Original Article

Relationship between refractive outcomes and quantitative retinal vascularization and severity of plus disease in eyes treated with intravitreal bevacizumab

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Purpose: The study aimed to investigate the relationship between refractive outcomes with the extent of retinal vascularization and severity of the plus disease in infants treated with intravitreal bevacizumab (IVB). **Methods:** Pre-IVB fundus images (PFIs), final fundus images (FFIs), and refractive outcomes of the 93 infants who underwent IVB monotherapy for type 1 and aggressive retinopathy of prematurity (A-ROP) were retrospectively evaluated. Quantitative measurements were performed on PFIs and FFIs. Pre-IVB plus severity was scored on a five-leveled scale. Correlation between spherical equivalent (SE) with pre-treatment and final extent of the temporal retinal vascularization and pre-treatment severity of plus disease was analyzed. **Results:** There was a linear and low positive correlation between the extent of pre-IVB and final temporal retinal vascularization with final SE (p = 0.000, r = 0.267; P = 0.002, r = 0.274, respectively). There was a low negative correlation between the pre-IVB plus severity score with final SE (p = 0.012, r = -0.192). Gestational age (GA), birth weight (BW), IVB dose, presence of additional IVB, or laser treatments were not correlated with refractive outcome. Out of 171 eyes, 38 eyes had >1 D myopia. In the univariate logistic analyses, pre-IVB retinal zone and pre-IVB and final extent of the temporal retinal vascularization were found to be related to the development of >1 D myopia (p = 0.002, odds ratio (OR) = 0.298; P = 0.000, OR = 0.281; P = 0.001, OR = 0.317; respectively). **Conclusion:** Our study indicates that the pre-treatment and final extent of retinal vascularization were the main parameters that were related to final refractive outcomes in IVB-treated eyes for type 1 and A-ROP.

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In a premature infant, the eye has not yet completed its development at birth. The eye shows significant improvements from 22 weeks postmenstrual age (PMA) to 40 weeks PMA.[1,2] During this process, critical structural-proportional changes evolve in the cornea, lens, anterior chamber, axial length, vitreous, and retina.[2] In this period, retinal vascularization progresses to the ora serrata starting from the optic disc. Cessation of the retinal vascularization may progress to total detachment via extraretinal fibrovascular proliferation. Although treatments such as cryotherapy, laser, and anti-vascular endothelial growth factor (VEGF) may prevent extraretinal fibrovascular proliferation, the mechanism pathways, the time for the treatment effect to be observable are different between these treatments.[3-5] Therefore, their effect on ocular developmental processes and refractive outcomes would be different.[6] The better refractive outcomes with anti-VEGF treatment may be related to more physiological development of ocular structures during critical weeks via rapid treatment effect of anti-VEGF and capability of progression of retinal vascularization after anti-VEGF treatment.

In studies that evaluate the extent of retinal vascularization in two subgroups, it was shown that more myopic results were obtained with VEGF treatment in eyes with posterior vascularization.[6,7] In the majority of the studies, pre-treatment retinal vascularization is roughly divided into two zone groups, but the extent of retinal vascularization shows a continuous spectrum.[3,4,6-8] Although a categorical relationship between retinal vascularization and the refractive outcome has been demonstrated, the linear relationship between pre-treatment retinal vascularization and the refractive outcome has not been investigated yet.[9] In addition, in eyes with a plus diagnosis, the severity of venous dilatation and arterial tortuosity may be at different levels and plus disease represents a continuous spectrum.[10,11] The effect of plus severity on refractive outcomes in infants treated with anti-VEGF has not been adequately studied.

The study aimed to investigate the relationship between refractive outcomes with retinal vascularization and plus disease by quantitatively measuring retinal vascularization and subjectively classifying plus disease in infants treated with intravitreal bevacizumab (IVB).

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Methods

This research was conducted by analyzing the data obtained from the University of Health Sciences, Kanuni Sultan Suleyman Training and Research Hospital Hospital, Tertiary ROP Center. The study was retrospective, single-centered, and observational. The study was conducted in concordance with the Declaration of Helsinki. The protocol of the study was reviewed and approved by the University of Health Sciences, Kanuni Sultan Suleyman Training and Research Hospital Training and Research Hospital Ethics Committee. Written informed consent had been obtained before the examination, photography, and treatment from legal guardians of all patients.

The patient charts of the 154 infants who underwent IVB monotherapy between May 2018 and December 2019 were retrospectively evaluated. