G-ROP Criteria for Predicting Retinopathy of Prematurity Among Neonates with Different Birth Weight Percentiles

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Abstract

Purpose: To determine whether being small for gestational age (SGA), appropriate for gestational age (AGA) and large for gestational age (LGA) affected the sensitivity and specificity of Postnatal Growth and Retinopathy of Prematurity (G-ROP) model.

Methods: We applied the G-ROP criteria, except hydrocephalus, for prematures retrospectively. The infants were divided into three subgroups according to birth weight percentiles (SGA, AGA, LGA), and the performance of the G-ROP criteria was tested for each group by calculating sensitivity and specificity for any stage retinopathy of prematurity (ROP) and severe ROP. Severe ROP was defined as ROP needing treatment.

Results: Three hundred and ninety neonates screened for ROP were included. The gestational age and birth weight of the neonates were 29.3±2.9 weeks and 1302.9±416 g, respectively. There were 41 (10.5%) SGA, 312 (80%) AGA and 37 (9.5%) LGA neonates. The sensitivity of the model for any ROP was 67.8%, 66.7%, 73.2%, 55.6% for all of the patients in the study, SGA, AGA, and LGA neonates, respectively. The sensitivity of the model for severe ROP in all group and for each subgroup was 100%. The specificity of the model for any ROP was 65.9%, 70.6%, 87.7%, 90% for all of the patients, SGA, AGA, and LGA neonates, respectively. The specificity for severe ROP was 46.4%, 50%, 44%, 63.6% for all of the patients, SGA, AGA, and LGA neonates, respectively.

Conclusion: The sensitivity and specificity of the G-ROP model in SGA infants were similar with the whole group, but was different between SGA, AGA and LGA neonates. Although the model did not miss any severe ROP, the specificity of the model for severe ROP was found low.

Introduction

Retinopathy of prematurity (ROP) is one of the leading causes of severe childhood visual impairment [1]. Neonates who develop a significant severity of disease known as type 1 ROP have an approximately 30% risk of adverse visual outcome, and with treatment this probability can be reduced substantially [1–4]. Because severe ROP can result in childhood blindness, screening criteria are set with a safety margin for cutoff values of gestational age (GA) and birth weight (BW) to avoid missing infants who will develop ROP [5, 6]. Current consensus recommendations by professional societies recommend screening of all infants born at <1501 g, or ≤30 weeks, or those between 1500 and 2000 g with hypotension or substantial oxygen exposure [5]. Serial retinal examinations with indirect ophthalmoscopy can reliably detect type 1 disease in high-risk infants in time for intervention to take place [5, 6].

Although the currently recommended guidelines have high sensitivity for detection of ROP, their specificity is low, and the great majority of screened infants never develop ROP that requires intervention [7, 8]. Also retinal examinations can be distressing for premature infants, represent a large use of resources, and in many areas limited availability of ophthalmologists with ROP expertise can be a barrier to screening [9]. Therefore, over the last 15 years, several predictive models have suggested that the addition of

suboptimal postnatal growth to BW and GA maintained sensitivity of screening criteria while substantially improving specificity [8]. The Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study examined a cohort of 7483 preterm infants to develop a predictive model that included such modified screening criteria, with resulting sensitivity of 100% and specificity of 32%, both superior to traditional BW and GA screening alone in the study cohort [10]. In that study, a model consisting of six criteria correctly predicted 100% of infants with type 1 ROP while reducing the number of infants who required examinations by 30.3% when only infants who met the criteria received examinations [10]. The criteria of the G-ROP study were found to show good accuracy as an exclusion tool in ROP screening among different racial/ethnic cohorts [11–13].

The condition of being born small for gestational age (SGA) is commonly defined as birth weight below the 10th percentile and occurs in approximately 13–20% of all preterm infants [14]. Infants born SGA as well as those born prematurely are at increased risk for postnatal growth failure (PNGF) in the early neonatal period, as they do not have a large storage of protein/energy, and at high risk of permanent short stature, with approximately 10% continuing to have stature below the third centile throughout childhood and adolescence and into adulthood [15, 16]. It was also demonstrated that up to the age of four, preterm SGAs gained less height and weight in comparison to preterm appropriate for gestational age (AGA) counterparts [16]. Different growth patterns of the preterm SGA neonates made us wonder if G-ROP model could be applied and validated among this group of infants. The primary aim of our study was to determine whether being SGA affected the sensitivity and specificity of G-ROP model. Secondarily, we aimed to assess the effects of BW centiles, in terms of being SGA, AGA and large for gestational age (LGA), and other perinatal morbidities on the sensitivity and specificity of G-ROP model.

