Incidence, timing and risk factors of type 1 retinopathy of prematurity in a North American cohort

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ABSTRACT

Background/Aims Early detection and timely treatment of type 1 retinopathy of prematurity (ROP) can reduce the risk of blindness. To evaluate the incidence, timing and risk factors of type 1 ROP in a large, broad-risk cohort of premature infants.

Methods Secondary analysis of data from the two Postnatal Growth and Retinopathy of Prematurity studies. Main outcomes are the incidence and timing of type 1 ROP.

Results Among 11 463 infants (mean birth weight (BW), 1095 g; mean gestational age (GA), 28 weeks), 677 (5.9%, 95% CI 5.5% to 6.3%) developed type 1 ROP. Rate of type 1 ROP decreased with larger GA (28.8% for GA ≤23 weeks, 0.2% for GA of 31–32 weeks) and no infants with GA >32 weeks developed type 1 ROP. Type 1 ROP was first diagnosed at a median postmenstrual age (PMA) of 36 weeks (range 30–46 weeks) or postnatal age (PNA) of 11 weeks (range 5–21 weeks). The mean PMA at diagnosis of type 1 ROP increased with GA (35 weeks for GA of 22–24 weeks, 41 weeks for GA of 29–30 weeks), but the mean PNA at diagnosis of type 1 ROP was similar (11–13 weeks) across GA of 22–29 weeks. GA and BW dominate the association (area under the receiver operating characteristic curve=0.87, 95% CI 0.86 to 0.88).

Conclusions Type 1 ROP developed in about 6% of premature infants over wide time windows in terms of both PMA and PNA. BW and GA are the dominant risk factors for type 1 ROP, while other prenatal factors add minimal predictive power for type 1 ROP.

INTRODUCTION

Retinopathy of prematurity (ROP) is a leading cause of blindness in children.[1] Type 1 ROP, as defined by the Early Treatment for ROP (ETROP) study, is severe ROP that requires prompt treatment to prevent progression to retinal detachment and blindness.[2] Early detection of type 1 ROP for timely treatment can reduce the risk of blindness.[3] Current US screening guidelines for ROP recommend initiating ROP examinations at 4 weeks after birth or 31 weeks postmenstrual age (PMA), whichever occurs later, in order to ensure timely diagnosis of type 1 ROP.[4] Therefore, for infants born at gestational ages (GAs) 22–30 weeks who are at risk of type 1 ROP, examinations begin at chronological age 4–9 weeks or at a PMA of 31–34 weeks. This recommendation was based on natural history data from the multicentre Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) and Light Reduction in ROP (LIGHT-ROP) studies, which only enrolled high-risk infants with birth weight (BW) <1251 g.[5] As type 1 ROP can occur in infants with BW >1250 g, evaluating the incidence and timing of ROP in a broad-risk cohort is needed.

The Postnatal Growth and Retinopathy of Prematurity (G-ROP-1 and G-ROP-2) studies are two large multicentre studies of broad-risk infants undergoing ROP screening examinations at hospitals in the USA and Canada between 2006 and 2017.[6 7] Specific BW and GA limits were not used for the G-ROP studies to make the cohort fully representative of all infants who were undergoing ROP examinations. However, typical criteria used during the study period included a BW <1501 g, a GA of 30 weeks 0 days or younger, or an unstable clinical course as determined by the neonatologist. Thus, G-ROP studies provide us a unique opportunity to evaluate the incidence and timing of type 1 ROP in a cohort more fully representative of infants undergoing ROP examinations. The purpose of this study was to evaluate the incidence, timing and risk factors of type 1 ROP in the G-ROP studies.

METHODS

We performed a secondary analysis of data from the G-ROP-1 and G-ROP-2 studies.[8 9] The G-ROP-1 study was a retrospective cohort study of 7483 premature infants from 29 hospitals born between 2006 and 2011 with the aim of developing postnatal weight gain-based G-ROP screening criteria. The G-ROP-2 study was a prospective cohort study of 3980 premature infants from 41 hospitals between 2015 and 2017 aiming to validate the G-ROP screening criteria. Both studies enrolled infants who underwent ROP screening examinations and had known ROP outcomes. Institutional Review Board approval for the study was obtained at all hospitals, and waiver of informed consent was granted at each center.

The primary outcomes of the current analysis were the incidence and timing of type 1 ROP. The incidence rates of type 1 ROP overall and stratified by BW and GA were assessed. The timing of type 1 ROP was evaluated based on both PMA and postnatal age (PNA) at the first diagnosis of type 1 ROP. Descriptive statistics (mean, SD, median and range) were used to summarise timing, and stratification was done by BW and by GA. The crude risks for type 1 ROP across PMA and PNA were calculated by dividing the number of infants with type 1 ROP by the number of infants at risk in each specific week and then plotted, again stratified by BW and by GA. We performed univariate and multivariate analyses of demographic

risk factors, including BW, GA, sex, maternal race, maternal ethnicity and birth location, using logistic regression models for the incidence of type 1 ROP and linear regression models for the timing of type 1 ROP. Multivariate analysis considered risk factors with $p<0.20$ from univariate analysis, and underwent backward variable selection by keeping risk factors with $p<0.05$ in the final multivariate model. To evaluate the prediction of risk factors for the incidence of type 1 ROP, area under the receiver operating characteristic curves (AUCs) and their 95% CIs were calculated from logistic regression models. All statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, NC, USA).

RESULTS

The analysis included 11 463 infants (figure 1, online supplemental figure 1). The mean (SD) BW was 1095 (358) g (range 310–3000 g) and mean (SD) GA was 28.4 (2.7) weeks (range 22.0–38.1 weeks); 47.6% of infants were female, 48.7% were Caucasian and 28.4% were African American; and 7.7% of infants were Hispanic.

Among 11 463 infants, 677 (5.9%, 95% CI 5.5% to 6.3%) developed type 1 ROP, and the rates were similar in both studies (6.1% in G-ROP-1 and 5.5% in G-ROP-2). The rates of type 1 ROP stratified by BW and GA are presented in table 1. The rate of type 1 ROP decreased with increasing GA; among 417 infants with a GA ≤23 weeks, 121 (29.0%) developed type 1 ROP, while only 3 (0.2%) of 1753 infants with a GA of 31–32 weeks and no infants with GA >32 weeks (n=440) developed type 1 ROP. The rate of type 1 ROP decreased with increasing BW as well; among 202 infants with a BW ≤500 g, 66 (32.7%) developed type 1 ROP, while 12 (0.3%) of 3824 infants with a BW ≥1251 g developed type 1 ROP. When considering both GA and BW together (table 1), higher type 1 ROP rates were found among infants with smaller BW and lower GA. For example, type 1 ROP was noted in 636(13.3%) of 4786 infants with GA <28 weeks and BW ≤1250 g, and among 1646 infants with GA >30 weeks and BW ≥1251 g, only 3 (0.2%) developed type 1 ROP.

Table 2 summarises the characteristics and timing of type 1 ROP at its first diagnosis among 1241 type 1 ROP eyes of 677 infants. Most type 1 ROP eyes (773 (62.3%)) had stage 3 ROP in zone II with plus disease, and remaining eyes had stage 2 zone II with plus (12.8%), stage 3 zone I with plus (8.4%) or without plus (8.2%), or plus disease with stage 2 (2.4%) or stage 1 (1.5%) in zone I. Type 1 ROP eyes with ROP in zone II tended to be diagnosed later (approximately at 37 weeks PMA) than type 1 ROP in zone I (at 34–35 weeks PMA).

The PMA and PNA at first diagnosis of type 1 ROP, stratified by GA and by BW, are presented in table 3. Median PMA at type 1 ROP diagnosis was 36 weeks (range 30–46 weeks), and increased with increasing GA: 35 weeks for infants with a GA of 22–24 weeks, up to 41 weeks for infants with a GA of

