Retrospective validation of the postnatal growth and retinopathy of prematurity (G-ROP) and Colorado retinopathy of prematurity (CO-ROP) models in a Turkish cohort

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ABSTRACT

Background. The aim of this study was to investigate the effectiveness of the Postnatal Growth and Retinopathy of Prematurity (G-ROP) and Colorado Retinopathy of Prematurity (CO-ROP) models in predicting the risk of Retinopathy of Prematurity (ROP) in preterm infants at a tertiary ROP diagnostic and treatment center.

Methods. The G-ROP and CO-ROP models were applied to the study group using the data obtained. The sensitivity and specificity of both models were then calculated.

Results. One hundred and twenty-six infants were included in the study. When the G-ROP model was applied to the study group, the model's sensitivity at detecting any stage ROP was 88.7%, while it was 93.3% for the treated group. The specificity of the model was 10.9% for any stage ROP, and 11.7% for the treated group. For the CO-ROP model in the same study group, the sensitivity at detecting any stage ROP was 87.3%, while it was 100% for the treated group. The CO-ROP model's specificity was 40% for any stage ROP, and 27.9% for the treated group. When cardiac pathology criteria were introduced to both models, the sensitivity of the G-ROP and CO-ROP model increased to 94.4% and 97.2%, respectively.

Conclusions. It was found that the G-ROP and CO-ROP models are simple and effective models for predicting any degree of ROP development, but that they are unable to be 100% accurate. When the models were modified by introducing cardiac pathology criteria, it was observed that they began to produce more accurate results. Studies with larger groups are needed in order to assess the applicability of the modified criteria.

Key words: retinopathy of prematurity, postnatal weight gain, G-ROP, CO-ROP.

Retinopathy of prematurity (ROP) is a proliferative vascular disorder of the immature retina characterized by the disruption of normal vascular development in retinal vessels and pathological retinal neovascularization in preterm infants.¹ This abnormal development

of vascular structures may lead to severe visual impairment and blindness in infants if left untreated.² Timely screening to identify infants in need of treatment is therefore essential in preventing serious long-term visual consequences and even blindness.^{1,2}

Currently, the recommended screening criteria for ROP are based on two commonly accepted risk factors for ROP, namely the gestational age (GA) and birth weight (BW) of the infant.³ However, ROP may also affect preterm infants with normal BW or above.^{4,5}

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On the other hand, fundus examination for ROP is burdensome on infants, and about one-tenth of infants who develop ROP require treatment.⁶ Therefore, many ROP prediction models have been proposed that attempt to reduce the number of unnecessary examinations in order to increase the efficiency of ROP screening, without overlooking severe forms of the disease that require treatment.⁷⁻¹⁰

Postnatal weight gain (WG) is considered an indirect indicator of the health and perinatal condition of an infant.¹¹ It is used as a common parameter by many ROP sampling algorithms.⁷⁻¹⁰ The Postnatal Growth and Retinopathy of Prematurity (G-ROP) and the Colorado Retinopathy of Prematurity (CO-ROP) are models that use GA, BW, and postnatal WG data to estimate the risk of ROP. These two models have been applied across different cohorts and shown to be a simple way of increasing the efficiency of ROP screening without the need for complex calculations.^{7,12}

The present study investigated the effectiveness of the G-ROP and CO-ROP models by applying them to a cohort of preterm infants in a tertiary neonatal intensive care unit in Türkiye.

Material and Methods

This was a retrospective study of preterm infants who underwent ROP screening at Gazi Yasargil Training and Research Hospital from January 2017 to July 2021, had a known ROP outcome, and whose weight data was available. The study was approved by the Institutional Review Board (IRB) of Gazi Yasargil Training and Research Hospital and followed the tenets of the Declaration of Helsinki.

