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The retinal vascular growth rate in babies with retinopathy of prematurity could indicate treatment need

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Purpose: To analyze the weekly rate of retinal vascular growth in treatment-naïve babies with various stages of retinopathy of prematurity (ROP) and validate if this could be a predictor of treatment need. **Methods:** Retrospective review of medical charts and retinal images of babies with various stages of ROP. The images were enhanced using red-green image enhancement software. Using the length of the horizontal disc diameter (DD) of each eye, the vessel growth was measured from the disc margin up to the vessel tip in fixed quadrants. The rate of vessel growth was the ratio of vessel length to the number of weeks it took to reach this length. The babies were divided into treatment warranting ROP (group 1), low-risk pre-threshold (type II) ROP (group 2,), and no-ROP (group 3) for analysis. The "no-ROP" group acted as normal control. Group 1 was further subdivided into 1A (threshold ROP), IB (aggressive posterior ROP), 1C (hybrid ROP), and ID (high-risk pre-threshold ROP). **Results:** Out of 436 eyes, groups 1, 2, and 3 had 238, 108, and 90 eyes, respectively. The mean rate of vascular outgrowth along with 95% confidence interval (CI) was 0.490 [0.487,0.520], 0.612 [0.599, 0.638], and 0.719 [0.703, 0.740] DD/week, respectively, for babies with "treatment warranting," "low risk pre-threshold" and "no ROP" groups, respectively. In our estimate, more than 80% of eyes with a vessel growth rate of 0.54 DD/week or less required treatment. **Conclusion:** A rate of retinal vascular growth less than 0.54 DD/week can be used to determine treatment requirements in babies with ROP.

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Retinopathy of prematurity (ROP) is a disorder of immature retinal vasculature. Several systemic risk factors affect the extent and severity of ROP.[1-13] These include prematurity, low birth weight, collateral health issues (such as poor weight gain, sepsis, respiratory distress, and apnea), excessive unmonitored oxygen supplementation, etc.[14-20] These factors directly or indirectly modulate the disease course via a common endpoint of retinal vascular growth. This, in turn, decides the extent of retinal avascularity and the vascular endothelial growth factor (VEGF) load in the vitreous. Predictive models have been developed to identify infants at risk of developing ROP based on the risk factors. However, these models have not been widely adopted because of limited generalizability and a small sample size.[1,21] The retinal vasculature is readily visualized by ophthalmoscopy. The retinal vasculature acts as a common endpoint of many systemic factors (known or unknown); thus, its analysis and correlation with the disease severity can be of immense importance. In the present study, we analyzed the rate of vascular growth vis-à-vis the treatment decision in babies with variable ROP severity to determine if this biological marker can help in the decision-making for treatment.

Methods

This retrospective study was conducted at a tertiary eye care center serving patients from Eastern India. All the prematurely born babies diagnosed with ROP of various degrees and the retina imaged with good image clarity were included in the study; the study period was from January 2010 to December 2019. Good retina image clarity was defined as the one where the optic disc and vascular endings were visible clearly for calculation. Those with insufficient or unclear images, clear images but the optic disc and the end of blood vessels are not visible in a single image (for example, retinopathy in extreme Zone III), short follow-ups, and stage 4 and 5 ROPs were excluded. The institute's review board approved the study, and it followed the Declaration of Helsinki in research involving

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human subjects. The eye examinations and fundus imaging was done after obtaining written consent from the parents/guardian about imaging and possible use of the anonymized images for teaching and research.

Two pediatric retinal imaging devices were used: RetCam (Clarity Medical Systems, Pleasanton, California) and 3 netra neo-Digital Wide-field imaging systems (Forus Health Pvt Ltd, Bengaluru, India). When needed, the images were enhanced with a red-green image enhancement option available in the device [Fig. 1]. The retinal imaging in these babies was as per the institute protocol. In brief, fundus images of most babies with ROP of any degree (and some of the babies with prematurity but no ROP) were obtained after obtaining informed and signed consent from the parents. The protocol allowed obtaining at least basic images covering disc and macula, superior, inferior, supero- and inferotemporal, supero- and inferonasal quadrant as far as possible. In this study, the images obtained and archived as a part of patient care were analyzed. Among the multiple visits, we included the last visit image where the disc and the end of blood vessels were imaged simultaneously within a single field. In group 1 with treatable ROPs, the calculations were done on the images taken on the day of or within a week before treatment.

