

need for ROP examinations, was used to predict the risk of ROP based on the CHOP ROP model described in a previous study (**Figure 1**) [3]. Four hundred and eighty premature infants met the inclusion criteria and the information was summarized in **Table 1**. One hundred and seventy-eight premature infants (36.8%) developed type I ROP and received laser retinal photocoagulation, of which, 34 premature infants received anti-VEGF therapy, 6 premature infants received vitrectomy, and 138 premature infants received laser photocoagulation. An additional 51 premature infants (10.8%) reached type II ROP but regressed spontaneously and did not require treatment. Of them, 23 premature infants were progressed to receive the final laser photocoagulation, and the fundus lesions of 11 premature infants were subsided and not received any treatment; other 251 premature infants were not received any treatment and had serious lesions. Median GA of type 1 ROP premature infants was 28 weeks (range: 24-30) and median GA of type 2 ROP premature infants was 30 weeks (range: 27-34 weeks). Median weight of type 1 ROP premature infants was 1100 g (range: 620-1800) and median weight of type 2 ROP premature infants was 1250 g (range: 750-1800 g).

The base model contained terms for BW, GA, and weight gain (**Table 2**). The probability of severe ROP was calculated on a weekly basis for each premature infants, and when the calculated risk was greater than 0.014, the child was flagged as needing examinations. The results showed that BW, GA, and weight gain were significantly associated with severe ROP in multivariate analyses. Application of the model correctly identified 210 premature infants (43.7%) with low ROP risk, and identified 270 premature infants (56.3%) with server ROP, as shown in **Table 3**. There were 200 premature infants (41.6%) who identified with low ROP risk and would not have been flagged to receive eye examinations, but 10 type I and II

Table 2. Multivariate Logistic Regression Analysis of the Association of Candidate Predictors (Gestational Age, Weight and Weight gain) with the Development of Severe ROP

	B	S.E.	Wald	df	*P*	95% CI
Gestational Age (weeks)	-0.124	0.057	4.718	1	0.03	78.9%-98.8%
Weight (g)	-0.004	0.000	59.42	1	0.00	99.5%-99.7%
Weight gain		0.031	52.69	1	0.00	75.0%-85.0%

Table 3. The sensitivity, specificity, positive predictive value and negative predictive value for predicting ROP by using CHOP ROP model

	Type 1	Type 1 and 2	Other	NPV	PPV	Reduced inspection ratio
Low risk	4	10	200	95.2%		41.6%
Severe	174	219	51		64.4%	
Sensitivity	97.7%	95.6%				
Specificity			80%			

NPV: Negative predictive value; PPV: Positive predictive value.

premature infants, who identified with low ROP risk, were received treatment (8 premature infants received laser photocoagulation and 2 premature infants received anti VEGF treatment) finally. There were 219 premature infants who identified with severe ROP risk (174 type I ROP and 45 type II ROP) and have been flagged to receive eye examinations, but 51 premature infants (10.6%) who need no treatment, were identified with severe ROP. According to this model, the premature infants who need repeated screening were reduced by 41.6%. The sensitivity, specificity, positive predictive value and negative predictive value for predicting type I ROP was 97.7%, 80%, 64.4% and 95.2%, respectively. Compared to the premature infants with mild ROP, the premature infants with severe ROP had more complex risk factors (**Tables 4** and **5**). Although the model is not related to these factors, in China, India and other developing countries, these factors must betakenintoaccountintheprocessofretinalscreening in premature infants.

Discussion

In this study, we used the CHOP ROP model to predict risk of severe ROP in 480 Chinese premature infants. The sensitivity of type I ROP was 97.7%, with a specificity of 80% and wound have reduced the number of premature infants requiring examinations by 42% (200 cases). To some extent, it not only reduces the suffering of premature infants, but also reduces the clinician's screening pressure.