Materials And Methods

This was a retrospective cohort study of preterm infants who underwent eye examinations and had a known ROP outcome in the neonatal intensive care unit (NICU) of a single institution from January 2016 to June 2020. The study was approved by the local ethics committee (date:18.08.2021, number:146) and was carried out in compliance with the principles of the Declaration of Helsinki (1964). All infants who were screened for ROP and had a documented outcome were included in the study. Infants were considered to have a known ROP outcome if (1) either eye had type 1 ROP, type 2 ROP, or ROP treatment according to Early Treatment of ROP (ETROP) Study or (2) both eyes had 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 [1]. Eligible infants who were discharged before the first screening and missed or did not complete all screening sessions, those who died before the first ophthalmic examination, and who had hydrocephalus and/or major congenital anomalies were excluded from the study.

We applied the G-ROP criteria for our premature infants. The original G-ROP criteria consist of six alarm levels including five quantitative thresholds and one qualitative description. In this study, we used the following five criteria of quantitative thresholds, except hydrocephalus, as a prediction model: GA < 28

weeks; BW < 1051 g; weight gain (WG) between postnatal day 10 and 19 <120 g; WG between postnatal day 20 and 29 < 180 g; or WG between postnatal day 30 and 39 < 170 g [10]. The WGs were calculated by using the absolute values of weight at the indicated postnatal days. These criteria were applied for eligible infants to determine whether each infant had a greater risk than the five alarm levels. Infants who met either the BW criterion or GA criterion did not require WG calculations, because infants only needed to meet one criterion to receive examinations.

The International Classification of ROP guidelines were used to record the stage of the disorder, location by zone and signs of plus disease [17]. All infants meeting the screening criteria were scheduled to have their first examination at between fourth and sixth weeks of life. Ophthalmic examinations were continued until full retinal vascularisation and the maximum stage of ROP for each infant was reported. The data were analysed for the most advanced stage of ROP in the eye with the most severe disease and severe ROP was defined as ROP needing treatment. Criteria for treatment of ROP were based on the ETROP, and if any the need for laser photocoagulation, intravitreal bevacizumab (IVB) and vitreoretinal surgery for ROP were also noted [1].

The routine ROP screening criteria used in our NICU were; GA ≤ 34 weeks or a BW < 1700 g or a poor postnatal clinical course determined by the neonatologist as recommended by Retinopathy of Prematurity study group for state hospitals in our country. Screening examinations were performed by two experienced ophthalmologists with binocular indirect ophthalmoscopy (GC, OK) until complete vascularization of the retina, regression of ROP or treatment was required, in accordance with the follow-up schedule recommended by the American Academy of Pediatrics (AAP) and American Academy of Ophthalmology (AAO) [5]. The body weights of infants were measured in the morning before feeding. Sepsis, respiratory distress syndrome (RDS), hemodynamically significant patent ductus arteriosus (hsPDA), necrotizing enterocolitis (NEC), broncopulmonary dysplasia (BPD) and intraventricular hemorrhage (IVH) were accepted as perinatal morbidities.

The Fenton growth charts for preterm infants were used to evaluate the BW percentiles of the infants [18]. Small for gestational age was considered as BW below the 10th centile for GA, AGA was considered as BW between 10th and 90th centile, and LGA was considered as BW above the 90th centile for GA. The infants were divided into three subgroups according to BW percentiles (SGA, AGA, LGA), and the performance of the G-ROP criteria was tested for each group by calculating sensitivity and specificity for severe ROP and any stage ROP. To evaluate the effects on ROP management, we calculated the reduction under the G-ROP screening in the number of infants requiring screening for ROP and in the number of retinal examinations for both whole study group and subgroups. The examinations of infants who did not meet any of the criteria were considered toward the reduction in number of retinal examinations.