All the measurements on the images were done from the mid-point of the nasal or temporal margin of the optic disc. The speed of temporal retinal vascularization (DD/week) was calculated as the ratio between the extent of temporal retinal vascularization (DD) and the time in weeks as per previously published literature.[20] Retinal arteries start from the optic disc at 16 weeks of gestational age and grow at 0.1 mm per day.[20] Taking the average optic disc diameter as 1.05 mm,[22-24] we presumed that the time taken for the blood vessels to reach the disc margin (0.5–0.6 mm) from the center of the optic disc would be 5–6 days. In other words, the vessels would be reaching the optic disc margin approximately at 17 weeks of gestational age. This presumption was made from the published report of vessel growth of 0.7 disc diameter (DD)/week after 20 weeks of gestational age (GA).[20] We used the caliper option available with the imaging device in RetCam [Fig. 2] and a manual measuring scale in the 3netra neo Digital Wide-field imaging system. The post-mensual age (PMA), defined as the sum of gestational age and number of days elapsed since birth) in weeks, was recorded at the measurement point. The following formula was used to calculate the speed of vascular outgrowth (S) in DD/week: $S = (A/D)/(P-17)$, where A is the radial distance of the end of blood vessels from the middle of the disc margin, D is the horizontal disc diameter, and P is the PMA at time of the rate calculation.

We calculated the vascular growth along supero- and inferotemporal quadrants (STQ, ITQ), supero- and inferonasal quadrants (SNQ, INQ), horizontal nasal (HNQ), and horizontal temporal (HTQ) quadrant, one or more for each eye (total of 6 or fewer measurements per eye). However, most of the time, the images were clearer, and calculations could be done in superotemporal (428 of 436 eyes), followed by inferotemporal (379 of 436 eyes), and horizontal temporal quadrant (345 of 436 eyes). The babies were divided [Table 1] into group 1 (Treatment warranting ROP) and group 2 (low-risk pre threshold/type II ROP). All the classifications were done as per the CRYOROP, ICROP revised, and ETROP study.[25,26] Group 1 was further subdivided [Table 1] into 1A [threshold ROP, Fig. 3a], 1B [aggressive posterior ROP, Fig. 3b], 1C [hybrid ROP, Fig. 3c], and 1D [high-risk pre threshold ROP, Fig. 3d]. "Hybrid ROP" refers to babies having ridge tissue, similar to staged ROP + flat new vessels, simulating APROP in the same eye, as described by Sanghi *et al*.[27]

Babies born prematurely with an immature retina but did not develop ROP until the last visit were considered controls (group 3). We excluded babies beyond 38 weeks PMA from the normative data calculation; the terminal ends of the retinal vessels in these babies' images were difficult to appreciate. As the horizontal disc diameter was used as the calculation unit in the study, we were aware of the possibilities

