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Intraocular Hemorrhages and ROP in the Telemedicine Approaches to Evaluating Acute-Phase Retinopathy of Prematurity (e-ROP) Study

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Abstract

Objective—To describe the clinical characteristics of intraocular hemorrhages in infants in the “Telemedicine approaches to evaluating acute-phase retinopathy of prematurity (e-ROP) Study” and to evaluate their potential use for prediction of disease severity.

Design—Secondary data analysis from a prospective study.

Subjects—Pre-term infants with birth weight (BW) ≥ 1250 g.

Methods—Infants underwent serial digital retinal imaging in both eyes starting at 32 weeks postmenstrual age. Non-physician trained readers evaluated all image sets from eyes that ever had intraocular hemorrhages (IOH) documented on either image evaluation or eye examination for the presence, location, type, area and relation of the IOH to the junction between vascularized and avascular retina. Associations of IOH with demographic and neonatal factors, and with the presence and severity of ROP were investigated by univariate and multivariate analysis. Sensitivity and specificity of the telemedicine system for detecting referral-warranted ROP (RW-ROP) were calculated with and without incorporating hemorrhage into the standardized grading protocol.

Main Outcome Measures—Retinal and vitreous hemorrhage.

Results—Among 1239 infants (mean (SD) BW =864 (212) g, gestational age (GA) =27(2.2) weeks) who underwent an average of 3.2 imaging sessions, 22% infants had IOH in an eye on at least one of the e-ROP visits. Classification of IOH was preretinal (57%), blot (57%), dot (38%), flame-shaped (16%) and vitreous (8%); most IOH were unilateral (70%). IOH resolved in 35% of

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eyes by the next imaging session and, in the majority (76%) of cases, by 8 weeks after initial detection. Presence of IOH was inversely associated with BW and GA and significantly ($p<0.0001$) associated with the presence and severity of ROP (BW and GA adjusted odds ratios of 2.46 for any ROP, 2.88 for Stage 3 and 3.19 for RW-ROP). Incorporating IOH into the grading protocol minimally altered the sensitivity of the system (94% vs 95%).

Conclusions—Approximately one in five pre-term infants examined had intraocular hemorrhages, generally unilateral. The presence of hemorrhage was directly correlated with both presence and severity of ROP and inversely correlated with BW and GA, though including hemorrhage in the grading algorithm only minimally improved the sensitivity of the telemedicine system to detect referral-warranted ROP.

Introduction

Intraocular (retinal and vitreous) hemorrhages (IOH) are common in infants whether delivery is vaginal or via Caesarean section.^{1–3} IOH occurring in pre-term infants has been well described but these previous studies are limited in sample size.^{4–11}

The Telemedicine Approaches to Evaluating Acute-Phase Retinopathy of Prematurity (e-ROP) Study demonstrated safety and validity of a telemedicine system for detecting referral-warranted retinopathy of prematurity (RW-ROP), defined as the presence of zone I ROP, Stage 3 retinopathy of prematurity (ROP), or plus disease.¹² However, early Stage 3 retinopathy (especially in zone I) and evolving plus disease may be difficult to detect with certainty, and the exact border between zone I and zone II in these infants is dependent upon ascertaining the exact center both of optic discs with various configurations and of very immature foveolas. Nevertheless, accurate assessment of all of these factors is necessary to correctly identify eyes with RW-ROP. IOH, on the other hand, are more easily and reproducibly distinguished from subtle features of stage 3 ROP or early plus disease and likely more consistently detectable than the border between zone I and zone II. Additionally, the presence of IOH may be easier to detect by non-physician readers who would most likely be employed in any widely used telemedicine system. Because of these factors, we postulated that incorporating IOH into the reading protocol could improve the performance of the ROP telemedicine system to detect RW-ROP.

This paper reports the incidence and clinical characteristics of IOH in premature infants with birth weight (BW) <1251g and gestational age (GA) of 22 to 35 weeks, and assesses the potential predictive value of incorporating IOH into the grading protocol of the e-ROP telemedicine system to identify infants with RW-ROP in one or both eyes.