Statistical analysis

SPSS v.21 (SPSS Inc., Chicago, IL, USA) and OpenEpi.com were used for statistical analysis. Results were presented as mean±standard deviation (SD) and median (minimum-maximum) for continuous variables.

Categorical variables were presented with frequency and percentage. Chi-square test was used to analyze categorical variables. Comparisons of the groups for continuous variables were made by Kruskal Wallis test. Sensivity, specificity and lower and upper 95% confidence intervals (CIs) were used for evaluation of G-ROP screening test at OpenEpi.com for presence of any ROP and severe ROP for whole group and subgroups. Sensivity, specificity and lower and upper 95% CIs of G-ROP model were reevaluated after adding the perinatal morbidities to the model one by one.

Results

A total of 486 neonates met current ROP screening criteria. Of these 486 infants, 390 underwent ROP screening, had a known ROP outcome, and were included in the data analysis. The GA and BW of the neonates were 29.3±2.9 w and 1302.9±416 g, respectively. There were 41 (10.5%) SGA, 312 (80%) AGA and 37 (9.5%) LGA neonates. Characteristics of the study population were represented at Table 1. There were 169 neonates identified who would not have been screened for ROP if only the G-ROP criteria had been applied, and 84 (49.7%) of them were diagnosed with any stage of ROP that did not require treatment. The GA and BW of those 84 neonates that were missed by G-ROP model were 30.3±1.59 w and 1489±217 g, respectively. Sixty one of those 84 neonates would have been screened for ROP, if AAP and AAO ROP screening criteria were used. Sensitivity and specificity of G-ROP criteria for predicting any stage ROP for whole group and subgroups were given at Table 2.

Table 1
Characteristics of the study population

	All cases (n=390)	SGA (n=41)	AGA (n=312)	LGA (n=37)	p
Gender, *n (%)*					
Female	194 (49.7)	19 (46.3)	163 (52.2)	12 (32.4)	0.067*
Male	196 (50.3)	22 (53.7)	149 (47.8)	25 (67.6)	
Gestational age, week					
Mean±SD	29.3±2.9	32 ± 2.6	29.2 ± 2.7	27.5 ± 2.9	<0.001**
Median	30	33	30	28	
(Min-max)	(21-34)	(24-34)	(22-34)	(21-32)	
Birth weight, g					
Mean±SD	1302.9±416.9	1196.1 ± 297	1298.8 ± 407.7	1456.1 ± 553.6	0.045**
Median	1290	1240	1290	1510	
(Min-max)	(390-2850)	(390-1640)	(480-2510)	(630-2850)	
Birth type, *n(%)*					
NVD	91 (23.3)	8 (19.5)	71 (22.8)	12 (32.4)	0.349*
C/S	299 (76.7)	33 (80.5)	241 (77.2)	25 (67.6)	

*Chi-square test, **Kruskal Wallis test

AGA: appropriate for gestational age, C/S: cesarean section, LGA: large for gestational age, NVD: normal vaginal delivery, SD: standard deviation, SGA: small for gestational age

Table 2
Sensitivity and specificity of G-ROP criteria for predicting any stage ROP for whole group and subgroups

	ROP (+), n	ROP (-), n	Total
All cases			
G-ROP (+), n	177	44	221
G-ROP (-), n	84	85	169
Total	261	129	390
Sensitivity 67.8%			
Specificity 65.9%			
SGA-neonates			
G-ROP (+), n	16	5	21
G-ROP (-), n	8	12	20
Total	24	17	41
Sensitivity 66.7%			
Specificity 70.6%			
AGA-neonates			
G-ROP (+), n	146	38	184
G-ROP (-), n	64	64	128
Total	210	102	312
Sensitivity 73.2%			
Specificity 87.7%			
LGA-neonates			
G-ROP (+), n	15	1	16
G-ROP (-), n	12	9	21
Total	27	10	37
Sensitivity 55.6%			
Specificity 90%			

AGA: appropriate for gestational age, G-ROP: Postnatal Growth and Retinopathy of Prematurity, LGA: large for gestational age, ROP: retinopathy of prematurity, SGA: small for gestational age

The G-ROP model identified all of the treated neonates (n=26, 100%, 95% CI 87.1%-100%), and the GA and BW of the them were 24.8±1.8 w and 756±183 g, respectively. In all three groups (SGA, AGA, LGA), G-ROP model was 100% successful for determining severe ROP. Sensitivity and specificity of G-ROP criteria for predicting severe ROP for whole group and and subgroups were given at Table 3. All the treated ROP patients were caught by GA and/ or BW criteria, recieved intravitreal bevacizumab, and a total of 50 eyes were treated (both eyes of 24 patients and only one eye of two patients).

Table 3
Sensitivity and specificity of G-ROP criteria for predicting severe ROP for whole group and subgroups

	ROP treatment (+), n	ROP treatment (-), n	Total
All cases			
G-ROP (+), n	26	195	221
G-ROP (-), n	0	169	169
Total	26	364	390
Sensitivity 100%			
Specificity 46.4%			
SGA-neonates			
G-ROP (+), n	1	20	21
G-ROP (-), n	0	20	20
Total	1	40	41
Sensitivity 100%			
Specificity 50%			
AGA-neonates			
G-ROP (+), n	21	163	184
G-ROP (-), n	0	128	128
Total	21	291	312
Sensitivity 100%			
Specificity 44%			
LGA-neonates			
G-ROP (+), n	4	12	16
G-ROP (-), n	0	21	21
Total	4	33	37
Sensitivity 100%			
Specificity 63.6%			

AGA: appropriate for gestational age, G-ROP: Postnatal Growth and Retinopathy of Prematurity, LGA: large for gestational age, ROP: retinopathy of prematurity, SGA: small for gestational age

These 390 infants underwent a total of 2659 ROP examinations (6.8 examinations per infant), of which 662 (24.9%) could be reduced by applying G-ROP model without missing severe ROP. Forty one SGA-neonates underwent a total of 208 ROP examinations, of which 56 (26.9%); AGA-neonates underwent a total of 2166 ROP examinations, of which 519 (23.96%); and LGA-neonates underwent a total of 285 ROP examinations, of which 87 (30.5%) could be reduced by applying G-ROP model without missing severe ROP.

When perinatal morbidities were added individually to the G-ROP model, the sensitivity of the model was increased for any stage ROP. Among all cases, the sensitivity of the model was highest when BPD was added to the model (92.9%), followed by NEC, hsPDA, IVH, sepsis, and RDS, respectively (91.5%, 89.1%, 83.6%, 78.2%, 74%, respectively). Sensivity and specificity of G-ROP model for any ROP when perinatal morbidities added to the model were given at Table 4. Fourty seven neonates (12%) had none of those aforementioned perinatal morbidities, and none of those 47 neonates had severe ROP. When G-ROP model applied to those 47 neonates, 13 of them would have ROP examinations. When all of the six perinatal morbidities were added to the G-ROP model together, 53 ROP examinations of those 13 neonates could be reduced without missing severe ROP, and the reduction of ROP examinations could be increased from 24.9–26.9%.

Table 4
Sensivity and specificity of G-ROP model for any ROP when perinatal morbidities added to the model

	Sensivity %	(95% CI)	Spesifity %	(95% CI)
All cases	67.8	61.9-73.2	65.9	57.4-73.5
Sepsis				
+	78.2	71.9-83.5	59	46.5-70.5
-	38.2	27.6-50.1	72.1	60.4-81.3
RDS				
+	74	67.7-79.5	66.7	54.4-77.1
-	43.4	30.9-56.7	65.2	53.1-75.5
hsPDA				
+	89.1	79.1-94.6	36.4	15.2-64.6
-	61.2	54.3-67.8	68.6	59.8-76.3
NEC				
+	91.5	80.1-96.7	50	23.4-74.6
-	62.7	56.1-69	67.8	58.8-75.7
BPD				
+	92.9	87.1-96.2	47.1	26.2-69
-	44	35.9-52.5	68.8	59.7-76.6
IVH				
+	83.6	72.9-90.6	76.9	49.7-91.8
-	62.4	55.4-68.9	64.7	55.6-72.8

BPD: broncopulmonary dysplasia, CI: confidence interval, hsPDA: hemodynamically significant patent ductus arteriosus, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, RDS: respiratory distress syndrome