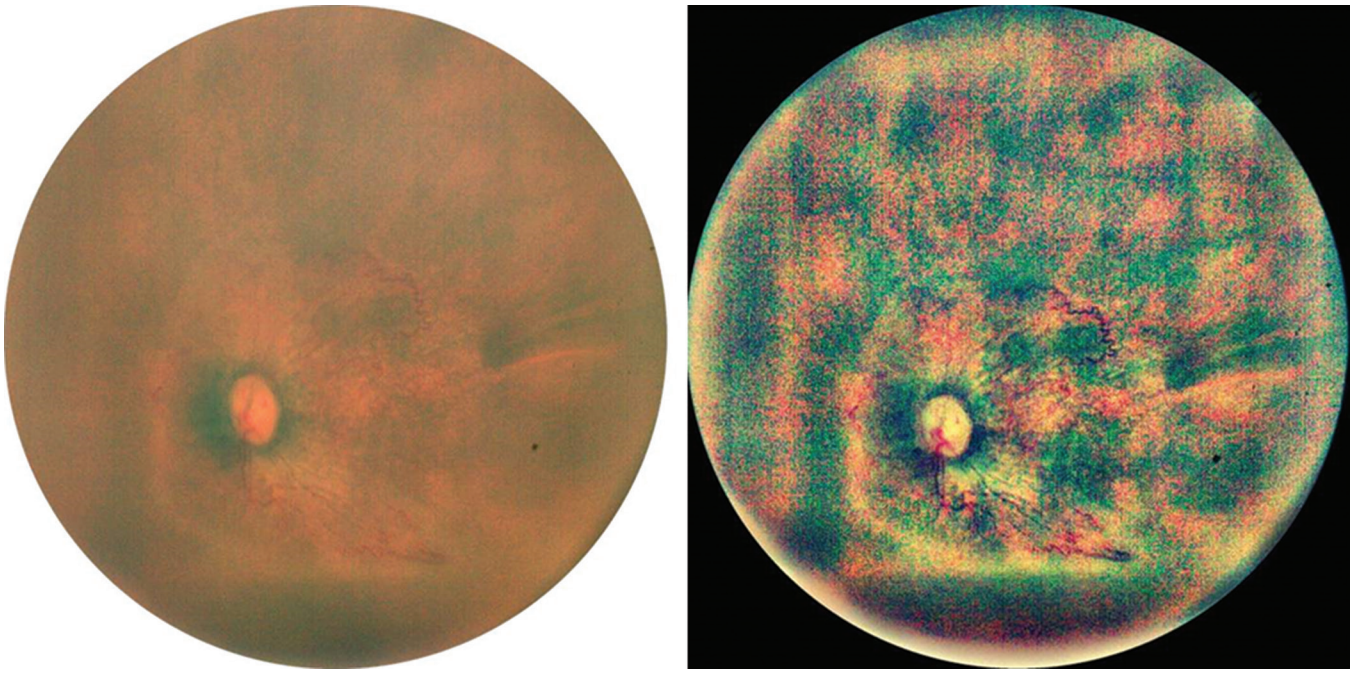

Figure 1: (Left) Color fundus image of the left eye taken with 3netra neo digital wide-field imaging system (Forus Health Pvt. Ltd) showing few tortuous vascular loops around the optic disc. Nasally, they hardly extend beyond 1.5 DD from the nasal border of the optic disc. (Right) Same eye after red-green enhancement making the blood vessels stand out with better clarity

Table 1: Speed of vascular out growth in eyes with treatable, low risk prethreshold and no ROP

Groups (251 babies, 436 eyes)	Description	STQ (*n*)	ITQ (*n*)	HTQ (*n*)	SNQ (*n*)	INQ (*n*)	HNQ (*n*)	All Quadrantstogether
Group 1 *n*=136 babies, 238 eyes								
All	Treatable ROP	0.522±0.136 (236)	0.514±0.131 (232)	0.475±0.149 (191)	0.373±0.113 (20)	0.315±0.103 (17)	0.227±0.099 (22)	0.490±0.121
1A	Threshold ROP (37 babies, 64 eyes)	0.480±0.101 (63)	0.475±0.091 (64)	0.444±0.114 (52)	0.301±0.267 (02)	0.233±0.165 (2)	0.107 (1)	0.461±0.123
1B	APROP (31 babies, 59 eyes)	0.432±0.104 (59)	0.427±0.111 (57)	0.343±0.095 (40)	0.384±0.115 (12)	0.326±0.104 (10)	0.224±0.094 (16)	0.386±0.104
1C	HybridROP (16 babies, 28 eyes)	0.538±0.132 (28)	0.512±0.126 (26)	0.461±0.142 (23)	0.363±0.067 (4)	0.329±0.083 (4)	0.247±0.126 (4)	0.480±0.112
1D	HRPTHROP (52 babies, 87 eyes)	0.610±0.124 (86)	0.602±0.118 (85)	0.571±0.132 (76)	0.4±0.043 (02)	0.306 (01)	0.328 (01)	0.592±0.069
Group 2 (64 babies, 108 eyes)	Low risk prethreshold ROP	0.632±0.105 (105)	0.613±0.104 (96)	0.589±0.108 (97)	-	-	-	0.612±0.106
Group 3, (51 babies, 90 eyes)	NOROP	0.721±0.090 (87)	0.705±0.093 (51)	0.731±0.097 (57)	-	-	-	0.719±0.093

APROP-Aggressive Posterior ROP, HNQ-Horizontal nasal quadrant, INQ-Inferonasal quadrant, HRPTH ROP-High Risk Prethreshold Retinopathy of Prematurity, HTQ-Horizontal temporal quadrant, ROP-Retinopathy of Prematurity, SNQ- Superonasal quadrant, STQ- Superotemporal quadrant

of difference among different subgroups and consequent bias. Thus, we calculated the average disc size among the various groups and looked for any statistical difference.

The gestational age (GA), birth weight (BW), PMA, and retinopathy status are shown in Table 2. The ROP screening had been done by multiple ROP specialists earlier. However, the images were read and analyzed retrospectively by only three of them. The average and range of weekly vascular growth rates were measured for all groups and subgroups by two examiners separately (SP, AP); they had at least one year of experience diagnosing and managing ROP and in the imaging devices used in the study. A third examiner (TRP, ROP specialist with 10 years of experience in ROP care) masked the treatment details, cross-checked the measurements, and his decision to accept one of the two measurements in case of a disagreement was final. The examiners were given only one image per eye to perform the calculations without showing the images in the other visits. For group 1, the images taken on the day or 1 week before treatment were selected, while for groups 2 and 3, the last follow-up image showing the optic disc and the end of the blood vessel together was selected. The same was also selected for group 1 from the images taken on the day or within 1 week before treatment. We analyzed the inter-observer (between observers 1 and 2) agreement in calculating the growth rate of blood vessels. The average rates were calculated for the two test groups (groups 1 and 2) and the control group (group 3). An intragroup comparison was made, and their statistical significance was calculated [Table 1]. Each eye's vascularization rate was arranged from lowest to highest value irrespective of the retinopathy and treatment. Finally, we calculated the strength of the correlation of vascular outgrowth rate with the treatment requirement. The decision for treatment was already taken in the past as per the ETROP guidelines.