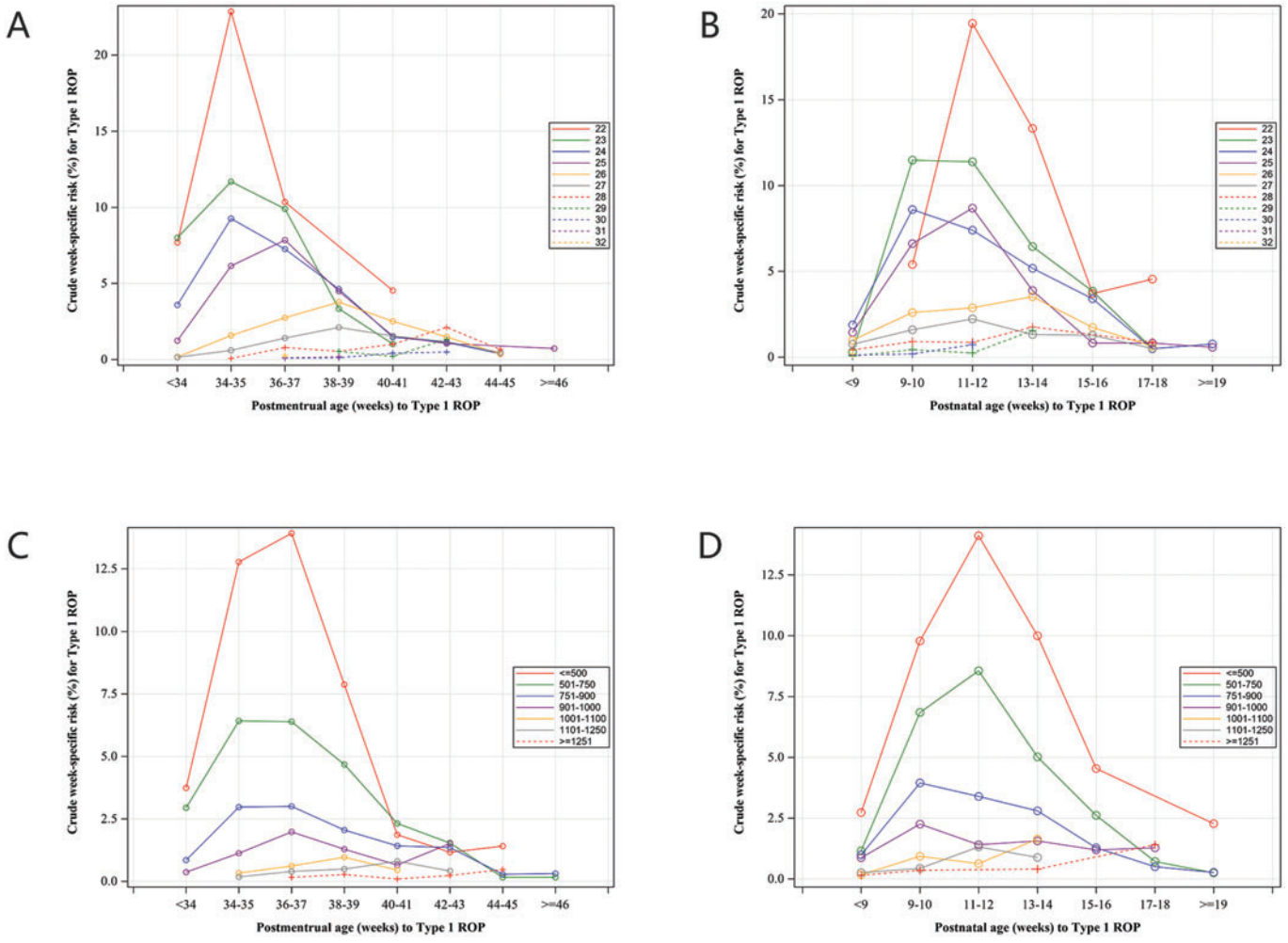

Figure 1 The crude risk of type 1 ROP across (A) postmenstrual age, (B) postnatal age stratified by gestational age; The crude risk of type 1 ROP across (C) postmenstrual age, (D) postnatal age stratified by birth weight. ROP, retinopathy of prematurity.

Table 1 Rate of type 1 ROP stratified by birth weight and gestational age

Gestational age (weeks)	Birth weight (g) ≤500	501–750	751–900	901–1000	1001–1100	1101–1250	≥1251	Total
22	6/14 (42.9%)	8/25 (32.0%)	1/1 (100%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	15/40 (37.5%)
23	12/41 (29.3%)	93/325 (28.6%)	1/11 (9.1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	106/377 (28.1%)
24	17/58 (29.3%)	139/604 (23.0%)	31/168 (18.5%)	0/15 (0%)	0/3 (0%)	0/1 (0%)	0/1 (0%)	187/850 (22.0%)
25	20/41 (48.8%)	87/451 (19.3%)	53/402 (13.2%)	13/102 (12.7%)	3/17 (17.6%)	1/4 (25.0%)	0/2 (0%)	177/1019 (17.4%)
26	8/31 (25.8%)	28/279 (10%)	32/440 (7.3%)	22/282 (7.8%)	6/150 (4.0%)	2/48 (4.2%)	0/8 (0%)	98/1238 (7.9%)
27	3/8 (37.5%)	23/179 (12.8%)	11/271 (4.1%)	7/277 (2.5%)	5/308 (1.6%)	4/230 (1.7%)	1/79 (1.3%)	54/1352 (4.0%)
28	0/5 (0%)	7/89 (7.9%)	6/185 (3.2%)	2/164 (1.2%)	1/252 (0.4%)	5/414 (1.2%)	3/317 (0.9%)	24/1426 (1.7%)
29	0/3 (0%)	2/44 (4.5%)	1/92 (1.1%)	0/95 (0%)	0/166 (0%)	2/330 (0.6%)	3/688 (0.4%)	8/1418 (0.6%)
30	0/0 (0%)	1/20 (5.0%)	0/53 (0%)	0/65 (0%)	1/113 (0.9%)	1/216 (0.5%)	2/1083 (0.2%)	5/1550 (0.3%)
31	0/1 (0%)	0/13 (0%)	0/28 (0%)	0/30 (0%)	0/63 (0%)	0/162 (0%)	2/868 (0.2%)	2/1165 (0.2%)
≥32	0/0 (0%)	0/8 (0%)	0/19 (0%)	0/25 (0%)	0/56 (0%)	0/142 (0%)	1/778 (0.1%)	1/1028 (0.1%)
Total	66/202 (32.7%)	388/2037 (19.0%)	136/1670 (8.1%)	44/1055 (4.2%)	16/1128 (1.4%)	15/1547 (1.0%)	12/3824 (0.3%)	677/11463 (5.9%)

ROP, retinopathy of prematurity.

Table 2 Characteristics of 1241 eyes with type 1 ROP

Type 1 ROP	Eyes, N (%)	Mean (SD) Birth weight, g	Gestational age, weeks	Postmenstrual age at diagnosis, weeks	Postnatal age at diagnosis, weeks
Stage 3 zone II and with plus	773 (62.3%)	725.1 (194.6)	25.4 (1.6)	37.3 (2.6)	11.9 (2.3)
Stage 2 zone II with plus	159 (12.8%)	729.6 (196.1)	25.4 (1.5)	36.9 (2.3)	11.5 (2.3)
Stage 3 zone I with plus	104 (8.4%)	603.8 (136.0)	24.3 (1.1)	34.5 (1.3)	10.3 (1.3)
Stage 3 zone I without plus	102 (8.2%)	631.3 (132.0)	24.3 (1.2)	35.1 (2.1)	10.8 (2.2)
Stage 2 zone I with plus	30 (2.4%)	637.9 (200.4)	24.9 (1.6)	34.9 (1.4)	10.1 (1.7)
Stage 1 zone I with plus	18 (1.5%)	683.7 (266.5)	25.7 (2.8)	34.1 (1.5)	8.4 (1.8)
Type 1 not specified	55 (4.4%)	683.3 (161.1)	25.0 (1.2)	38.2 (2.5)	13.2 (2.4)
All combined	1241	703.2 (190.4)	25.2 (1.6)	36.8 (2.6)	11.6 (2.3)

ROP, retinopathy of prematurity.

Table 3 Timing of type 1 ROP based on postmenstrual age and postnatal age stratified by gestational age and by birth weight

GA (weeks)	n/N	Postmenstrual age (weeks) at first diagnosis of type 1 Mean (SD)	Median (Q1, Q3)	Minimum, maximum	Recommended timing for beginning examinations*	Chronical age (weeks) at first diagnosis of type 1 Mean (SD)	Median (Q1, Q3)	Minimum, maximum	Recommended timing for beginning examinations*
22	15/40	35.4 (2.1)	35.0 (34.1, 36.9)	32.0, 40.7	31	12.8 (2.1)	12.3 (11.6, 14.3)	9.7, 18.3	9
23	106/377	35.3 (1.9)	34.9 (33.7, 36.4)	32.0, 41.9	31	11.8 (1.9)	11.4 (10.4, 13.1)	8.7, 18.1	8
24	187/850	36.1 (2.4)	35.6 (34.4, 37.6)	32.1, 44.6	31	11.8 (2.4)	11.3 (10.0, 13.3)	7.6, 19.7	7
25	177/1019	36.8 (2.3)	36.9 (35.3, 37.9)	30.7, 46.4	31	11.5 (2.3)	11.4 (10.0, 12.6)	5.7, 21.1	6
26	98/1238	38.1 (2.4)	38.1 (36.4, 39.6)	33.3, 44.1	31	11.8 (2.3)	11.8 (10.0, 13.3)	6.7, 17.9	5
27	54/1352	38.4 (2.5)	38.6 (36.4, 40.1)	33.1, 45.1	31	11.1 (2.5)	11.4 (9.4, 12.4)	5.9, 17.6	4
28	24/1426	39.2 (2.8)	38.3 (37.1, 41.5)	34.3, 45.7	32	10.9 (2.7)	10.0 (8.9, 13.2)	6.3, 17.1	4