ROP screening and classification

The screening criteria used at the study center were GA <32 weeks, BW <1500 g, or infants with an unstable clinical course who were determined as being at high risk by the neonatologist. Screening was conducted after pupillary dilation with 2.5% phenylephrine and 1% tropicamide using a binocular indirect ophthalmoscope. Infants included in the study were classified into three subsets in accordance with the Early Treatment for Retinopathy of Prematurity (ETROP) study.² The No ROP Group included infants who did not develop any form of ROP. Group 1 included infants with any ROP requiring treatment, such as Type 1 ROP and aggressive ROP (A-ROP); and Group 2 included infants with Type 2 ROP, which spontaneously regressed. ROP screening was continued until treatment was required or complete vascularization of the retina occurred. All treatments was conducted according to ETROP Study guidelines.²

Clinical data collection

The following clinical data was collected: the infants' demographics, GA, BW, serial weight measurements, age at the time of diagnosis (weeks), days of mechanical ventilation and oxygen administration, length of stay in neonatal intensive care unit (days), and details of systemic disease including intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), cardiac disease (atrial septal defect, ventricular septal defect, and patent ductus arteriosus), sepsis, and necrotizing enterocolitis (NEC). For diagnoses of ROP the following data was also collected: location of ROP, severity of ROP, vascular characteristics of ROP, treatment status, treatment modality, and retinal vascular development. Infants whose follow-up could not be completed because of incomplete data regarding GA, BW, weight measurements and ROP outcome were excluded from the study.

G-ROP model

The G-ROP model consists of six consecutive criteria used to make an ROP screening decision. The criteria in the model are checked sequentially, and infants who meet at least one of the criteria are tested for ROP. ROP examination is not performed if none of the criteria are met. The G-ROP model criteria are: 1) GA <28 weeks, 2) BW <1051 g, 3) WG between postnatal days

10 and 19 <120 g, 4) WG between postnatal days 20 and 29 <180 g, 5) WG between postnatal days 30 and 39 <170 g, and 6) hydrocephalus.¹²

CO-ROP model

To make a screening decision for ROP, the CO-ROP model requires all of the criteria for both BW and GA to be met, rather than one criterion, plus an additional WG measured at 4 weeks (28 days). The CO-ROP model calls for ROP examination in an infant to meet all of the following criteria: 1) GA \leq 30 weeks, 2) BW \leq 1500 g, and 3) WG between birth and postnatal 4 weeks \leq 650 g.⁷

Study outcomes

The G-ROP and CO-ROP models were applied separately to the study group using the data obtained. The sensitivity and specificity of both models were then calculated.

Results

The study included 126 infants who underwent retinal examinations and had a known ROP outcome. All infants were eligible for G-ROP and CO-ROP analysis. Of 126 infants, 65 (51.6%) were male and 61 (48.4%) were female. The median GA was 28 weeks (range 23–35 weeks), and the median BW was 1050 g (range 550–2250 g). In 55 of the cases (43.7%) no degree of ROP was detected (No ROP Group), whereas in 15 (11.9%) infants, Type 1 ROP or A-ROP (ROP 1 Group) was detected and treatment was initiated. All infants included in the study completed their final ROP screening at follow-

up. Table I shows the descriptive data for the infants.

When the G-ROP model was applied to the study group, it identified 112 out of 126 infants as high-risk and showed that they needed to be screened for ROP. The G-ROP model based 78 of the 126 infants on the criteria of GA <28 weeks, eight on the BW <1051 g, 12 on the WG between postnatal days 10 and 19 <120 g, 11 on the WG between postnatal days 20 and 29 <180 g, and three on the WG between postnatal days 30 and 39 <170 g criteria. The G-ROP algorithm correctly identified 63 of the 71 infants who developed any stage ROP, and 14 of the 15 infants in Group 1. The G-ROP algorithm was not able to identify eight infants who developed any stage ROP and one infant who developed ROP, requiring treatment. The model's sensitivity at detecting any stage ROP was 88.7%, while it was 93.3% for the treated group. The specificity of the model was 10.9% for any stage ROP, and 11.7% for the treated group. Application of the G-ROP model reduced the number of infants examined by 11.1%, based on current scanning criteria (Table II).

