Original Article

Retinal immaturity at first screening and retinopathy of prematurity: Image-based validation of 1202 eyes of premature infants to predict disease progression

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Purpose: To use the extent of retinal immaturity at the first visit to predict progression to any stage and treatment-requiring retinopathy of prematurity (ROP). **Methods:** Retrospective, multicenter, nonrandomized, observational, clinical, validation study. In all, 601 Asian Indian preterm infants born < 2000 g and/or < 34 weeks of gestation completing ROP screening with RetCam images taken during each visit were included. A total of 1202 eyes of these infants were classified into three groups based on the retinal immaturity at the first screening visit into "mild" (Group 1), vessels reaching the posterior boundary of zone 3; "moderate" (Group 2), vessels entering zone 2 anterior; and "severe" (Group 3), vessels in zone 1 or zone 2 posterior. RetCam images at each subsequent visit were evaluated and the proportion of eyes that progressed to Type 1 or Type 2 ROP was correlated with the degree of retinal immaturity. **Results:** Of the 958 eyes in Group 1, 200 eyes in Group 2, and 44 eyes in Group 3, any stage ROP developed in 15% of eyes in Group 1, 46.5% of eyes in Group 2, and 100% of eyes in Group 3 ($P < 0.001$). Sixteen of 128 eyes (12.5%), 12 of 72 (16.6%), and 28 of 44 of eyes (63.6%) in Groups 1, 2, and 3, respectively, required treatment ($P < 0.001$). **Conclusion:** Retinal immaturity at first screening visit predicts Type 1 and Type 2 ROP. "Severe" immaturity is more likely to progress to "treatment-requiring" disease. This could be a useful tool for prognostication, counseling, and scheduling follow-up.

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Over 30 years ago, the International Classification of Retinopathy Of Prematurity (ICROP) provided an objective approach to diagnose retinopathy of prematurity (ROP), a disease of premature infants in which vascularization of the retina is incomplete or "immature," progressing to more advanced stages in some.[1] Wide-field imaging has made it possible to accurately document the retina upto the ora serrata to categorize ROP and study its outcome.[2,3]

The ROP classification was revisited over a decade ago, receiving a more robust and technical definition.[2] However, the precursor of ROP, namely, the extent of "immaturity" of the retina, has never been the focus. The progressive tapering of the retinal blood vessels in the absence of disease characterizes immature retina. The ICROP classification has defined incompletely vascularized retina as "immature" with no further subdivision.[2] There has been no quantification, stratification, or classification of the degree of avascularity that precedes the development of ROP despite the clinical reality that infants present with different extents of avascularity. This provides little prognostic value in predicting which of the infants with "immature" retina would progress to treatment-requiring disease and which ones would resolve spontaneously.

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In this report, we evaluate the feasibility of predicting the course of ROP by classifying "disease-free," "immature" retina on the *first* screening visit documented using wide-field imaging. We aimed to study the correlation between the "severity of immaturity" and progression to disease, which would allow more intuitive follow-up and prognostication. Using this clinical validation, based on 1202 eyes, we discuss its clinical utility in helping to predict which babies may progress to Type 1 or Type 2 ROP and hence help in prognostication and follow-up.

Methods

This is a retrospective, multicenter, nonrandomized, observational, clinical validation study that was performed using the image database of the Karnataka Internet Assisted Diagnosis of Retinopathy of Prematurity (KIDROP) multicenter tele-ROP network.[4-11] The KIDROP program and the study have met the approval of the Institute Research Board and the Institute Ethics Committee, and informed consents were obtained from the parents or guardians of all cases enrolled,

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analyzed, or treated. The study adhered to the tenets of the Declaration of Helsinki.

KIDROP currently performs tele-ROP screening in 104 neonatal units situated in rural, semi-urban, and urban areas of 30 districts of the south Indian state of Karnataka. Infants born ≤2000 g and or ≤34 weeks of gestation are enrolled into the program.[5,6,9] Inclusion criteria for this study included those infants who had completed the mandated ROP screening visits as per the national guidelines,[12] with the eyes having been imaged using a modified PHOTO-ROP protocol with a minimum of seven images (dilated anterior segment, disc, and macula center, and the four peripheral quadrants with the ora serrata included) on all visits. A RetCam Shuttle (Clarity MSI, USA) was used to obtain images of infants from these centers by a trained and accredited Level III technician during the study period of July 2013–December 2014.[6]

The "first visit" images of 601 Asian Indian premature infants (1202 eyes) were retrieved from the KIDROP server database. Images of the first visit which demonstrated an "immature" retina alone with no evidence of any stage of ROP were selected. The rest of the images of these patients were also retrieved from the database, and the details of the course of the disease and patient demographics were collated on a Microsoft Excel worksheet (Microsoft Corporation, Redmond, WA, USA). The 601 infants had a median of four screening visits. Each visit had a median of 14 images per session. Of the 38,656 images retrieved, 135 images were discarded (0.35%), and the rest were reviewed and analyzed.

Based on the appearance of the first visit images of these enrolled infants, we classified the extent of immaturity of the retina as mild (Group 1), moderate (Group 2), and severe temporal avascular retina (TAR) (Group 3). Fig. 1 shows the schematic representation and Fig. 2 the clinical (RetCam) image. "Mild" retinal immaturity [Figs. 1a and 2a] denoted that the retinal vessels were detected upto the posterior border of zone 3 (as defined by the ICROP classification) in the temporal quadrant, "moderate" immaturity denoted the intervening areas, where the retinal vessels had tapered and stopped at zone 2 anterior [Figs. 1b and 2b], and "severe" TAR denoted that the primary posterior pole vessels had grown to the edge of zone 1 or zone 2 posterior [Figs. 1c and 2c].

After dividing the cohort into the above three groups, all serial follow-up visits of these babies were reviewed by two ROP specialists, masked to the group order to determine whether these babies had reached (during any subsequent visit) treatment-requiring ROP (Type I ROP), any stage ROP (Type II ROP), or vascularized spontaneously without developing any ROP. The outcome of these groups was then correlated with group order to determine whether the initial presentation could predict the final outcome by studying the association of the first visit immaturity with the final outcome. The secondary outcome of the study was to correlate the group order with the number of screening visits that the infant had undergone before the infant was discharged from the ROP screening program.

Statistical analysis

Descriptive statistics included mean and standard deviation for normally distributed variables and median and interquartile range (IQR) for non-normally distributed variables. Associations between the grades of immaturity and the outcome measures, namely, the presence of disease and the need for treatment, were evaluated in separate logistic regression models. Multivariate logistic regression models also included known risk factors associated with the outcome measures, namely, the birth weight, period of gestation, postmenstrual age (PMA), and gender. Statistical analyses were performed using a commercial software (Stata ver. 13.0; StataCorp, College Station, TX, USA). A P value of ≤ 0.05 was considered statistically significant in the multivariate regression models.

Results

Study cohort demographics

During the study period of 18 months, 1202 eyes of 601 premature infants fulfilling the inclusion criteria were enrolled for analysis. The mean birth weight was 1385 ± 290 g. The mean gestational age was 31.5 ± 2.5 weeks. The mean PMA at first screening was 35.58 ± 2.4 weeks. The distribution of the study groups with respect to the birth weight, gestational age, PMA, and the number of screening visits is summarized in Table 1. The mean birth weight was found to be 1419 ± 274 g in Group 1, 1435 ± 308 in Group 2, and 1219 ± 290 in Group 3 ($P < 0.05$, one-way analysis of variance test). After applying Bonferroni's correction, the difference in means was found to be significant between mild and moderate versus severe but not between mild and moderate groups. The mean gestational age was found to be significantly different between the three groups: 32.2 ± 2.5 in Group 1, 31.1 ± 2.1 in Group 2, and 30.0 ± 2.6 in Group 3 ($P < 0.05$). *Post hoc* analysis noted a significant difference only between mild versus moderate and severe ($P < 0.001$) but not between moderate and severe ($P = 0.241$).

ROP distribution

Any stage ROP developed in 15% of eyes in Group 1, 46.5% of eyes in Group 2, and 100% of eyes in Group 3 during the entire follow-up period. While only 16 of 128 eyes (12.5%) in Group 1 required treatment, 12 of 72 (16.6%) and 28 of 44 of eyes (63.6%) in Groups 2 and 3, respectively, required treatment during their follow-up. Median (with IQR in brackets) number of visits in Group 1 was 4 (3–4), Group 2 was 4 (4–5), and Group 3 was 10 (8–11). Multivariate logistic regression evaluating the associations between birth weight, gender, PMA, grade of immaturity, and number of visits with the presence of disease and need for treatmentis represented in Table 2. The results show that lower birth weight and lower PMA had greater odds of developing disease and requiring treatment. Lower birth weight was also associated with a greater number of visits. Male children had greater odds of developing disease and requiring treatment and needed more number of visits.

Predicted probability versus level of immaturity

Grade of immaturity at first visit showed a positive association with the development of disease, need for treatment, and higher number of visits, when adjusted for the other confounders (birth weight and PMA). The more severe the grade of immaturity at first visit, the greater the odds of developing disease and requiring treatment. Overall, predicted probability of developing any stage disease, according to our regression model, was 14% (12%–16%) in Group 1, 36% (30%–42%) in Group 2, and 67% (55%–77%) in Group 3. Similarly, predicted probability of requiring treatment, according to our regression model, was 1% (0%–2%) in Group 1, 5% (3%–9%) in Group 2, and 25% (13%–42%) in Group 3. In addition, the more severe

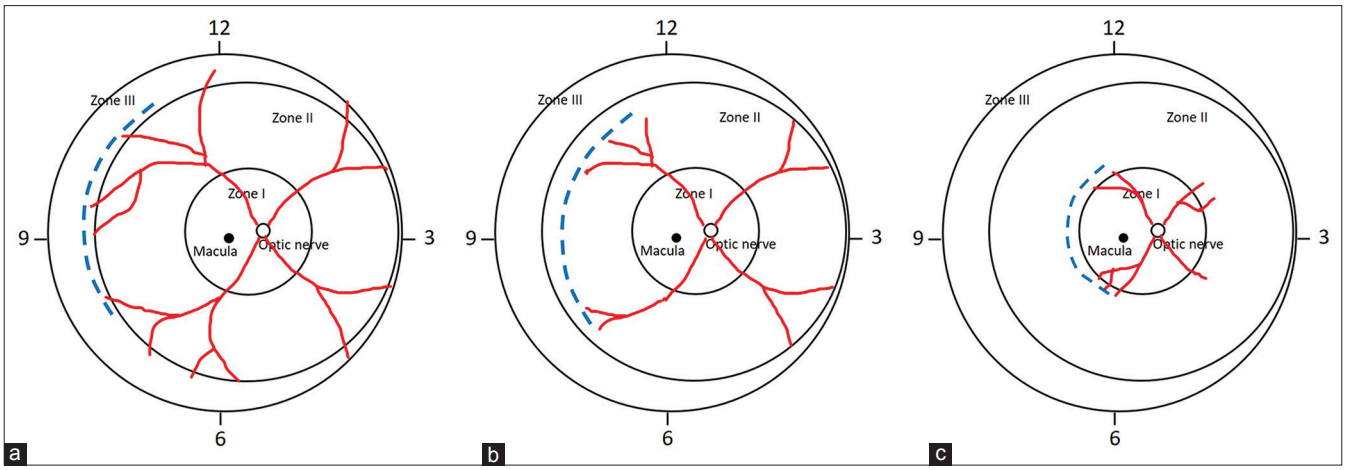

Figure 1: Schematic diagram representing (a) "mild" retinal immaturity (Group 1) in which the retinal vessels are detected up to the posterior border of zone 3 in the temporal quadrant, (b) "moderate" retinal immaturity (Group 2) in which the retinal vessels have tapered and stopped at zone 2 anterior, and (c) "severe" retinal immaturity (Group 3) in which the primary posterior pole vessels have grown to the edge of zone 1 or zone 2 posterior

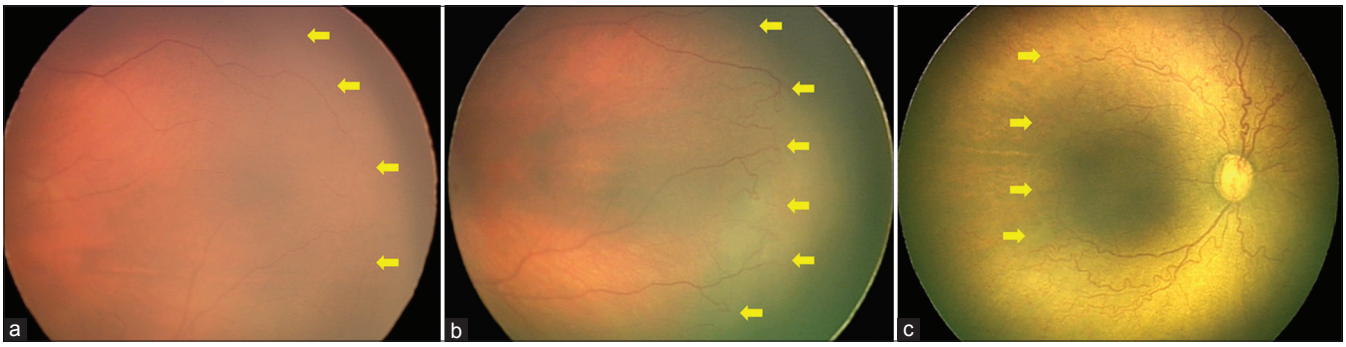

Figure 2: Clinical (RetCam) image describing (a) "mild" retinal immaturity (Group 1) in which the retinal vessels are detected up to the posterior border of zone 3 in the temporal quadrant, (b) "moderate" retinal immaturity (Group 2) in which the retinal vessels have tapered and stopped at zone 2 anterior, and (c) "severe" retinal immaturity (Group 3) in which the primary posterior pole vessels have grown to the edge of zone 1 or zone 2 posterior

the grade of immaturity, the greater the number of follow-up visits. The predicted number of visits in Group 1 was 4, Group 2 was 5, and Group 3 was 7.

Furthermore, we assessed the predicted probability of developing ROP at various birth weights and PMA according to the severity of immaturity [Fig. 3a and b]. Thus, the predicted probability of developing disease, according to our model, for an infant with a birth weight of 1500 g was 15% [95% confidence interval (CI): 13%–17%] in Group 1. This increased to 35% (28%–42%) in Group 2. The probability of developing ROP in Group 3 was 100% irrespective of the birth weight. Similarly, the probability of developing ROP according to our model for a child with a PMA of 36 weeks was 14% (95% CI: 12%–16%) in Group 1. This increased to 28% (21%–37%) in Group 2. The probability of developing disease in Group 3 was 100% irrespective of the PMA.

Case illustrations

Example 1: A male infant born at 28 weeks with 1050 g of weight had "severe TAR" (Group 3 immaturity) at 30 weeks PMA [Fig. 4a], progressed to pre-plus at 32 weeks PMA [Fig. 4b] and further to aggressive posterior ROP (APROP) at 33 weeks PMA [Fig. 4c]. This was subsequently treated with laser resulting in a favorable outcome [Fig. 4d].

Example 2: A female infant born at a gestational age of 32 weeks and 1350 g was first screened at 34 ± 5 PMA [Fig. 5a] and had severe TAR (Group 3 immaturity). Three weeks later at PMA of 37 ± 5 weeks, the infant developed stage 3 ROP in zone 1 with plus disease [Fig. 5b], which successfully resolved after laser treatment [Fig. 5c].

Example 3: A male infant born at a gestational age of 32 weeks and 1350 g of weight first presented with moderate TAR (Group 2 immaturity) at a PMA of 35 weeks, which progressed to Type 2 ROP at 38 weeks PMA which spontaneously resolved [Fig. 6 a-d].

Discussion

Immature retina, the precursor of ROP in preterm infants, has not been adequately categorized. The definition of "immature retina" according to the ICROP classification has been restricted to the "absence of disease marked by the progressive tapering of retinal bloods vessels stopping short of the ora serrata."[1,2] The clinical relevance of retinal immaturity may be summarized

as follows: (1) The degree of immaturity can extend from the posterior pole to a small, residual area in zone 3. Although these extremes receive an identical nomenclature of "immature retina," it is obvious that these do not have a similar clinical connotation in the real-world scenarios. (2) The extent of retinal immaturity correlates with the gestational and postnatal

Table 1: Distribution of 1202 eyes with respect to birth weight, gestational age, postmenstrual age at disease, and number of visits

	No. of eyes	Birth weight (g)	Mean±SD birth weight (g)	Gestational age (weeks)	Mean±SD Gestational age (weeks)	PMA at disease (weeks)	Mean±SD PMA at disease (weeks)	No. of visits	Mean±SD no. of visits
Total	1202		1385±290		31.5±2.5		35.58±2.4		6.7±2.5
Group 1 Mild TAR (958 eyes)	Type 1 ROP 16, 12.5%	1362±167	1419±274	30.6±1.8	32.2±2.5	35.3±1.9	38.2±2.9	9.5	5.9±1.8
	Type 2 ROP 128, 15%	1424±282		32.4±2.5		38.5±2.8		5	
Group 2 Moderate TAR (200 eyes)	Type 1 ROP 12, 16.6%	1650±243	1435±308	30±2.3	31.12±2.1	34.5±1.7	36.8±2.1	10	6.3±2.4
	Type 2 ROP 72, 46.5%	1420±309		31.2±2.0		36.9±2.1		6	
Group 3 Severe TAR (44 eyes)	Type 1 ROP 28, 63.6%	1213±273	1219±290	30.5±2.6	30±2.6	35.8±2.3	35.8±2.4	10.5	9.61±2.3
	Type 2 ROP 44, 100%	1229±219		29.9±2.7		35.7±2.5		9	

SD=Standard deviation; PMA=Postmenstrual age; TAR=Temporal avascular retina

Table 2: Multivariate logistic regression evaluating the associations between birth weight, gender, postmenstrual age, grade of immaturity, and number of visits with the presence of disease and need for treatment

	Presence of disease		Need of treatment		No. of visits	
	OR (95% CI)	*P*	OR (95% CI)	*P*	Coefficient (95% CI)	*P*
Birth weight	0.99 (0.99, 1.00)		0.99 (0.99, 1.00)	0.05	−0.001 (−0.001, −0.001)	<0.001
Male child	1.39 (1.01, 1.91)	0.05	2.51 (1.22, 5.18)	0.01	0.24 (0.07, 0.41)	0.01
Postmenstrual age	0.88 (0.82, 0.94)	<0.001	0.78 (0.67, 0.91)	0.001	−0.23 (−0.27, −0.20)	<0.001
Grade of immaturity	3.57 (2.68, 4.75)	<0.001	5.82 (3.71, 9.13)	<0.001	1.49 (1.31, 1.66)	<0.001

OR=Odds ratio; CI=Confidence interval

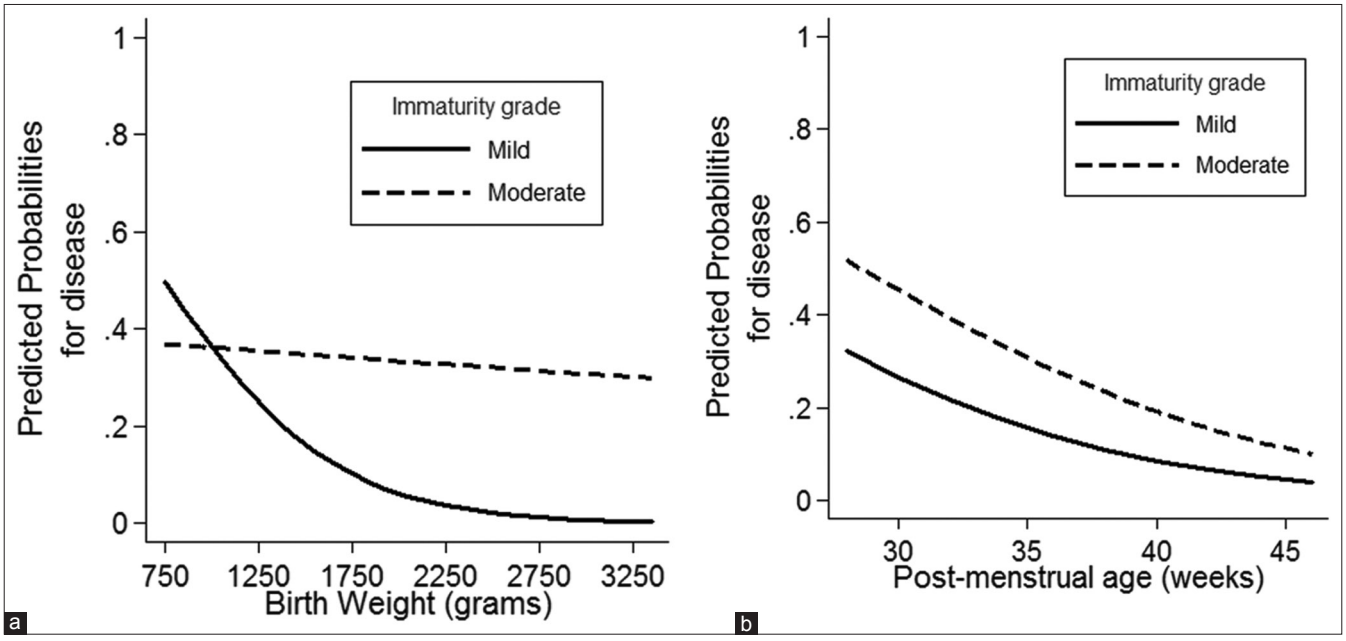

Figure 3: Results of multivariate logistic regression models showing the predicted probability of disease at (a) different birth weights according to the grades of retinal immaturity and (b) different postmenstrual ages according to the grades of retinal immaturity

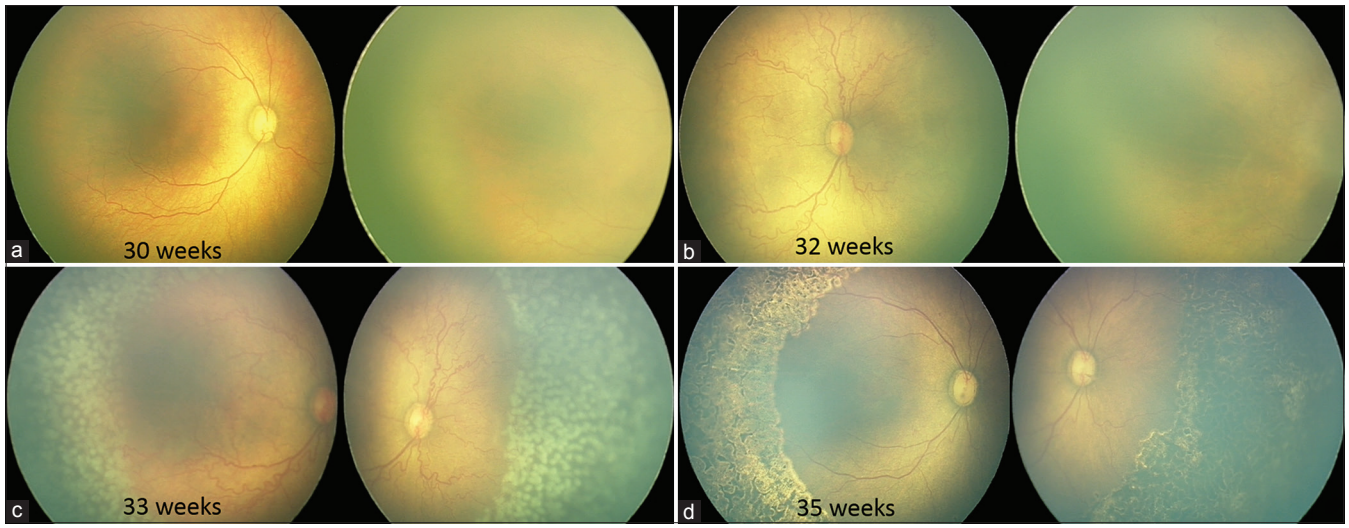

Figure 4: (a) An infant born at 28 weeks with 1050 g of weight had severe temporal avascular retina at 30 weeks, (b) progressed to pre-plus at 32 weeks, (c) aggressive posterior retinopathy of prematurity at 33 weeks, and (d) which then responded to laser treatment (35 weeks)

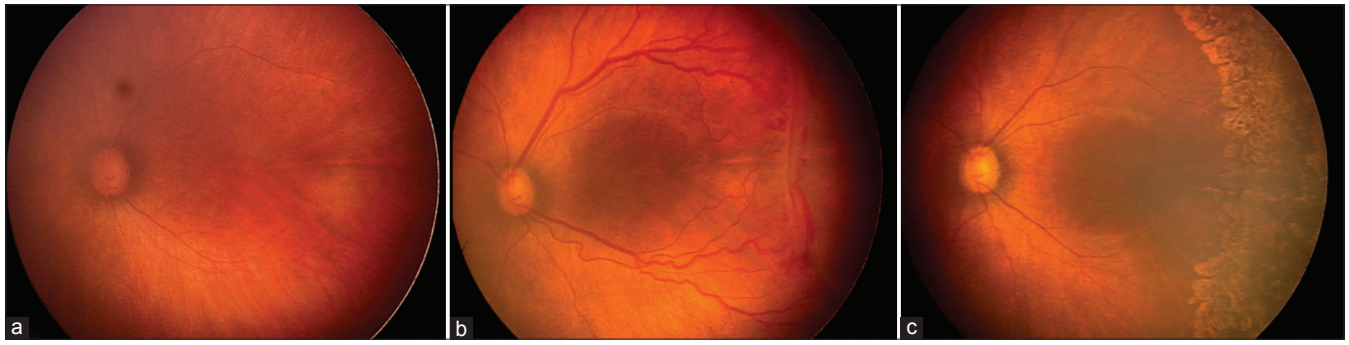

Figure 5: (a) An infant born at 32 weeks with 1350 g of weight first seen at 34 ± 5 PMA had severe temporal avascular retina, (b) 3 weeks later the infant developed stage 3 retinopathy of prematurity in zone 1 with plus disease, and (c) which successfully resolved after laser treatment

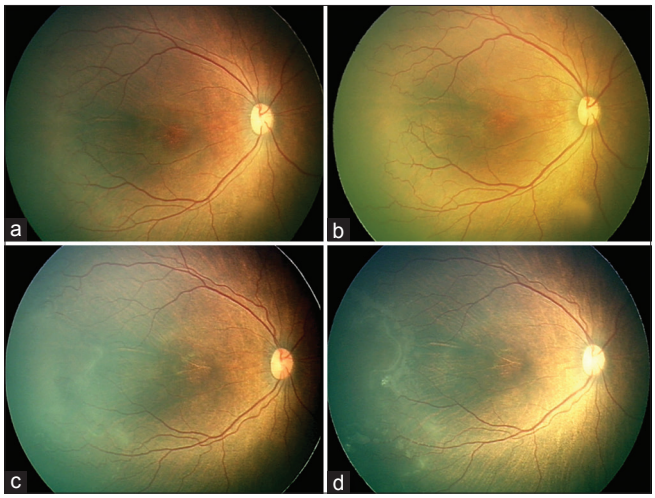

Figure 6: (a-d) An infant born at 32 weeks with 1350 g of weight first presented with moderate temporal avascular retina, which progressed to disease that did not require treatment

ages. Vasculogenesis starts from the center of the optic nerve around 10–12 weeks of gestation and reaches the ora serrata by 38–40 weeks of gestation.[13] (3) The larger the retinal avascular area, the larger the area that is potentially ischemic and higher are the chances of possible abnormal vascularization influenced by proangiogenic factors such as vascular endothelial growth factor.[13]

The degree of retinal immaturity could be influenced by the level of postnatal care even before disease sets in. This is particularly true of developing nations where there is variable level of neonatal care that can result in severe immaturity that progresses to APROP.[14,15] Hence, evaluating the level of immaturity especially before ROP develops could provide us with a method to predict which of these progresses to treatment requiring disease and when. In our program, all babies undergo serial RetCam imaging for all visits which allows us the opportunity to analyze the level of immaturity and compare it with the final ROP outcome.

In most circumstances, the subsequent follow-up after the first ROP screening visit is determined by the condition of the retina at the first event.[12,16] If there is a "stage" of ROP, most screening protocols recommend weekly or fortnightly visits, unless it is Type 1, for which immediate treatment is recommended. However, scheduling the "right" follow-up date when there is "no stage" of ROP is more ambiguous with most protocols recommending a two-weekly visit if there is no disease but there is evidence of retinal immaturity. This poses a social, economic, and logistical challenge, especially where

mothers have to travel long distances from the rural interiors for ROP screening of their infants.[8,9,17] Repeated or frequent follow-up visits have also been shown to increase the rate of attrition.[17] Incomplete ROP screening is both medicolegally[18] and clinically an unacceptable situation.[8,10]

To our best knowledge, this study is the first attempt to present a subclassification of the "immature" yet "not normal" retinal vascularization with the aim to predict the level of immaturity that could predict future disease and need closer follow-up [PubMed MeSH terms: immature retina, TAR, ROP].

ROP screening programs that rely predominantly on wide-field retinal imaging, wherein images are either read on site or remotely by experts, are becoming necessary and popular,[5,6,8,19-24] especially in middle-income countries,[6,8,9,11] where there are limited number of ROP specialists and millions of babies to screen.[4,25] In the Indian context, ROP screening recommends that the first screening be done before 30 days of life and for all infants born less than 2000 g at birth or born less than 34 weeks of gestation. The first screening is performed between 3 and 4 weeks of life for those born >28 weeks and 2–3 weeks for those born <28 weeks or <1200 g at birth.[5] Most babies require an average of four to five screening sessions, performed weekly or twice a month, until full vascularization of the retina is documented or the PMA is over 42–44 weeks or it reaches the threshold for treatment (Type 1 ROP).[5,6] With an average incidence of 40% of any stage ROP[6,7] and about 5%–10% of those requiring treatment, the number of "needless visits" before documenting a mature retina to be fit for discharge from the screening program poses a scientific, social, and logistic challenge.[8-11]

Our study shows that 100% of infants who had immature retina extending from zone 1 or posterior zone 2 would go on to develop some disease, and of these almost two-thirds would eventually require treatment. On the other end of the spectrum, only 15% of infants with retinal immaturity into zone 3 would develop any stage disease. Hence, the appearance of the retina at "first contact" could be used as a surrogate marker for predicting which babies are more likely to develop disease or more importantly need treatment. This is particularly relevant in ROP screening programs managed by nonphysician-based tele-ROP models using wide-field digital imaging in regions that lack experts. These units are required to give the clinical decision to the parents before the latter leave the center.[6,9,17,26] A validated nomenclature of retinal immaturity would help them make a more prudent decision. Similarly, in physician-based screening programs, the ROP specialist who encounters a "severe" grade of immaturity could caution the mother about the impending progression and suggest a "closer follow-up." Furthermore, while babies get transferred from one neonatal intensive care unit to another, the extent of retinal immaturity can be quantified using this classification so that comparisons may be more uniformly objective when two or more physicians who share in the care of these infants examine and opine on these infants during ROP screening. Thus, the clinical utility of a "mild," "moderate," and " severe" immaturity includes a "closer watch" for infants with the "severe" grade of immaturity, with more detailed counseling, and warning and reminders if they miss any scheduled follow-up. As a corollary, infants who present initially with "milder" immaturity may have their next follow-up even 3–4 weeks later or closer to the expected due date to ensure and document a fully vascularized retina. Although the risk of progression to treatment-requiring disease is small, even these mildly immature retinae must be certified as "normal" before they are discharged from ROP screening. We also observed that more number of visits were needed in those with lower birth weights. Interestingly, male children had greater odds of developing disease or requiring treatment or needing more visits. All these factors can provide indicators for a closer follow-up in a community setup.

Our statistical model showed a predicted probability of developing disease to be 14% in Group 1, 36% in Group 2, and 67% in Group 3. The predicted probability of treatment-requiring disease was 1% in Group 1, 5% in Group 2, and 25% in Group 3. Additionally, the more severe the grade of immaturity, the greater the number of visits. The predicted number of visits in Group 1 was 4, Group 2 was 5, and Group 3 was 7. These indicate the need and rationale behind a more rigorous monitoring for those with severe TAR as against a conservative approach for those with mild or moderate TAR. The predictive probability estimates from our model closely mimic the observed values in the three groups of immaturity, serving therefore a reliable indicator of the model developed.

It is important to elaborate the differences between our results and the ETROP study[27] which had defined "low-risk" and "high-risk" prethreshold disease. Based on their definition and the RM-ROP2 risk assessment software, the low-risk group was defined as stage 2 ROP in zone 3 with no plus. It was observed that 44 of 292 (15%) of the low-risk group developed threshold ROP and <1% progressed to unfavorable outcome at 6 months. However, going by our classification of avascularity, eyes would have been classified to have "low risk" even before they developed any stage of ROP. Interestingly, and quite similarly, 14% of our "mild" (low risk) avascular group developed any stage ROP and 1% required treatment. This highlights the importance of classifying immature retina at the first screening visit.

The limitations of the study must be noted. First, this is a retrospective study. A prospective follow-up of these babies would provide a more chronological sequence of the worsening or improvement of the retinal immaturity. We have addressed this disadvantage by the inclusion of a relatively large sample of 1202 eyes. The *post hoc* power of the study for the given sample size was calculated and found to be 80%. Second, systemic risk factors and neonatal care practices have not been included in the correlation of the level of immaturity and its outcome. In the same ethnic group, we have previously reported the spontaneous regression for severe plus disease in a case of APROP by correction of thrombocytopenia.[28] Hence, other risk factor analysis may provide further insight into the extent of immaturity and the progression of disease. Third, we have used the posterior border of the clinically visible junction to classify the groups. While this is useful clinically and resembles the ICROP methodology of classifying disease based on the posterior most extent, it would disregard the fact that the posterior border dips especially at the temporal horizontal meridian, while the rest of the border may be more anterior resulting in a variable area of avascularity. The solution for this would be calculating the area using a third-party software like Image J, which could be used to determine the exact area of avascularity digitally in pixels. Finally, the study

subjects belong exclusively to Asian Indian ethnicity and the cohort included for screening is much "heavier" and "older" than the screening criteria of developed countries such as the United States with mixed ethnicities.[29,30] In the United States, the average birth weights and gestational ages would be significantly lower than this study, and hence the influence of these lower ages on the level of retinal immaturity and its subsequent progression to maturity is unknown, making these results less generalizable.

Conclusion

In conclusion, this suggested new subclassification of retinal immaturity and correlates clinically with the final disease outcome. Its clinical utility lies in offering the opportunity to the ROP specialist to schedule, follow-up, and prognosticate the level of disease and the timing of subsequent examinations while screening the baby for the first time. This could go a long way in reducing the economic burden and increasing compliance among mothers of ROP infants. With advances in automated imaging reading softwares,[31,32] it may be possible, in the future, to predict which infants will progress to treatment-requiring disease based on metrics on these vascular patterns and which will spontaneously resolve. A prospective study involving multiple ethnicities and a lower range of birth weight and gestational ages would be needed to study the correlation of early retinal immaturity with the course of ROP.

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Conflicts of interest

There are no conflicts of interest.

References

1. An international classification of retinopathy of prematurity. The Committee for the Classification of Retinopathy of Prematurity. Arch Ophthalmol 1984;102:1130-4.
2. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005;123:991-9.
3. Photographic Screening for Retinopathy of Prematurity Cooperative G, Balasubramanian M, Capone A, Jr., Hartnett ME, Pignatto S, Trese MT. The Photographic Screening for Retinopathy of Prematurity Study (Photo-ROP): Study design and baseline characteristics of enrolled patients. Retina 2006;26:S4-10.
4. Hungi B, Vinekar A, Datti N, Kariyappa P, Braganza S, Chinnaiah S, *et al*. Retinopathy of prematurity in a rural neonatal intensive care unit in South India – A prospective study. Indian J Pediatr 2012;79:911-5.
5. Vinekar A, Avadhani K, Dogra M, Sharma P, Gilbert C, Braganza S, *et al*. A novel, low-cost method of enrolling infants at risk for Retinopathy of Prematurity in centers with no screening program: The REDROP study. Ophthalmic Epidemiol 2012;19:317-21.
6. Vinekar A, Gilbert C, Dogra M, Kurian M, Shainesh G, Shetty B, *et al*. The KIDROP model of combining strategies for providing retinopathy of prematurity screening in underserved areas in India using wide-field imaging, tele-medicine, non-physician graders and smart phone reporting. Indian J Ophthalmol 2014;62:41-9.
7. Vinekar A. IT-enabled innovation to prevent infant blindness in rural India: The KIDROP experience. J Indian Bus Res 2011;3:98-102.
8. Vinekar A, Jayadev C, Bauer N. Need for telemedicine in retinopathy of prematurity in middle-income countries: e-ROP vs KIDROP. JAMA Ophthalmol 2015;133:360-1.
9. Vinekar A, Jayadev C, Mangalesh S, Shetty B, Vidyasagar D. Role of tele-medicine in retinopathy of prematurity screening in rural outreach centers in India – A report of 20,214 imaging sessions in the KIDROP program. Semin Fetal Neonatal Med 2015;20:335-45.
10. Jayadev C, Vinekar A, Bauer N, Mangalesh S, Mahendradas P, Kemmanu V, *et al*. Look what else we found – Clinically significant abnormalities detected during routine ROP screening. Indian J Ophthalmol 2015;63:373-7.
11. Vinekar A, Govindaraj I, Jayadev C, Kumar AK, Sharma P, Mangalesh S, *et al*. Universal ocular screening of 1021 term infants using wide-field digital imaging in a single public hospital in India – A pilot study. Acta Ophthalmol 2015;93:e372-6.
12. Pejaver R, Vinekar A, Bilagi A. National Neonatology Foundation's Evidence Based Clinical Practice Guidelines 2010. Retinopathy of Prematurity (NNF India, Guidelines) 2010:253-62.
13. Mutlu FM, Sarici SU. Treatment of retinopathy of prematurity: A review of conventional and promising new therapeutic options. Int J Ophthalmol 2013;6:228-36.
14. Shah PK, Narendran V, Kalpana N, Gilbert C. Severe retinopathy of prematurity in big babies in India: History repeating itself? Indian J Pediatr 2009;76:801-4.
15. Vinekar A, Jayadev C, Kumar S, Mangalesh S, Dogra MR, Bauer NJ, *et al*. Impact of improved neonatal care on the profile of retinopathy of prematurity in rural neonatal centers in India over a 4-year period. Eye Brain 2016;8:45-53.
16. Fierson WM, American Academy of Pediatrics Section on Ophthalmology; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus; American Association of Certified Orthoptists. Screening examination of premature infants for retinopathy of prematurity. Pediatrics 2013;131:189-95.
17. Vinekar A, Jayadev C, Dogra M, Shetty B. Improving follow-up of infants during retinopathy of prematurity screening in rural areas. Indian Pediatr 2016;53(Suppl 2):S151-4.
18. Supreme Court Judgement on ROP. Supreme Court of India, 2015. Available from: http://supremecourtofindia.nic.in/FileServer/2015-07-02_1435823185.pdf. [Last accessed on 2019 Mar 09].
19. Quinn GE, Ying GS, Daniel E, Hildebrand PL, Ells A, Baumritter A, *et al*. Validity of a telemedicine system for the evaluation of acute-phase retinopathy of prematurity. JAMA Ophthalmol 2014;132:1178-84.
20. Fijalkowski N, Zheng LL, Henderson MT, Wang SK, Wallenstein MB, Leng T, *et al*. Stanford University Network for Diagnosis of Retinopathy of Prematurity (SUNDROP): Five years of screening with telemedicine. Ophthalmic Surg Lasers Imaging Retina 2014;45:106-13.
21. Breidenstein BG, Dai S. Wide-field digital retinal imaging for retinopathy of prematurity screening in Australasia: A survey of practicing ophthalmologists. J Pediatr Ophthalmol Strabismus 2014;51:375-8.
22. Lorenz B, Spasovska K, Elflein H, Schneider N. Wide-field digital imaging based telemedicine for screening for acute retinopathy of prematurity (ROP). Six-year results of a multicentre field study. Graefes Arch Clin Exp Ophthalmol 2009;247:1251-62.
23. Myung JS, Paul Chan RV, Espiritu MJ, Williams SL, Granet DB, Lee TC, *et al*. Accuracy of retinopathy of prematurity image-based diagnosis by pediatric ophthalmology fellows: Implications for training. J AAPOS 2011;15:573-8.
24. Paul Chan RV, Williams SL, Yonekawa Y, Weissgold DJ, Lee TC, Chiang MF. Accuracy of retinopathy of prematurity diagnosis by retinal fellows. Retina 2010;30:958-65.
25. Sanghi G, Dogra MR, Katoch D, Gupta A. Demographic profile

of infants with stage 5 retinopathy of prematurity in North India: Implications for screening. Ophthalmic Epidemiol 2011;18:72-4.

26. Vinekar A, Jayadev C, Mangalesh S, Kurian M, Dogra M, Bauer N, *et al*. Initiating retinopathy of prematurity screening before discharge from the neonatal care unit: effect on enrolment in rural India. Indian Pediatr 2016;53(Suppl. 2):S107-11.
27. Good WV, Early Treatment for Retinopathy of Prematurity Cooperative G. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. Trans Am Ophthalmol Soc 2004;102:233-48; discussion 248-50.
28. Vinekar A, Hegde K, Gilbert C, Braganza S, Pradeep M, Shetty R, *et al*. Do platelets have a role in the pathogenesis of aggressive posterior retinopathy of prematurity? Retina 2010;30:S20-3.
29. Vinekar A, Dogra MR, Sangtam T, Narang A, Gupta A. Retinopathy of prematurity in Asian Indian babies weighing greater than 1250 grams at birth: Ten year data from a tertiary care center in a developing country. Indian J Ophthalmol 2007;55:331-6.
30. Vinekar A, Trese MT, Capone A, Jr., Photographic Screening for Retinopathy of Prematurity (PHOTO-ROP) Cooperative Group. Evolution of retinal detachment in posterior retinopathy of prematurity: Impact on treatment approach. Am J Ophthalmol 2008;145:548-55.
31. Jayadev C, Vinekar A, Mohanachandra P, Desai S, Suveer A, Mangalesh S, *et al*. Enhancing image characteristics of retinal images of aggressive posterior retinopathy of prematurity using a novel software, (RetiView). Biomed Res Int 2015;2015:898197.
32. Rajashekar D, Srinivasa G, Vinekar A. Comprehensive retinal image analysis for aggressive posterior retinopathy of prematurity. PLoS One 2016;11:e0163923.