Continued

Table 3 Continued

GA (weeks)	n/N	Postmenstrual age (weeks) at first diagnosis of type 1			Recommended timing for beginning examinations*	Chronical age (weeks) at first diagnosis of type 1			Recommended timing for beginning examinations*
		Mean (SD)	Median (Q1, Q3)	Minimum, maximum		Mean (SD)	Median (Q1, Q3)	Minimum, maximum	
29	8/1418	40.9 (2.2)	40.6 (38.9, 43.1)	38.3, 43.6	33	11.3 (2.2)	10.9 (9.7, 13.4)	8.4, 14.4	4
30	5/1550	39.8 (2.5)	40.7 (38.6, 41.3)	36.0, 42.4	34	9.4 (2.7)	10.1 (7.7, 11.3)	5.7, 12.3	4
≥31	3/2193	37.8 (0.9)	37.9 (36.9, 38.7)	36.9, 38.7	–	6.3 (1.3)	6.9 (4.9, 7.1)	4.9, 7.1	4
BW (g)									
≤500	66/202	36.5 (2.4)	36.1 (34.4, 37.9)	32.1, 44.6		11.9 (2.4)	11.7 (10.0, 13.3)	8.0, 19.7	
501–750	388/2037	36.6 (2.6)	36.3 (34.6, 38.1)	32.0, 46.4		11.8 (2.2)	11.7 (10.3, 13.0)	6.0, 20.6	
751–900	136/1670	37.0 (2.7)	36.9 (35.0, 38.2)	30.7, 46.1		11.4 (2.5)	11.0 (9.7, 12.7)	5.7, 21.1	
901–1000	44/1055	37.4 (2.6)	36.9 (35.6, 38.7)	33.3, 43.3		11.1 (2.7)	10.6 (9.3, 12.8)	6.3, 18.3	
1001–1100	16/1128	37.7 (2.0)	37.8 (36.0, 39.3)	34.7, 40.9		10.9 (2.7)	11.1 (9.0, 13.2)	5.7, 14.4	
1101–1250	15/1547	38.6 (2.5)	38.3 (36.7, 40.4)	34.9, 43.4		10.5 (2.0)	11.0 (8.7, 11.9)	7.3, 14.1	
≥1251	12/3824	39.3 (2.6)	38.6 (37.5, 40.1)	36.9, 45.7		9.5 (3.3)	9.0 (7.4, 10.0)	4.9, 17.1	
Total	677/11 463	36.8 (2.6)	36.6 (34.9, 38.4)	30.7, 46.4		11.6 (2.4)	11.4 (10.0, 13.0)	4.9, 21.1	

Recommended timing for beginning examinations was from the current US screening guidelines for ROP (Fierson WM. Screening Examination of Premature Infants for Retinopathy of Prematurity. *Paediatrics.* 2018;142(6):e20183061).
BW, birth weight; GA, gestational age; ROP, retinopathy of prematurity; Q1, first quartile, Q3, third quartile.

29–30 weeks. Median PNA at type 1 ROP was 11 weeks (range 5–21 weeks) and was similar across GA of 23–27 weeks. Compared to currently recommended times for beginning ROP examinations, almost all infants developed type 1 ROP during the recommended ROP examination windows except for one outlier infant with GA of 25 weeks who developed type 1 two days before the currently recommended age for starting examinations.

The PMA and PNA at first diagnosis of type 1 ROP, stratified by BW, are also presented in table 3. Median PMA at type 1 ROP was 36–37 weeks for infants with BW <1001 g and 38 weeks for infants with a BW of ≥1001 g. Median PNA at type 1 ROP was 11–12 weeks across BWs <1251 g except for infants with a BW of 901–1000 g (median PNA at type 1 ROP, 10.6 weeks) or BW >1250 g (median PNA at type 1 ROP, 9 weeks).