When the CO-ROP model was applied to the study group, 95 infants who met all of the CO-ROP criteria were shown as requiring screening for ROP. The model correctly recognized 62 of the 71 infants who developed any stage ROP, and all the 15 infants who developed ROP that required treatment. The CO-ROP algorithm missed nine infants who developed any stage ROP. With regard to the CO-ROP criteria, the model's sensitivity at detecting some degree of ROP was 87.3%, while it was 100% for the

	All	No ROP	Group 2	Group 1
	(n=126)	(n=55, 43.7%)	(n=56, 44.4%)	(n=15, 11.9%)
Female, n	61	28	27	6
Gestational age, wk, median (range)	28 (23-35)	29 (25-35)	27 (23-34)	25 (23-29)
Birth weight, gr, median (range)	1050 (550-2250)	1200 (750-2250)	1000 (550-2200)	740 (600-1360)
NICU stay, days, median (range)	56 (0-300)	49 (0-240)	60 (3-300)	110 (55-110)
Supplemental O2, days, median (range)	38 (0-300)	49 (0-240)	48 (0-300)	101 (52-79)

NICU: neonatal intensive care unit, ROP: retinopathy of prematurity.

	ROP (+)	No ROP	Total	Group 1	Group 2	Total
G-ROP (+)	63	49	112	14	98	112
G-ROP (-)	8	6	14	1	13	14
Total	71	55	126	15	111	126
Sensitivity	63/71		88.7%	14/15		93.3%
Specificity		6/55	10.9%		13/111	11.7%

Table II. Sensitivity and specificity of G-ROP study criteria.

ROP: retinopathy of prematurity.

Table III. Sensitivity and specificity of CO-ROP study criteria.

	ROP (+)	No ROP	Total	Group 1	Group 2	Total
CO-ROP (+)	62	33	95	15	80	112
CO-ROP (-)	9	22	31	0	31	14
Total	71	55	126	15	111	126
Sensitivity	62/71		87.3%	15/15		100%
Specificity		22/55	40%		31/111	27.9%

ROP: retinopathy of prematurity.

treated group. The CO-ROP model's specificity was 40% for any stage ROP, and 27.9% for the treated group. Application of the CO-ROP model reduced the number of infants examined by 24.6%, based on current scanning criteria (Table III).

Additional risk factors for infants that could not be identified by either model are examined and presented in Table V. All of the infants were also in Group 2. Concomitant cardiac pathology that the G-ROP model was unable to identify was observed in four of the eight infants. Similarly, concomitant cardiac pathology that the CO-ROP was unable to identify was observed in seven of the nine infants (Table IV, Table V). When cardiac pathology criteria were introduced, the sensitivity of both the G-ROP and CO-ROP models for detecting any stage ROP increased to 94.4% and 97.2%, respectively. When the modified G-ROP and CO-ROP model were applied, four and two infants who did not require treatment would be missed, respectively.

					-						
ROP(+)		$C\Lambda$	BW/	Stay in	Mechanical	Oxygen					Cardiac
G-ROP (-)	ROP	GA (wooka)	(grame)	NICU	ventilation	administration	Sepsis	IVH	NEC	BPD	Pathology
Cases		(weeks)	(grams)	(days)	(days)	(days)					1 attiology
1	Group 1	29	1100	55	23	52	+	-	-	_	+
2	Group 2	28	1100	48	10	15	-	_	_	_	-
3	Group 2	28	1100	38	8	35	+	-	-	-	+
4	Group 2	29	1150	41	3	5	-	_	_	_	-
5	Group 2	32	1200	42	3	5	+	_	_	_	+
6	Group 2	30	1200	37	3	36	_	_	_	_	_
7	Group 2	28	1250	40	9	33	-	_	_	_	+
8	Group 2	28	1300	55	23	50	_	_	_	+	_

Table IV. Demographics of infants undetected by G-ROP criteria.

ROP: retinopathy of prematurity, NICU: neonatal intensive care unit, IVH: cerebral intraventricular hemorrhages, NEC: necrotizing enterocolitis, BPD: bronchopulmonary dysplasia.