Methods

The e-ROP Study and the methodology developed for use in e-ROP to evaluate digital images of pre-term infants by the University of Pennsylvania Ophthalmology Reading Center has been described.^{13–15} Briefly, using standardized e-ROP equipment, a software interface that allowed image enhancement by adjustment of magnification, brightness and contrast and a web-based form was employed by trained and certified non-physician readers (TRs) to grade independently eye image sets consisting of 6 standard images for posterior

for vascular pathology (plus or pre-plus disease) and the stage and location of any ROP. Readers documented the presence of hemorrhage in the comments section of the grading form. The TRs were masked to all clinical diagnostic examination details and demographic data of the infants who were enrolled in e-ROP, as well as to the grading results of fellow eyes. Discrepancies between two readers were adjudicated by the Reading Center Director.

This study is a secondary data analysis of the primary prospective cohort study. All 1705 image sets from 406 eyes that had IOH at any visit documented either by the diagnostic examinations by ophthalmologists or by the TRs on grading the image sets were selected for hemorrhage grading. An additional 100 image sets were also randomly selected from eyes that were never noted to have hemorrhage at any visit on either image grading or diagnostic examination. The combined image sets were presented for single grading by the TRs. A small set of these images (n=41) were subjected to double grading as well as re-grading for quality assurance.

In the primary e-ROP study, the readers who were experienced in diabetic retinopathy grading were not required to characterize any hemorrhage in grading of image sets. For the current study, the readers had training sessions led by both the Study Chair and the Reading Center Director to characterize hemorrhages noted on e-ROP images by type, location, size and their location in relation to the ROPTRs graded the presence of hemorrhage in any of the images of each eye set and the specific types of hemorrhages, namely dot, blot, flame-shaped, preretinal or vitreous. Dot hemorrhages were small, round hemorrhages and smaller than 125 μ ; blot hemorrhages were larger than dot hemorrhages and could be of any size but are not aligned with the course of the retinal nerve fibers; flame hemorrhages were superficial hemorrhages of any size that were located within and following the course of the retinal nerve fiber layer; preretinal hemorrhages were typically linear hemorrhages often found in close proximity to the avascular/vascular junction and could be located adjacent to or on top of ROP; vitreous hemorrhages were situated in the vitreous or in the interface of the vitreous with the retinal surface (Figure 1). TRs also determined location of each individual type of retinal hemorrhages by zone and quadrant, the number of hemorrhages (1 to >20) the approximate area of non-dot hemorrhages in proportion to disc area, and the relationship of the hemorrhages to the junction of the vascularized and avascular retina. In eyes with ROP, the position of preretinal hemorrhages (posterior or anterior or at the junction of vascular and avascular retina) was recorded. Quality assurance for the hemorrhage grading was performed using a random sample of 41 eyes. The inter-reader and grade-regrade agreements were acceptable (Table 1)

Institutional Review Board (IRB)/Ethics Committee approval was obtained and the study was compliant with Health Insurance Portability and Accountability Act regulations and adhered to the tenets of the Declaration of Helsinki.

Statistical Methods

We calculated the proportion, mean, standard deviation (SD) and range to describe the characteristics of any ocular hemorrhage and hemorrhage by type. We used the univariate and multivariate logistic regression models to determine the risk factors of hemorrhage including BW, GA, race, and the respiratory status at the imaging session. Kaplan-Meier

curves were used to estimate the time to resolution of hemorrhage. Cross-sectional associations between presence, type, location, and size of hemorrhage and presence of any ROP, Stage 3 ROP, or RW-ROP were assessed using logistic regression models. Odds ratios and their 95% confidence intervals (95% CI) were calculated from multivariate logistic regression models adjusting for BW and GA. Sensitivity and specificity of the telemedicine system for detecting RW-ROP were calculated, both with and without considering intraocular hemorrhage as RW-ROP positive in images. All the statistical analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC), and p -value <0.05 was considered to be statistically significant.