Statistics

The data were analyzed with SPSS V.21.0 (SPSS Inc, Chicago, IL, USA). Student's *t* test was applied to compare the average speed of vascularization in subjects with and without ROP in different quadrants. The mean, median, and range of GA, BW, and PMA measurements in different groups were calculated. The average vascular growth in groups 1 and 2 was compared

Figure 2: Snapshot image showing the method of measurement of vascular growth done on the laptop screen and the caliper option available with RetCam (Clarity Medical Inc.). The eye shown here shows threshold retinopathy of prematurity (ROP) in zone I. The disc dimensions are measured both horizontally and vertically, and the ends of the blood vessels are measured in supero, infero, and horizontal temporal quadrants

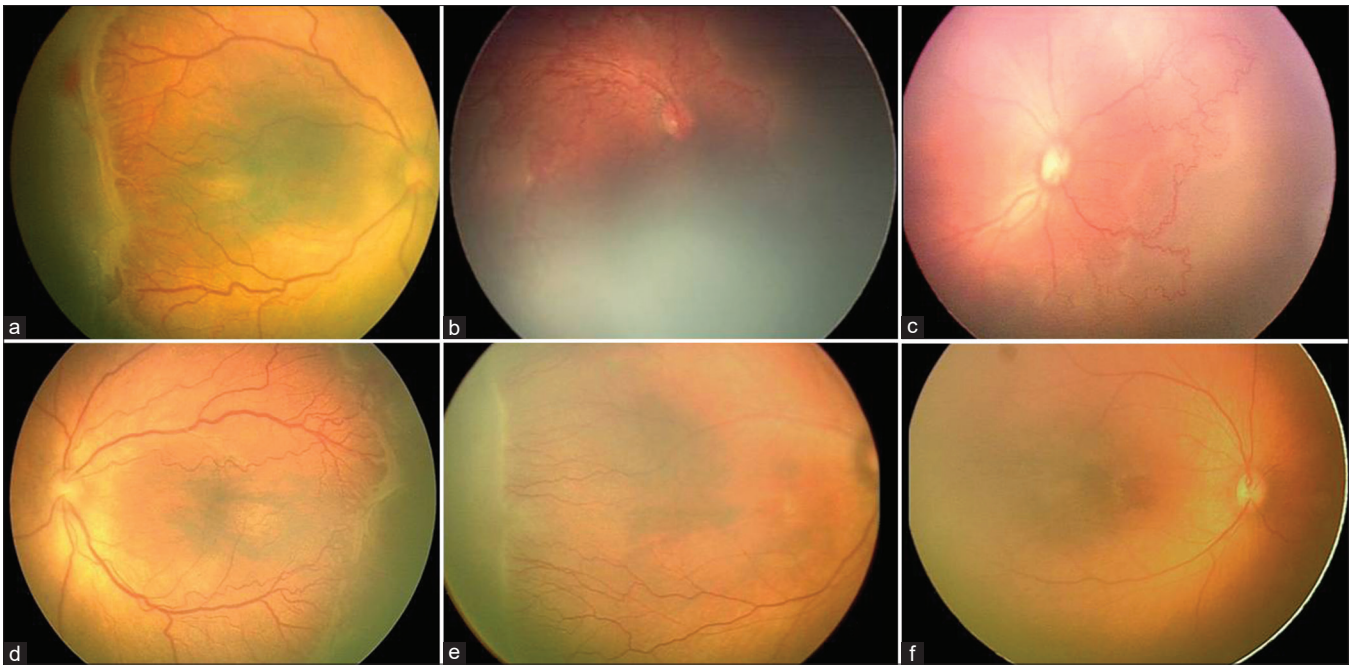

Figure 3: Collage of representative fundus images from different groups and subgroups analyzed in the present study. (a) Right eye showing threshold Retinopathy of prematurity (ROP) in zone II posterior. (b) Right eye of a case with aggressive posterior retinopathy of prematurity (APROP). (c) Case of hybrid ROP showing features of both APROP and staged ROP in the same eye. (d) Left eye showing stage 3 zone II plus ROP (high risk pre threshold). (e) Right eye showing stage 2 Zone II pre plus (low risk pre threshold) ROP. (f) Zone III Immature retina, no ROP in the right eye

with the normative control (group 3), and the significance of the difference was estimated. The intraclass correlation coefficient test was used to assess the reliability of the observations made by observers 1 and 2. $P < 0.05$ was taken as statistically significant. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) was used to evaluate the predictive value and determine the cutoff point in vascularization speed as a predictor of treatment need.