Discussion

Our hypothesis was that the sensitivity of the G-ROP model would increase and specificity of the model would decrease due to the slow growth rate of SGA babies, but the sensitivity and specificity of the model in SGA infants was found to be similar with the whole group. This might be due to the higher GA of SGA babies included in the study than their AGA and LGA counterparts. The sensitivity of G-ROP for predicting any stage ROP was lower in our study than it was reported in the literature [12, 13], but the sensitivity of

the model for predicting severe ROP was excellent (100%). Although all severe ROP patients were seemed to be detected by the model, 84 (21.5%) neonates with any stage ROP were missed and this rate was higher than reported in the literature [12]. It might be due to that G-ROP model did not exactly fit the neonates with older GA and higher BW, as ROP was considered as a morbidity of more immature neonates by the developers of this model [10]. Therefore, new ROP prediction models should be developed for low income countries which could both detect more mature neonates with ROP and decrease the number and cost of ROP examinations.

Binenbaum et al. [10] indicated that in countries with developing neonatal care systems, high oxygen use is likely to play a more central role in the pathogenesis of ROP, because endogenous insulin-like growth factor-I production is not deficient in older GA infants [19], making postnatal weight gain a less reliable predictor of severe ROP [20, 21]. In our NICU, we strictly follow the European Consensus Guidelines of RDS and in preterm babies receiving oxygen the saturation target is between 90 and 94% [22]. The reason of detection of ROP in newborns with older GA and higher BW in our NICU might be that our NICU is one of the largest referral perinatal centers in Istanbul, and the newborns admitted to our unit are the ones who need more intensive life support and have worst clinical course.

Similar to the literature, the application of G-ROP model was found to make significant reduction in the number of neonates requiring ROP screening of about 25% in whole group and 23.96%-30.5% among neonates with different BW percentiles without missing severe ROP [10–13, 23]. As the main aim of ROP prediction models is detecting severe ROP while making reductions of ROP examinations, the G-ROP model was found successful in serving this purpose in our study. In a study conducted in Turkey, G-ROP model was found to miss some neonates requiring ROP treatment, and all treatment requiring neonates were caught when BPD was added to the model [12]. Contrary to this study, we found that all treatment requiring cases were detected with one forth decrease in ROP examinations even without adding any perinatal morbidity to the model.

Several perinatal morbidities including BPD, NEC, hsPDA, IVH, and sepsis were significantly associated with severe ROP [6]. When we added those perinatal morbidities to G-ROP model one by one the sensitivity of the model was found to increase for any stage ROP, and also when all the six perinatal morbidities were added to the model together the percentage of reduction of ROP examinations increased without missing severe ROP. Further studies should be conducted by incorporating these perinatal morbidities to the model to reduce ROP examinations.

This study has some limitations. Firstly, it was a retrospective, single-centre study with a small number of cases. Secondly, although the developers of the model recommended to use this model for newborns with a GA 32 weeks or younger, we applied the criteria to more mature neonates. This might have caused the sensitivity of model to be low for any ROP and the specificity of model to be low for severe ROP.

Conclusion

The sensitivity and specificity of the G-ROP model in SGA infants were similar with the whole group, but was different between SGA, AGA and LGA neonates. The model was found to be able to reduce one forth of the ROP examinations without missing severe ROP. We screen newborns with a greater gestational age and higher birth weight for ROP than recommended by the AAP and AAO [5, 6], and this might have caused the specificity of the model for severe ROP was found low. Therefore, it might be more important to set new criteria to decrease unnecessary ROP examinations for our premature infant population. Prospective studies among larger groups are required to assess the applicability of a modified new ROP model.

Declarations

Funding: No funds, grants, or other support was received.

Compliance with Ethical Standards

Conflicts of interest: The authors have no relevant financial or non-financial interests.

Human and animal rights: Research involving human participants.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Local Ethical Committee approval number is: 146, date: 18.08.2021.

Informed consent: No informed consent was obtained from participants as data collected were retrospective in nature and part of the standard of care examination.

Availability of data and material: Study data can be provided.

Consent for publication: The Research Ethics Committee approved our request to publish anonymized data for this study.

Consent to participate: Due to the retrospective nature of the study, no patient consent was required for this study.

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