Results

Incidence and Characteristics of Hemorrhage

Among 7905 image sets from 1239 pre-term infants (mean (SD) BW=864 (212) g, GA=27(2.2) weeks), 267 (21.5%) infants had IOH in at least one eye in any one of the imaging visits. The mean (SD) number of imaging sessions per infant was 3.2 (2.0) (median, 3; range, 1–12) and 36% had 4 or more imaging sessions. The mean (SD) postmenstrual age (PMA) of infants when IOH was first identified was 34.7 (2.1) weeks ranging from 32 weeks to 40 weeks PMA. Preretinal (57%) and blot (57%) IOH were the most frequent types followed by dot (38%), flame-shaped (16%) and vitreous (8%) (Table 2). The majority of IOH (56%) were identified during the first imaging session while 26% were identified in the second image session. The presence of IOH over time stratified by the number of image sessions is given in Table 3 available at <http://aaojournal.org>.

At the first detection of IOH, the majority of IOH (78%) presented as a single type; preretinal (32%), blot (23%), dot (20%), vitreous (2%) and flame shaped (1%). In 19% of eyes there was a combination of two types of hemorrhage including blot and preretinal (8%), dot and blot (5%), blot and flame (3%), dot and preretinal (2%) and blot and vitreous (1%). Fewer than 4% of eyes presented with a combination of three or more types of IOH. When IOH were first identified at any visit, they were predominantly unilateral (83%) and when all imaging sessions were taken into account 70% were unilateral. Forty-one percent of IOH occurred in zone I only, 35% in zone II only and 24% in both zones. In zone I, the majority of IOH was observed in the nasal (57%) region followed by the temporal (55%), superior (45%) and inferior (36%) regions. In zone II, most IOH were observed in the temporally (69%) with the remainder in the nasal (30%), superior (23%) and inferior (21%) areas. Flame (92%) and dot (83%) IOH were observed mostly in zone I, while preretinal IOH were observed predominantly in zone 2 (88%), mostly associated with ROP. Non-dot hemorrhages had a mean (SD) disc area of 1.1 (2.6) and a median (1st quartile, 3rd quartile) of 0.40 (0.2, 1.1). Reader assessment on the 100 image sets that were presumed not to have IOH during earlier diagnostic or image evaluations disclosed that 9 of them had IOH with the majority being dot hemorrhages.

Risk factors of IOH

In multivariate analysis that included the BW, GA, race and respiratory status (Table 4), lower BW was significantly associated with a higher incidence of IOH ($p<0.001$, Figure 2a).

Similar associations were observed in blot ($p<0.001$), preretinal ($p<0.001$) and flame shaped IOHs ($p=0.03$), but were not significant for dot IOH ($p=0.07$) or vitreous IOH ($p=0.66$). The adjusted multivariate regression for blot and preretinal IOH with birth weight are shown in Table 5 available at <http://aaojournal.org>. Similarly, IOH had a significant association with lower GA ($p<0.001$, Figure 2b). This dose-response relationship was maintained for blot ($p<0.001$) and preretinal IOHs ($p<0.001$) but not the other types. The adjusted multivariate regression values for blot and preretinal IOH with gestational age are shown in Table 5 available at <http://aaojournal.org>. Respiratory status of the infant was associated with IOH in the univariate analysis, but this association was not significant after adjusting for BW, GA and race. White infants had more IOH (25%) than African-American infants (15%, $p<0.001$). Male infants had more vitreous type of IOH than female infants (2% vs 1%, $p=0.04$) after adjusting by BW, GA and race.

Resolution of IOH

Among eyes undergoing a subsequent imaging session after initial detection of IOH, 35% resolved completely by the next imaging session. Flame-shaped IOH resolved most frequently (79%) followed by blot (52%), preretinal (46%), dot (41%) and vitreous (38%). The Kaplan-Meier estimates for the cumulative proportion of IOH resolution over time for any IOH and by type of retinal IOH are shown in Table 6 and examples of resolution of IOH are given in Figure 3. Overall, the rate of resolution was 21% in the first week, 38% the second week, 48% by the third week, and 76% by week 8 (Figure 4, available <http://aaojournal.org>). Vitreous and dot IOHs resolved more slowly than flame-shaped or preretinal IOH. Flame IOH resolved in all eyes by week 4. By 8 weeks, majority of blot (86%), preretinal (98%) and blot (79%) IOH had resolved (Table 6).