Results

This study recruited 233 babies (bilateral: 203, unilateral: 30) and 436 eyes- 238 eyes (n = 136 babies) in group 1 (treatment warranted, Fig. 3a–d), 108 eyes (n = 64 babies) in group 2 (low risk pre threshold ROP, Fig. 3e), and 90 eyes (n = 51 babies) in group 3 (no- ROP, Fig. 3f) as shown in Table 1. The subgroup of group 1 was as follows: 1A (threshold ROP, Fig. 3a) 64 eyes; 1B (aggressive posterior ROP, Fig. 3b) 59 eyes; and 1C (hybrid ROP, Fig. 3c) 28 eyes; 1D (high-risk pre-threshold ROP, Fig. 3d) 87 eyes. There were 18 babies, with each eye falling in a different group. For the baby falling into two groups, we allotted the same subject in the two groups. The GA, BW, and PMA calculations of babies in each group are presented in Table 2. Of 436 eyes, the measurements could be easily made in 428 (98.1%), 376 (86.2%), 344 (78.8%), 20 (4.0%), 17 (3.8%), and 22 (5.0%) eyes in STQ, ITQ, HTQ, SNQ, INQ, and HNQ, respectively. The examiners succeeded in making calculations in STQ more often than the other quadrants. The inter-observer (between observers 1 and 2) agreement in the calculation of the rate of growth of blood vessels was considered excellent in the STQ (0.982; 95% Confidence Interval (CI): 0.079–0.985) and good in the ITQ and HTQ [Table 3]. The average rate of vascular growth (average of the rates in different quadrants) was 0.49 ± 0.12, 0.612 ± 0.10, and 0.719 ± 0.09 DD/week in group 1 (treatable ROP), group 2 (low-risk pre threshold ROP), and group 3 (No ROP) eyes, respectively [Table 1 and Fig. 4]. The ROP in group 2 was observed to regress spontaneously in all eyes. The rate was lowest in subgroup 1B, followed by groups A, C, and D. We observed that the average horizontal disc diameter (the numerator for speed calculation in the study) of the eyes imaged with RetCam was not statistically different ($P = 0.069$) between the three groups (58.98, 61.08, and 58.9 RetCam units for groups 1, 2, and 3, respectively).

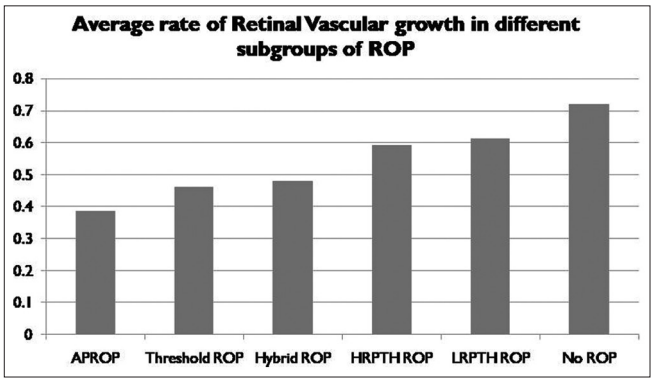

Figure 4: Diagram showing the average speed of retinal vascularization in babies with retinopathy of prematurity of varying severity

In babies with treatment warranting ROP (group 1), the vascular growth rate was lower in the nasal than in the temporal quadrant [Table 1]. It was lowest in the HNQ (0.22 DD/week) and highest in the STQ (0.52 DD/week). The vascular growth rate in the HNQ was 43.48% of the rate of vascular growth in the STQ and 47.7% of the rate of vascular growth in the HTQ. In the low-risk pre threshold and no-ROP groups, we did not have enough measurements in the nasal quadrants to compare the speed with the temporal quadrant. The ROC showed that

Table 2: Gestational age (GA), birth weight (BW), and postmenstrual age (PMA) at the calculation of babies within three subgroups in the present study