ROP (+) CO-ROP	ROP	GA	BW	Stay in NICU	Mechanical ventilation	Oxygen administration	Sepsis	IVH	NEC	BPD	Cardiac
(-) Cases		(weeks)	(grams)	(days)	(days)	(days)	1				Pathology
1	Group 2	28	1000	33	12	33	_	+	_	+	+
2	Group 2	32	1006	40	17	35	+	_	_	_	+
3	Group 2	28	1100	38	8	35	+	_	-	_	+
4	Group 2	32	1150	37	0	10	_	_	-	_	+
5	Group 2	32	1200	42	3	5	+	_	-	_	+
6	Group 2	30	1200	37	3	36	_	_	-	_	-
7	Group 2	31	1300	49	7	11	_	_	_	_	-
8	Group 2	34	1600	37	10	30	-	+	_	+	+
9	Group 2	30	2200	93	4	16	+	_	_	_	+

Table V. Demographics of infants undetected by CO-ROP criteria.

ROP: retinopathy of prematurity, NICU: neonatal intensive care unit, IVH: cerebral intraventricular hemorrhages, NEC: necrotizing enterocolitis, BPD: bronchopulmonary dysplasia.

Discussion

Retinopathy of prematurity is one of the leading causes of childhood blindness worldwide. An effective screening program is needed to prevent blindness associated with ROP. An ideal screening program should reduce the number of stressful examinations for premature infants and the workload on healthcare personnel, while at the same time having high levels of sensitivity and specificity.

Vascular endothelial growth factor (VEGF) plays an important role in retinal vascularization. Insulin-like growth factor 1 (IGF-1) is critical for VEGF activation.13 Low IGF-1 levels are an indirect indicator of decreased VEGF activity, resulting in poor retinal vessel development and ROP. Slow postpartum WG is accepted as a marker that serum IGF-1 levels are increasing more slowly than normal.14,15 Models using postpartum WG as a screening criterion for ROP have therefore been proposed.7,12 Two of these are the G-ROP and CO-ROP models. The G-ROP and CO-ROP models include criteria for GA, BW, and postnatal WG and are advantageous for clinical use as they do not involve calculations that require a nomogram or a computational program, or complex statistical algorithms. These two models have been applied to different populations from different countries in further studies, and different sensitivity and specificity results have been reported. For this retrospective study on Turkish premature infants, two different models were applied to the same cohort to determine which model has a higher sensitivity and specificity.

The G-ROP model was developed as a screening model that includes postnatal slow WG measurements using data from 7483 infants at 29 hospitals in the United States and Canada. In this study, it was shown that the G-ROP criteria had a 100% sensitivity rate when flagging 459 infants who developed Type 1 ROP, reducing the number of infants to be screened for ROP by 30%.12 In a validation study for the G-ROP model, Binenbaum et al. reported that the model was 100% sensitive for a prospective validation cohort (G-ROP-2) and validated the criteria, concluding that when used clinically in the United States and Canada the model could reduce the number of infants receiving treatment.¹⁶ Shiraki et al.¹⁷ applied the G-ROP model to a Japanese cohort of 537 infants, reporting that the model had a sensitivity of 91.9% for any degree of ROP and 100% for Type 1 ROP. Similarly, a validation study conducted on an Egyptian and UK cohort of patients found that the model had a 100% sensitivity when detecting Type 1 ROP. In the same study, the sensitivity level for the detection of some degree of ROP was found to be 97.1% in the Egyptian cohort and 97.3% in the UK cohort.¹⁸ In a validation study conducted on the Turkish population, which included a cohort of 242 infants, the sensitivity of the G-ROP model at detecting some degree of ROP was 88.3%, and was 91.2% for the treated group.¹⁹ In our cohort, the G-ROP model had a sensitivity rate of 88.7% when identifying infants at risk of developing some degree of ROP. When the model was applied to the treated group who were diagnosed with Type 1 ROP or A-ROP, the level of sensitivity rose to 93.3%. The different sensitivity levels in different populations may be due to differences in demographics, ethnic features, and postnatal care services, as well as variability in infants' oxygen requirements.