Löfqvist *et al.* developed WINROP (Weight, IGF-1 Neonatal Retinopathy of prematurity), a computer based surveillance algorithm, to predict risk of severe ROP on the basis of BW, GA, and postnatal weight gain. Published reports in which this complex algorithm is used have been limited to 2 low-risk, retrospective cohorts but potential to reduce examinations considerably is suggested [7, 8]. In 2010, researchers developed the PINT (Premature Infants in Need of Transfusion) ROP model, a logistic regression-based prediction model that includes terms for GA, BW, and weight gain rate, which is evaluated on a weekly basis to determine a need for examinations and can be represented as a clinical nomogram or used with a hand calculator. In the high-risk, multicenter prospective cohort of 367 infants with BW<1000 g, the PINT ROP model accurately identified all 33 infants requiring laser treatment, while leading to the reduction in the number of infants requiring examinations by 30%. As infants with higher BW are at lower risk for developing treatment-requiring ROP, application of the same approach to a cohort more representative of current screening guidelines may lead to a greater reduction in the number of infants requiring diagnostic examinations [9]. Afterwards, they sought to develop a predictive model applying the same modeling approach as the PINT ROP model in a cohort of infants meeting current US screening guidelines, named CHOP ROP model. This model demonstrated a large reduction in the number of ROP examinations and accurate ROP risk assessment as compared with current screening guidelines, which also can be calculated by hand or represented as a nomogram for easy clinical use [3].

This study is an application of the CHOP ROP model, the sensitivity for prediction type I ROP

Table 4. The statistical analyses of the association of Clinically relevant single factor with the Development of Severe ROP

	Type 1 and 2	Other	T value	*P* value
Gestational Age (weeks)	28.7±1.5	29.1±2.2	6.969	0.009
Weight (g)	1136.6±247.7	1236.3±302.9	4.233	0.04
Total time with oxygen (days)	35.2±19.7	27.6±23.2	5.185	0.02

Table 5. The statistical analyses of the association of Clinically relevant single factor with the Development of Severe ROP

	Type 1 or 2	Other	λ^2 value	*P* value
Septicemia	55	34	36.66	<0.01
NEC	11	4	0.21	0.646
IVH	31	29	5.43	0.02
BPD	112	85	11.6	0.01
PDA	123	52	2.59	0.11
Invasive ventilation	195	27	10.08	0.01
Metabolic acidosis	155	103	7.84	0.005
Male/female	186/130	103/61	0.79	0.373

was 97.7% (missed 4 infants of type I ROP, with a gestational age of 32 weeks or more), which is different from the results (the sensitivity was 100%) from the Children's Hospital of Philadelphia [10]. Besides, no premature infants with GA≥29 weeks developed type I ROP, 1 case with BW≥1000 g developed type I ROP [10]. However, in our study, 59 cases (33%) with GA≥29 weeks developed type I ROP, and 105 cases (59%) with BW≥ 1000 g developed into type I ROP. This indicated that the older gestational age and higher birth weight still had a higher ROP risk in premature infants. The model may be more sensitive to the prediction of preterm infants with younger gestational age and lower birth weight and the prediction sensitivity of preterm infants with GA≥29 weeks and birth weight BW≥1000 g will decrease. Moreover, the alarm point 0.014 set in this model was according to the US premature infants, it is more suitable the prediction of US ROP premature infants, which may explained why 4 cases of severe type I ROP were missed (gestational age ≥32 weeks) in our study. In view of the specificity of the development of premature infants in China, complete application of this model for clinical prediction may result in missed alarm information, especially for infants with high gestational age and birth weight. In the present study, we found that premature infants with type I or type II ROP with also had more complex risk factors, such as sepsis, intracranial hemorrhage (IVH), bronchopulmonary, metabolic acidosis and other factors, which is consistent with previous studies [11, 12], however, these factors were neglected in other studies. To sum up, the recalibrated or even restructured models will need to be developed separately for different populations. For example, the sensitivity of WINROP was only 90% in Brazil and 55% in Mexico (85% for GA<32 weeks, 5% for GA≥32 weeks) [13, 14]. Finally, the performance of the model may be altered by the selection of the alarm cut point level, with a trade-off between sensitivity and reduced examinations.

In summary, though CHOP ROP prediction model provides an early identification for severe ROP in Chinese premature infants, it may also result in omission and over-screening and this model could not completely replace the retinal screening. For premature infants with several clinical risk factors, this model can only be used as an auxiliary tool to minimize the number of retinal screening. Throughout the current ROP risk prediction model, its ultimate goal is to identify the degree of disease in premature infants and to reduce the number of repeated retinal screening and clinicians' pressure. The above mentioned WINROP model and CHOP ROP model have high potential in predicting risk and assisting ROP screening, and may open up more ideas for ROP screening guidelines. However, the changes in the study sample size had great effects on the sensitivity and specificity of the prediction and other statistical results. Due to the level of national treatment of premature infants, the differences may also occur in the application of the models, thus, before the clinical application of the model, we still need to collect a larger sample and the cooperation of various clinicians to develop a more suitable method to provide a more accurate secondary clinical work.

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Disclosure of conflict of interest

None.

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