Predictive Value for RW-ROP

As shown in table 7, the presence of any ROP was nearly 2.5 times more likely to occur in an eye with IOH after adjusting BW and GA, increasing to 10–12 times more likely in an eye with preretinal or vitreous IOH. RW-ROP was 3 times more likely to occur in eyes with any IOH and approximately 5 times more likely in eyes with preretinal or vitreous IOH. The BW and GA adjusted OR for any ROP in an eye with IOH in zone II only was 7.01 ($p<0.05$) but was not significant for eyes with IOH in zone I. However, for eyes with IOH in zones 1 and 2 both, the OR for any ROP was 6.85. Larger areas of hemorrhages were associated with higher presence and more severe forms of ROP in a dose response manner. Compared to eyes without IOH, the odds ratios associated with hemorrhage size of <1 DA, 1 to 2 DA and >2 DA were 3.6, 4.4 and 5.2 respectively for presence of ROP, 3.1, 4.1 and 8.5 respectively for RW-ROP. The sensitivity of the telemedicine system for detecting RW-ROP increased slightly by incorporating the presence of IOH in the grading protocol determination of RW-ROP positive in the images. Considering IOH presence at any imaging session in an eye, the sensitivity of the system increased from 90% to 92% and specificity decreased from 84% to 79%; considering any imaging session per infant, sensitivity increased from 94% to 95%, but the corresponding specificity decreased from 80% to 73% (Table 8). Similarly, considering only hemorrhage associated with vascular/avasascular junction did not change much the sensitivity and specificity of the telemedicine system (Table 8). Eyes ($n=34$ eye sessions) captured with RW-ROP after considering IOH were

more likely to have only a single RW-ROP component (91%) in comparison to 67% in the eyes that detected RW-ROP without considering hemorrhage ($p=0.004$), less likely to have stage 3 or above ROP (77% vs. 88%, $p=0.048$) and less likely to have plus disease (15% vs. 32%, $p=0.03$).

Discussion

The rate of IOH in this study was higher than other large studies.^{9,10} A retrospective study of 194 pre-term infants with GA <32 weeks and BW <1500 g cared for in a neonatal intensive care unit (NICU) over a period of nine years (1992–2000) with ophthalmological examinations starting at the 4th week of life reported 7.7% of infants with IOHs. This lower rate could have resulted from the inclusion of infants between 1250g and 1500g or because data were extracted retrospectively from diagnostic examinations.¹⁰

However, IOHs have been observed in a number of studies in newborn full-term infants, with ranges of 3% to 50%.^{1–3,15,16} A study of 149 newborn infants without known or suspected systemic or ocular disease examined within 30 hours after birth reported a retinal IOH prevalence of 34%.²⁰ Paradoxically, the prevalence of IOH in pre-term infants appears to be less than that observed in newborn full-term infants. Some of this difference could be explained by the transient nature of these IOH and the variable time period between birth and the fundus photography or clinical examination. Since imaging in the e-ROP study was not done until well after birth, it is reasonable that at least some of the IOH had resolved.

In contrast to full-term newborn infants (reported prevalence of 59% for bilateral IOH), bilateral IOH in this study occurred in just under one third of infants at any point in time, a finding similar to a previous study of pre-term infants.^{1,10,15}

Limitations of this study include not having data related to maternal health and lack of information on the mode of delivery and Apgar status of the infant at birth. The first imaging session was performed at variable postnatal ages, as would be expected in any ROP surveillance program, but still this is an independent variable. It is also likely that we underestimated the prevalence of IOH as not all the e-ROP image sets were evaluated for the detection of IOH in this study, only those that had been documented as having IOH previously. Additionally, 9 of 100 image sets randomly selected for re-reading were observed to have IOH when they were not documented as having one earlier, though most were dot hemorrhages. Strengths of the study include the large number of infants with <1251g BW and the systematic examination of standardized digital image sets by trained and certified non-physician readers and the comprehensive evaluation of IOH characteristics.

In summary, one in five pre-term infants with BW <1251g present with IOH at the time of ROP examination, and approximately 1 in 3 of these infants develop bilateral IOH at some point. IOH are detected on average at 34–35 weeks PMA. Most IOH are blot or preretinal, unilateral, and more likely to be present in lower BW and lower GA infants of white ethnicity. Resolution of IOH, as in full-term infants, takes place within a few weeks. IOH are strongly associated with both the presence and severity of ROP, especially when they are preretinal or vitreous. Adding the presence of IOH to the reading algorithm only minimally

increased the sensitivity of this telemedicine system to detect RW-ROP. Nevertheless, even incremental improvements in sensitivity may be valuable in a disease with a relatively rapid temporal profile and potentially severe visual consequences. In addition, the relative ease of identification of IOH and the minimal cost to the system that would incur with this modification may lend credence to such a change.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
(A) Dot hemorrhages (blue arrows). (B) Flame shaped hemorrhages (green arrows) and Blot hemorrhages (yellow arrows). (C) Preretinal hemorrhages adjacent to the retinopathy of prematurity (red arrow). (D) Vitreous hemorrhage (violet arrow).

Figure 2.
Percentage of any intraocular hemorrhage by birth weight and by gestational age.

Figure 3.

Examples of resolution and persistence of retinal hemorrhages. (A1) Blot hemorrhage observed on 7/10/12 resolve completely (A2) on 7/18/12 and no hemorrhages are observed on the third visit (A3) on 7/24/12. (B1) No hemorrhage at initial image session on 10/01/12. (B2) At the subsequent imaging visit on 10/15/12 there are several blot and flame shaped hemorrhages. (B3) At the third imaging visit on 10/29/12 complete resolution of all hemorrhages is observed. (C1) Preretinal hemorrhage at the ridge inner posterior border on 7/19/12 that (C2) persists in a location slightly away from the ridge on 8/7/12 with (C3) the distance between the persisting hemorrhage and the ridge increased when observed on 8/14/12.

Table 2

Presence and type of intraocular hemorrhage at any imaging session

	Number of eyes	Number of babies
Any type of hemorrhage		
No	2127 (86%)	972 (78.46)
Yes	347 (14%)	267 (21.54%)
Specific type of hemorrhage among those with hemorrhage		
Dot (%)	127 (36.60%)	102 (38.20%)
Blot (%)	192 (55.33%)	152 (56.93%)
Flame (%)	46 (13.26%)	42 (15.73%)
Pre-retinal (%)	192 (55.33%)	153 (57.30%)
Vitreous (%)	23 (6.63%)	20 (7.49%)

Univariate and multivariate analysis for risk factors associated with any intraocular hemorrhage in premature infants with birth weights 1500g

Table 4

Risk Factors	N	Any hemorrhage (%)	Unadjusted Analysis		Adjusted Analysis*	
			Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Birth weight (grams)				<0.001		<0.001
<= 500	42	18 (43%)	1.00		1.00	
501–750	379	136 (36%)	0.75 (0.39, 1.42)		0.72 (0.36, 1.42)	
751–900	267	57 (21%)	0.36 (0.18, 0.71)		0.48 (0.23, 1.01)	
901–1000	180	29 (16%)	0.26 (0.12, 0.53)		0.41 (0.18, 0.93)	
1001–1100	164	17 (10%)	0.15 (0.07, 0.34)		0.27 (0.11, 0.66)	
1101–1250	207	10 (5%)	0.07 (0.03, 0.16)		0.13 (0.05, 0.34)	
Gestational Age (weeks)				<0.001		<0.001
<= 23	82	38 (46%)	1.00		1.00	
24	154	65 (42%)	0.85 (0.49, 1.45)		0.88 (0.50, 1.55)	
25	191	46 (24%)	0.37 (0.21, 0.63)		0.42 (0.23, 0.75)	
26	214	45 (21%)	0.31 (0.18, 0.53)		0.38 (0.21, 0.69)	
27	199	35 (18%)	0.25 (0.14, 0.44)		0.44 (0.23, 0.85)	
28	172	17 (10%)	0.13 (0.07, 0.25)		0.26 (0.12, 0.57)	
29	92	12 (13%)	0.17 (0.08, 0.37)		0.39 (0.17, 0.90)	
>= 30	135	9 (7%)	0.08 (0.04, 0.18)		0.23 (0.09, 0.61)	
Race				<0.001		<0.001
White	696	177 (25%)	1.00		1.00	
Black	380	56 (15%)	0.51 (0.36, 0.71)		0.40 (0.28, 0.57)	
Others	163	34 (21%)	0.77 (0.51, 1.17)		0.87 (0.55, 1.36)	
Respiratory status				<0.001		0.08
No respiratory support	353	43 (12%)	1.00		1.00	
High Frequency Oscillatory Ventilation	13	3 (23%)	2.16 (0.57, 8.17)		0.57 (0.13, 2.41)	