Despite the high sensitivity rates reported in these studies, specificity rates are low. Shiraki et al.¹⁷ reported that the specificity of the G-ROP model for any degree of ROP and for the Type 1 ROP Group in the Japanese cohort was 28.9% and 45.3%, respectively. In the Turkish cohort, the specificity of the G-ROP model was 51.7% for any degree of ROP and 34.1% for ROP requiring treatment.¹⁹ In our study, the specificity of the G-ROP model was 10.9% for any degree of ROP, while it was 11.7% for the treated group—lower than the rates reported in previous studies.

The CO-ROP model was originally developed at a tertiary center in Colorado to investigate the association between postpartum WG and the risk of ROP. In the first CO-ROP study with 499 infants, the sensitivity rate for detecting severe ROP was 100%, while the sensitivity rate for detecting any degree of ROP was 96.4%. The number of infants requiring screening decreased by 23.7%.17 In a validation study that included 858 cases from four centers in the United States, the sensitivity of the CO-ROP algorithm was 98.1% for Type 1 ROP and 95% for detecting any degree of ROP.20 A subsequent validation study in a large population of 7438 infants from different ethnic groups reported a sensitivity level of 96.9%, and a specificity level of 40.9% when detecting infants who developed ROP, reporting a 23.9% reduction in the number of infants screened for CO-ROP.21

Similarly, in another study involving different ethnic groups, the CO-ROP model was applied to 374 premature infants and it was found to have a sensitivity level of 93.1% for Type 1 ROP as opposed to a sensitivity level of 84.8% when identifying any stage ROP.²² When the CO-ROP model was applied to our cohort, the model's sensitivity at detecting any stage ROP was 87.3%, while it performed very well for the treated group with a 100% rate. In addition, application of the model reduced the number of infants examined by 24.6%, based on current scanning criteria. Meanwhile, the specificity of the CO-ROP model was 40% for any stage ROP, and 27.9% for the treated group.

When the risk of missing even a single infant who requires ROP treatment is so serious, it is imperative that an efficient screening algorithm of the highest sensitivity levels is developed. The G-ROP algorithm used in the present study was unable to identify eight infants who developed some degree of ROP and one infant who developed ROP that required treatment. Meanwhile, the CO-ROP algorithm missed nine infants who developed some degree of ROP. This highlights the need for further modifications to the models. Multiple studies show that many risk factors have been associated with developing ROP such as bronchopulmonary dysplasia, cardiac pathologies, intraventricular hemorrhage and sepsis.^{23,24} A significant finding of the present study was that the infants the models failed to diagnose had sepsis and cardiac pathology. When the criteria in this study were modified and cardiac pathology was determined as a criterion, the sensitivity of the G-ROP model increased to 94.4%. The CO-ROP model's sensitivity at detecting any stage ROP increased to 97.2% when cardiac pathology criteria were added to the screening criteria. In addition to this, when applying the modified criteria the model was 100% successful at detecting all infants who developed ROP that required treatment.

This study has some limitations. Primarily, it is a retrospective study. However, despite its retrospective design, the clinical data included in our analyses were obtained from reliable sources in neonatal intensive care units and routinely recorded. Secondly, it is a singlecenter study with a relatively small sample size compared to other validation studies. Despite these limitations, our study adds to the growing evidence that postpartum WG may be a predictor of ROP, which could be a useful detail to include in ROP screening guidelines.

To conclude, this study found that the G-ROP and CO-ROP models have a high degree of sensitivity when predicting the development of ROP, but that they are not 100% accurate. The CO-ROP model proved to be more efficient at detecting cases developing ROP that required treatment. It was observed that the sensitivity of both models was increased by adding cardiac pathology criteria to detect all cases requiring treatment. Our findings should be confirmed by multicenter studies with a larger cohort.

Ethical approval

The study was approved by the Institutional Review Board (IRB) of Gazi Yasargil Training and Research Hospital Ethics Committee (09.07.2021-Number: 851).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: DYE, OLŞ, NO; data collection: DYE, OLŞ; analysis and interpretation of results: HB; draft manuscript preparation: DYE,OLŞ,HB,NO. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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