Figure 1A and B shows the crude risk of type 1 ROP across PMA weeks (figure 1A) and PNA weeks (figure 1B), stratified by GA. The crude peak risk for type 1 ROP shifted up consistently in terms of PMA as GA increased, while the peak risk of type 1 ROP in terms of PNA varied more across GA groups. However, in general, the risk of type 1 ROP was spread over a wide range in terms of both PMA and PNA.

Figure 1C and D shows the crude risk of type 1 ROP across PMA weeks (figure 1C) and across PNA week (figure 1D) stratified by BW. The crude peak risk for type 1 ROP occurred at a PMA of 37 weeks regardless of BW for infants with a BW <1001 g, while the crude peak risk for type 1 ROP in terms of PNA varied more across BW groups.

Univariate risk factor analysis for type 1 ROP is presented in online supplemental table 1. BW, GA, maternal race, maternal ethnicity and birth location were significantly associated with type 1 ROP. GA and BW predicted type 1 ROP very well, with an AUC of 0.86 (95% CI 0.85 to 0.87) and 0.84 (95% CI 0.83 to 0.85), respectively, and an AUC of 0.87 (95% CI 0.86 to 0.88) jointly. Other factors had poor discriminatory power, with an AUC between 0.5 and 0.6.

In multivariate analysis (table 4), higher risk of type I ROP was associated with lower BW (OR=14.1, 95% CI 6.4 to 31.3 for ≤500 g vs ≥1251 g), smaller GA (OR=37.6, 95% CI 12.8 to 110 for 22 weeks vs ≥30 weeks), male gender (OR=1.3; 95% CI 1.1 to 1.6), Caucasian race (OR=2.4, 95% CI 1.9 to 3.0 vs African American), Hispanic ethnicity (OR=1.4, 95% CI 1.0 to 1.9), and outborn status at the study hospital (OR=1.8, 95% CI 1.5 to 2.2). Considering all of these risk factors together provided an AUC of 0.89 (95% CI=0.88–0.90).

Risk factors for the timing of type 1 ROP (in terms of PMA and PNA) are presented in online supplemental table 2 for univariate analysis and in online supplemental table 3 for multivariate analysis. In multivariate analysis, only GA and birth location were significantly associated with timing of type 1 ROP. Higher GA was significantly associated with later PMA but earlier PNA of type 1 ROP. Outborn infants developed type 1 ROP slightly earlier in terms of both PMA (36.5 vs 37.1 weeks, p=0.001) and PNA (11.3 vs 11.8 weeks, p=0.003) compared with inborn infants.

DISCUSSION

This secondary analysis of data from a large cohort of broad-risk preterm infants determined the incidence, timing and risk factors of type 1 ROP. We found that type 1 ROP occurred in approximately 6% of premature infants. No infants with GA >32 weeks, regardless of BW, developed type 1 ROP. Smaller BW and lower GA were the dominant risk factors of type 1 ROP.

Although the majority of type 1 ROP developed in less mature, lower BW infants, more mature and larger infants were also at risk. We found that 3 (0.2%) of 1646 infants with a BW >1250 g and a GA >30 weeks developed type 1 ROP. Current ROP guidelines recommend screening of infants who have a BW <1501 g or a GA earlier than 30 weeks, and higher BW greater GA infants with an unstable clinical course. While lowering the BW screening threshold from 1501 g to 1251 g would greatly reduce the number of low-risk infants requiring examinations, a small number of infants with type 1 ROP would be missed, some of who would develop retinal detachment and blindness. Therefore, simply lowering the current threshold would not be clinically acceptable. However, the inclusion of additional criteria to flag slow postnatal weight gain, which is predictive of severe ROP, permits lowering of both BW (<1050 g) and GA (<28 weeks) criteria while maintaining 100% sensitivity for type 1 ROP by the validated G-ROP screening criteria.[6 7]