Risk Factors	N	Any hemorrhage (%)	Unadjusted Analysis		Adjusted Analysis*	
			Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Controlled mechanical Ventilator	146	58 (40%)	4.75 (3.00, 7.53)		1.78 (1.05, 3.03)	
CPAP/NIPPV/HFNC >2 liters**	351	88 (25%)	2.41 (1.62, 3.60)		1.00 (0.63, 1.59)	
Nasal canula (<= 2 liters)	364	73 (20%)	1.81 (1.20, 2.72)		1.00 (0.64, 1.57)	
Other/Unknown	12	2 (17%)	1.44 (0.31, 6.80)		0.51 (0.10, 2.62)	

* From multivariate logistic regression with birth weight, gestational age, race and respiratory status.

** CPAP= Continuous Positive Airway Pressure HFNC=High Flow Nasal Cannula, NIPPV=Nasal Intermittent Positive Pressure Ventilation

Table 6

Resolution of intraocular hemorrhage over time

Intraocular hemorrhage	Number of eyes	Kaplan-Meier estimate of cumulative proportion of hemorrhage resolved (95% CI) *					
		Day 7	Day 14	Day 21	Day 28	Day 42	Day 56
Any hemorrhage	266	0.21 (0.17, 0.27)	0.38 (0.33, 0.45)	0.48 (0.42, 0.55)	0.56 (0.49, 0.64)	0.72 (0.63, 0.80)	0.76 (0.66, 0.85)
Any hemorrhage except dot	219	0.24 (0.19, 0.30)	0.43 (0.37, 0.51)	0.56 (0.48, 0.63)	0.63 (0.55, 0.71)	0.80 (0.70, 0.88)	0.84 (0.74, 0.92)
Dot	103	0.24 (0.17, 0.34)	0.40 (0.31, 0.50)	0.53 (0.42, 0.64)	0.68 (0.57, 0.79)	0.79 (0.66, 0.90)	0.79 (0.66, 0.90)
Blot	155	0.30 (0.23, 0.38)	0.55 (0.47, 0.64)	0.70 (0.61, 0.78)	0.77 (0.68, 0.84)	0.83 (0.73, 0.90)	0.86 (0.76, 0.94)
Flame	33	0.30 (0.18, 0.49)	0.67 (0.50, 0.83)	0.96 (0.84, 1.00)	1.00	1.00	1.00
Pre-retinal	134	0.32 (0.25, 0.41)	0.57 (0.49, 0.66)	0.73 (0.64, 0.81)	0.79 (0.70, 0.87)	0.98 (0.90, 1.00)	0.98 (0.90, 1.00)
Vitreous	13	0.23 (0.08, 0.56)	0.42 (0.20, 0.74)	0.62 (0.35, 0.88)	0.62 (0.35, 0.88)	0.62 (0.35, 0.88)	0.62 (0.35, 0.88)