Parameters	Treatable ROP as a whole (Gr 1)	Subgroup 1A (Threshold)	Subgroup 1B (APROP)	Subgroup 1C (Hybrid)	Subgroup 1D (HRPTH)	Low risk pre threshold ROP (Gr 2)	NO ROP (Gr 3)
GA in weeks	23-36	25.28-34	26.71-34	28.29-35	23-36	25-38	29-38
(Range, Avg±SD)	30.091±1.97	29.72±1.98	30.07±1.48	30.95±2.09	30.089±2.098	30.60±2.03	32.44±2.17
BW in g	640-2100	640-1900	850-1700	1000-1900	840-2100	700-2500	900-2400
(Range, Avg±SD)	1261.61±292.56	1218.98±290.57	1210.33±205.11	1319.28±265.71	1309.19±305.85	1432.33±363.69	1634.54±324.45
PMA in weeks at calculation	29-44.57	34-43.57	31-41.71	33-39.14	29-44.57	31-45.97	32.85-41
(Range, Avg±SD)	36.52±2.37	37.92±2.29	35.06±2.14	35.74±2.13	36.73±3.02	38.65±2.92	37.49±1.72

ROP-Retinopathy of Prematurity, SD-Standard deviation, Postmenstrual age is defined as a sum of gestational age and number of days elapsed since birth

the rate of vascular growth was a significant predictor of the requirement of treatment at a cutoff value of ≤0.569 (STQ), ≤0.57 (ITQ), and ≤0.542 (HTQ) with a chance of correctly predicting the requirement of treatment in 81%, 79%, and 81% of cases, respectively [Table 4 and Fig. 5].

Discussion

Retinopathy of prematurity has classically been described as a biphasic disease where the events start with delayed growth of retinal vasculature, resulting in a peripheral avascular retina (Phase 1). Later, vaso-proliferation (intravitreal angiogenesis) can occur at the junction of the avascular and vascularized retina (phase 2).[28] In addition to prematurity, low birth weight, possible genetic factors, and other factors (such as extent and duration of oxygen supplementation, post-natal weight gain, sepsis, hyaline membrane disease, cerebral hemorrhage, exchange transfusion, and intubation for 10 days or longer) also play an important role in the vascular development in prematurely born infants.[28,29] A slow rate of retinal vascularization causes a larger avascular retina to persist for a longer period, resulting in a greater VEGF load with an increase in the severity of retinopathy. The rate of vascularization is a quantifiable observation, but its correlation with ROP and treatment requirement has not been studied in detail. The developing retina is supplied principally by the blood vessels from the developing hyaloid system and a contribution from the choroidal vasculature up to 12 weeks of fetal life. Major retinal arteries begin from the center of the optic disc at 16 weeks of gestation and grow peripherally at a rate of 0.1 mm per day.[30] It is also known that the internal vascular plexus of the retina grows 0.094–0.1 mm/day from 28 weeks of gestational age;[31] this is equivalent to a vascularization rate of 0.7 mm/week or approximately 0.7 DD/week,[32] taking mean horizontal optic diameter as 1.05 mm.[22-24]

de Larraya *et al*.[20] evaluated the efficacy of the rate of vascular growth in predicting the treatment requirement by using an indirect ophthalmoscope. They showed that the rate of temporal retinal vascularization was significantly higher in no ROP (0.73 ± 0.22 DD/week) than in stage 1 (0.58 ± 0.22 DD), stage 2 (0.46 ± 0.14 DD/week), and stage 3 ROP (0.36 ± 0.18 DD/week). In a study in 185 babies, they concluded that the slower rate of temporal retinal vascularization could alert a clinician of treatment need. The present study was conducted on a larger sample of patients; we measured the vascular growth in different quadrants around the optic disc, compared the speed of vessel development in ROP subtypes (helps treatment decision in a real-life situation), and used newer technology such as the red-green enhancement of the images when required (for easier identification of the course and termination of the artery). We used two separate observers to ensure reproducibility and compared it with an ROP expert's final treatment decision.

In our study, the average vascular growth rate in babies without ROP (group 3) was 0.719 ± 0.093DD/week and was similar to two earlier reports.[30,31] In our analysis, the vascular growth rate was at least 20% slower in babies who needed treatment than those who did not (0.54–0.56 DD/week versus 0.72 DD/week). We also observed that the examiners could measure the speed easily in the superotemporal quadrant and preferred this quadrant over other quadrants to calculate the speed of vascular growth calculation.