Table 4 Multivariate analysis for risk factors of type 1 ROP

	Infants (N)	Type 1 ROP, N (%)	Adjusted OR (95% CI)	Adjusted p value
Birth weight (g)				<0.001
≤500	202	66 (32.7%)	14.10 (6.36 to 31.27)	
501–750	2037	388 (19.0%)	6.85 (3.29 to 14.27)	
751–900	1670	136 (8.1%)	3.56 (1.71 to 7.42)	
901–1000	1055	44 (4.2%)	2.56 (1.19 to 5.49)	
1001–1100	1128	16 (1.4%)	1.28 (0.55 to 2.95)	
1101–1250	1547	15 (1.0%)	1.37 (0.60 to 3.11)	
≥1251	3824	12 (0.3%)	1.00	
Gestational age (weeks)				<0.001
22	40	15 (37.5%)	37.56 (12.77 to 110.45)	
23	377	106 (28.1%)	31.30 (13.04 to 75.10)	
24	850	187 (22.0%)	26.38 (11.21 to 62.10)	
25	1019	177 (17.4%)	24.50 (10.46 to 57.36)	
26	1238	98 (7.9%)	12.90 (5.50 to 30.28)	
27	1352	54 (4.0%)	9.06 (3.86 to 21.27)	
28	1426	24 (1.7%)	4.85 (2.03 to 11.60)	
29	1418	8 (0.6%)	2.00 (0.73 to 5.43)	
≥30	3743	8 (0.2%)	1.00	
Sex				0.001
Female	5452	303 (5.6%)	1.00	
Male	6011	374 (6.2%)	1.33 (1.12 to 1.59)	
Maternal race				<0.001
Black/African American	3252	133 (4.1%)	1.00	
White/Caucasian	5580	361 (6.5%)	2.41 (1.93 to 3.01)	
Asian/Asian American	353	21 (5.9%)	2.70 (1.59 to 4.57)	
American Indian/Alaskan Native	65	4 (6.2%)	3.70 (1.18 to 11.58)	
Native Hawaiian/Other Pacific Islander	115	3 (2.6%)	1.04 (0.31 to 3.52)	
Other	765	57 (7.5%)	1.63 (1.12 to 2.38)	
Unknown	1225	94 (7.7%)	1.67 (1.22 to 2.30)	
>1 Race checked	108	4 (3.7%)	1.13 (0.39 to 3.31)	
Maternal ethnicity				0.001
Not Hispanic or Latino	7948	388 (4.9%)	1.00	
Hispanic or Latino	884	65 (7.4%)	1.39 (1.01 to 1.90)	
Unknown	2631	224 (8.5%)	1.46 (1.19 to 1.79)	
Birth location				<0.001
Inborn	8558	370 (4.3%)	1.00	
Outborn	2905	307 (10.6%)	1.80 (1.51 to 2.15)	

ROP, retinopathy of prematurity.

Our observed 6.5% incidence of type 1 ROP among infants with a GA <32 weeks is lower than the 8.5% incidence rate of type 1 ROP observed in a US retrospective study of 1706 infants with GA <32 weeks.[10] The difference in incidence could due to different selection criteria of infants. Our study had no restriction for enrolment, whereas for infants with a BW of 1500–2000 g or GA >30 weeks, only 'high risk' infants were included in their study.[10] We could not directly compare the incidence of type 1 ROP in our study with those reported in the CRYO-ROP and ETROP studies,[11 12] because both earlier studies used 'pre-threshold ROP' and not 'type 1,' which is a subtype of pre-threshold ROP, to classify disease. Although we found that prenatal factors, such as sex, maternal race, maternal ethnicity and birth location were significantly associated with type 1 ROP in multivariable analysis, these factors did not improve the prediction of type 1 ROP beyond the combination of only BW and GA, as the AUC was minimally higher when these factors were included in comparison to BW and GA alone. This finding is consistent with a previous study that examined perinatal risk factors and severe ROP.[13]

We found that about one-fifth of type 1 ROP cases involved zone I disease, which has potential treatment implications. Infants with type 1 ROP are treated with laser or increasingly with intravitreal injection of an anti-vascular endothelial growth factor (anti-VEGF) agent. The latter agents have shown particular benefit compared to laser for Zone I ROP.[14] However, possible systemic effects of anti-VEGF agents in developing premature infants require further investigation.