* 95% CI = 95% Confidence Interval

Table 7

The association of intraocular hemorrhage with any ROP, Stage 3 ROP and RW-ROP*

	Adjusted Odds ratio (95% CI)**		
	Any ROP	Stage 3 ROP	RW-ROP
Presence of hemorrhage***			
Any type	2.46 (1.79, 3.38)	2.88 (2.15, 3.86)	3.19 (2.44, 4.17)
Non-dot hemorrhage	3.80 (2.69, 5.37)	3.28 (2.42, 4.45)	3.70 (2.79, 4.90)
Blot	2.74 (1.83, 4.11)	1.77 (1.15, 2.71)	2.27 (1.61, 3.20)
Flame	2.28 (0.87, 5.97)	1.10 (0.45, 2.66)	1.45 (0.69, 3.03)
Preretinal	12.6 (6.21, 25.6)	4.40 (3.15, 6.14)	4.85 (3.50, 6.72)
Vitreous	9.92 (2.58, 38.1)	3.24 (1.61, 6.51)	5.40 (2.18, 13.4)
Location of any hemorrhage			
Zone I only	1.34 (0.88, 2.03)	1.81 (1.12, 2.94)	2.26 (1.45, 3.52)
Zone II only	7.01 (3.71, 13.25)	4.62 (3.22, 6.62)	4.38 (3.05, 6.29)
Both Zone I and Zone II	6.85 (3.59, 13.10)	2.53 (1.65, 3.89)	3.23 (2.27, 4.60)
Size of any hemorrhage (Disc Area)			
<1	3.55 (2.42, 5.19)	2.84 (2.02, 4.01)	3.10 (2.27, 4.22)
1–2	4.44 (1.98, 9.95)	3.95 (2.42, 6.44)	4.09 (2.56, 6.54)
>2	5.22 (1.54, 17.72)	6.72 (4.08, 11.06)	8.52 (5.31, 13.68)

* ROP = Retinopathy of Prematurity, RW-ROP = Referral Warranted Retinopathy of Prematurity.

** From multivariate logistic regression model with adjustment of birth weight and gestational age, as compared to infants without intraocular hemorrhage. 95%CI = 95% Confidence Interval

*** An eye can have more than one type of hemorrhage

Table 8

The sensitivity and specificity for detecting RW-ROP with and without considering intraocular hemorrhage in retinal images as being RW-ROP positive

	Sensitivity (95% CI)	Specificity (95% CI)
Cross-sectional all session, per eye analysis		
Not considered hemorrhages	0.78(0.75, 0.81)	0.85(0.84, 0.86)
Considered hemorrhages	0.82(0.79, 0.85)	0.80(0.79, 0.81)
Only considered hemorrhages associated with vascular/avascular junction	0.80(0.77, 0.82)	0.84(0.83, 0.85)
Only considered preretinal hemorrhages posterior to ROP	0.79(0.76, 0.81)	0.85(0.84, 0.85)
Only considered preretinal hemorrhages anterior to ROP	0.79(0.76, 0.82)	0.84(0.83, 0.85)
Only considered at least two types of hemorrhages	0.79(0.76, 0.82)	0.84(0.83, 0.85)
Any session, per eye analysis		
Not consider hemorrhages	0.90(0.87, 0.92)	0.84(0.82, 0.85)
Consider hemorrhages	0.92(0.89, 0.94)	0.79(0.77, 0.81)
Only considered hemorrhage associated with vascular/avascular junction	0.91(0.88, 0.93)	0.83(0.82, 0.85)
Only considered preretinal hemorrhages posterior to ROP	0.90(0.87, 0.93)	0.84(0.82, 0.85)
Only considered preretinal hemorrhages anterior to ROP	0.90(0.87, 0.93)	0.84(0.82, 0.85)
Only considered at least two types of hemorrhages	0.91(0.88, 0.93)	0.83(0.81, 0.84)
Any session, per infant analysis		
Not consider hemorrhages	0.94(0.90, 0.96)	0.80(0.78, 0.83)
Considered hemorrhages	0.95(0.92, 0.97)	0.73(0.70, 0.76)
Only considered hemorrhages associated with vascular/avascular junction	0.95(0.91, 0.97)	0.80(0.77, 0.82)
Only considered preretinal hemorrhages posterior to ROP	0.95(0.91, 0.97)	0.80(0.77, 0.82)
Only considered preretinal hemorrhages anterior to ROP	0.94(0.90, 0.96)	0.80(0.78, 0.83)
Only consider at least two types of hemorrhages	0.95(0.91, 0.97)	0.79(0.76, 0.81)

ROP = Retinopathy of Prematurity, RW-ROP = Referral Warranted Retinopathy of Prematurity.
95%CI = 95% Confidence Interval