ROP has been described to have nasal-temporal asymmetry.[33-35] Gallagher *et al*.[33] reported that at any given point, the retinopathy tends to be 2–3 mm closer to the disc

Table 3: Interobserver correlation coefficient between observers 1 and 2

Treatment Required	STQ		ITQ		HTQ	
	Interobserver correlation	95% Confidence interval	Interobserver correlation	95% Confidence interval	Interobserver correlation	95% Confidence interval
Single measures	0.9664	0.9593-0.9722	0.7789	0.7128-0.8282	0.7804	0.7261-0.8231
Average measures	0.9829	0.9792-0.9859	0.8757	0.8323-0.9060	0.8767	0.8413-0.9030

HTQ-Horizontal temporal quadrant; ITQ-Inferotemporal quadrant; STQ-Superotemporal quadrant Values less than 0.5 are indicative of poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values greater than 0.90 indicate excellent reliability

Table 4: Receiver operating characteristic curve of STQ, ITQ, and HTQ for predicting requirement of treatment

Treatment Required	STQ	ITQ	HTQ
Area under the ROC curve (AUC)	0.817	0.791	0.819
Standard Error	0.0202	0.0232	0.0229
95% Confidence interval	0.777-0.853	0.747-0.831	0.774-0.858
P	<0.0001	<0.0001	<0.0001
Cutoff	≤0.569	≤0.578	≤0.542
Sensitivity (95% CI)	66.95% (60.6-72.9%)	73.71% (67.5-79.3%)	67.37% (60.2-74.0%)
Specificity (95% CI)	82.29% (76.1-87.4%)	71.23% (63.2-78.4%)	83.66% (76.8-89.1%)
PPV (95% CI)	82.3% (76.1-87.4%)	80.3% (74.3-85.4%)	83.7% (76.8-89.1%)
NPV (95% CI)	66.9% (60.6-72.9%)	63% (55.2-70.4%)	67.4% (60.2-74.0%)
Diagnostic accuracy	73.83%	72.75%	74.63%

CI-Confidence interval; HTQ-Horizontal temporal quadrant; ITQ-Inferotemporal quadrant; NPV-Negative predictive value, PPV-Positive Predictive Value, ROC-Receiver Operating Characteristic curve; STQ-Superotemporal quadrant

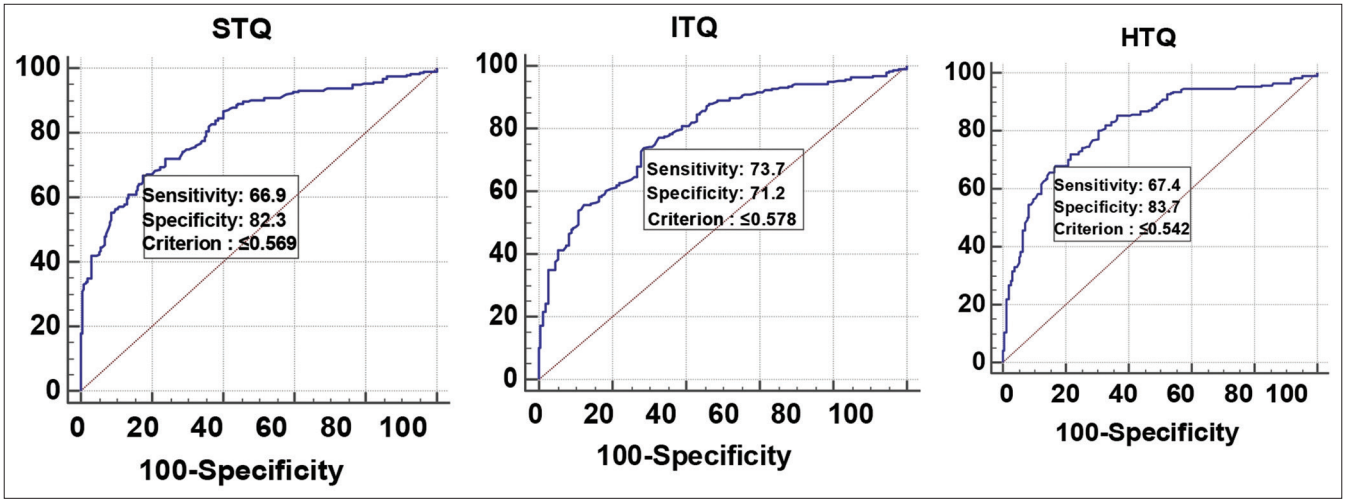

Figure 5: The receiver operating characteristic curve (ROC) to find out the area under the curve and cutoff point of vascular growth in superotemporal quadrant (STQ), inferotemporal quadrant (ITQ), and horizontal temporal quadrant (HTQ) for predicting the requirement of treatment. ROC curves above the diagonal line are considered to have a reasonable discriminating ability to predict the requirement of treatment. The discriminatory power of the rate of vascular growth (area under curve: 0.819, 0.791, and 0.819; 95% confidence interval: 66.95, 73.71, and 63.37, respectively, for STQ, ITQ, and HTQ) was acceptable. The rate of vascular growth was a significant predictor of the requirement of treatment at a cutoff value of ≤ 0.569 (STQ), ≤0.57 (ITQ), and ≤ 0.542 (HTQ) with a chance of correctly predicting the requirement of treatment in 81%, 79%, and 81% of the cases, respectively