In the CRYO-ROP and ETROP studies of infants with BW <1251 g, the median PMA at 'pre-threshold' ROP was 36 weeks (range 32–42 weeks), and the median PNA at 'pre-threshold' ROP was 10 weeks (range 7–16 weeks).[11 15] Although we could not

directly compare the timing of type 1 ROP to the timing of pre-threshold ROP in those two earlier studies, both those studies and our studies suggested that severe ROP occurs over a wide range of time in terms of PMA or PNA. In the recent Swedish National Register for Retinopathy of Prematurity (SWEDROP) study of infants with a GA of 22–30 weeks, the peak risk of ROP treatment occurred at PNA of 12 weeks regardless of GA, but the peak risk varied in terms of PMA.[16] Our study found instead that the peak risk of type 1 ROP varies across GA groups in terms of both PMA and PNA. In contrast to the CRYO-ROP and ETROP studies, we evaluated the incidence and timing of type 1 ROP among infants with BW >1250 g in addition to smaller infants. Although only 12 (0.3%) of 3824 infants with BW >1250 g developed type 1 ROP, they tended to develop type 1 ROP later in PMA (median 38.6 weeks) and earlier in PNA (median 9.0 weeks) than infants with BW <1251 g. Our cohort also differed from the SWEDROP study in that we included infants with GA >30 weeks. We found only 3 (0.1%) of 2193 infants with GA >30 weeks developed type 1 ROP, and their type 1 ROP tended to occur earlier than infants with GA ≤30 weeks. It is important to acknowledge that despite the patterns noted above for the median times, type 1 ROP occurred across a wide range of PMA for most GA and BW groups, which has important clinical implications for timing examinations early enough and continuing to closely monitor infants who remain at risk well past the median times for type 1 ROP.

In multivariate analysis, we found that while the timing of type 1 ROP was significantly associated with GA, it was not associated with BW. The PMA at peak risk for type 1 ROP increased with higher GA, while the PNA at the peak risk of type 1 ROP varied substantially across GA groups. These findings indicate that using PMA or PNA alone cannot safely predict the timing of severe ROP.[17]

Due to the small number of infants with GA <24 weeks in previous large-scale ROP studies, the USA screening guidelines pertaining to timing of ROP screening of infants with GA <24 weeks was extrapolated from infants with larger GA.[4] Our study had 417 infants with GA 22 or 23 weeks, and 121 (29.0%) developed type 1 ROP at earliest time of 31 weeks' PMA and 8.7 weeks' PNA, which are all within the recommended ROP screening time windows of 31 weeks' PMA or 4 weeks' PNA. These findings suggest that even for extremely premature infants, the currently recommended initiation time for examinations can safely detect type 1 ROP.

Our study has several strengths. First, this study includes a large sample of racially and geographically diverse infants, making it representative of infants undergoing ROP screening examinations in the USA. Second, the infants in this study were at broad risk of ROP, providing a unique opportunity to study the epidemiology of type 1 ROP. We did not restrict inclusion based upon a maximum BW or GA, which further makes the cohort representative of infants undergoing ROP examinations in actual practice, Third, both prospective and retrospective high-quality data were collected and error checked with formal study procedures and data quality measures.[8] Fourth, ROP examinations were performed by paediatric ophthalmologists and retinal specialists with clinical expertise in ROP management, using standard International Classification of ROP terminology with regards to the diagnosis of ROP. One limitation to our study is reliance on inter-examination intervals determined at the discretion of the examining ophthalmologists. Typically, ROP rounds occur on only a weekly basis at most hospitals. In addition, some infants may have received examinations in a 2- or 3-week interval, depending on current examination findings. Therefore, it is not possible to identify with greater precision the onset of type 1 ROP; we could only extract the date of diagnosis. Another important limitation is that generalisability to settings with developing neonatal care systems, such as in low- or middle-income countries, may be limited, due to differences in neonatal care that might impact the prevalence, onset and clinical risk factors for ROP.[18]

In summary, type 1 ROP developed in about 6% of at-risk premature infants over wide time windows in terms of both PMA and PNA. The earliest occurrences of type 1 with regard to PMA and PNA aligned with current national recommendations for the timing of initiating ROP examinations, providing reassurance that current practice safely captures infants who require treatment early to reduce the risk of progression to retinal detachment. Birth weight and GA continue to be the two most dominant demographic risk factors for type 1 ROP, and other prenatal factors add only minimal additional predictive power. Additional research into inter-examination intervals and timing of termination of examinations using these large datasets may provide further validation of ROP scheduling practices or result in suggestions for modifications to ROP screening schedules to ensure both timely and efficient diagnosis of type 1 ROP.

Contributors YY and G-SY had full access to study data and take responsibility for the integrity of the data and accuracy of the analysis. YY, GB and G-SY participated in study design, manuscript writing and critically reviewing the manuscript. LAT participated in study design and critically reviewing the manuscript. YY performed the statistical analysis. All authors approved the final manuscript.

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