nasally than temporally. Nissenkorn *et al*.[36] and Fielder *et al*.[37] observed that ROP develops in the nasal retina about 2 weeks earlier than in the temporal retina. The reasons for this asymmetry in both time and location are unclear. The distance of disc to nasal ora (18.5 mm) is shorter, and it is 78.7% of the distance of disc to temporal ora (23–24 mm) long.[38] However, the rate of vascular growth along the horizontal nasal quadrant, as seen in subjects with ROP in this study, was less than 50% of that in the temporal quadrant. This means that the distance between the optic disc to ora serrata is shorter nasally than temporally, and the speed of vascular growth is disproportionately less nasally than temporally. As a result, one should expect a larger avascular retina nasally than temporally. This could partly explain the naso-temporal asymmetry in ROP.

We recognize that slow retinal vascular growth may not be the only determining factor to treat ROP. Many systemic and ocular factors (plus disease, new vessels, zone of involvement, etc.) are taken into account before planning treatment. Our study suggests that at a retinal vascular growth rate slower than 0.54 DD/week, the possibility of the treatment need is high. Thus, these eyes should be monitored closely with extra attention to correcting systemic risk factors, if any. Our study's results also suggest to pay an additional weightage to the nasal quadrant while examining an eye for ROP.

This study is not without limitations. The measurements of the optic nerve and vascular outgrowths were done on a flat computer screen, while in reality, the optic nerve head lies on a curved surface and retinal blood vessels course on a curved surface. In an inclined image, the optic nerve dimension could be different. We did not have an easy way to calculate the distance of the end of the blood vessels along the vessel wall. Thus, the measurements were performed along the chord length, which is approximate to the actual length and velocity. Exact measurements of the end of the retinal blood vessels from disc margin without fundus fluorescein angiography (FFA); (currently, we do not have it) is another limitation. FFA has been shown to improve visualization of the peripheral vasculature not easily seen in color fundus photography.[39,40] We tried to circumvent the limitation by using red-free image enhancement that aids in better identifying the blood vessels. Speed of vascularization in any quadrants normalized by the optic nerve-ora serrata distance in that quadrant could have supported our claim that the speed is disproportionate in the nasal versus temporal quadrants. Unfortunately, we did not have an ultra-wide field pediatric retina imaging device that could image optic disc and ora serrata in one imaging field. We constructed a wide-field image by using several images of the posterior pole and peripheral retina. This had its limitations and was prone to errors. We overcome the problem of image magnification by using the ratios of distance with the disc diameter as the unit of measurement instead of the absolute values. This ratio is unaffected by the magnification factor (number of disc diameters per week). This was further supported because there was no statistical difference in the individual horizontal disc diameter for measurement ($P = 0.069$). The rate of vascularization could be different in different quadrants measured in the same subject and same time. This was overcome by measuring in specific quadrants in every eye. A good inter-observer correlation coefficient [Table 3] and a uniform time point of calculation (last follow-up visit) further reduced the variabilities.

We had difficulty calculating the speed of vascular growth in APROP and hybrid ROP because of large vascular loops with areas of capillary free zone behind it.[27] We took the anterior-most shunt vessel in a fixed direction. However, this might have caused a falsely higher speed, and a future study could aim to calculate the speed with respect to the anterior and posterior-most vessel in a particular quadrant. The measurements were done for whatever quadrants the images were available and clear. The nasal quadrant images of groups 2 and 3 were not available and were not clearer for many. As the vascular growth rate is less nasally than temporally, eliminating the nasal quadrants in groups 2 and 3 could have given a higher total average in these groups of eyes. Peripheral diseases in the zone III anterior are not adequately visualized in the cameras used in the study, especially when trying to include optic disc and vessel end in the same image field. Thus, the speed mentioned here cannot be universally applicable to all types of ROP, especially those in zone III. In the current study, all calculations were done at a fixed point of time, assuming that the vascularization rate was uniform over the period studied. This might not be true. The vascular growth depends on many systemic factors that change over time, and so would be the speed. This calls for a prospective study to document the weekly increase in eyes under observation for ROP. Once validated, this parameter would be easily adaptable to clinical settings.

Conclusion

In conclusion, this study showed a good correlation between the weekly rate of vascular growth and the decision to treat babies with ROP. The vessel growth rate was inversely proportional to the disease severity and was lowest in the APROP group. The growth rate nasally was slower than on the temporal side. Measuring vascular growth in the superotemporal was easier than in other quadrants.

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Conflicts of interest

There are no conflicts of interest.

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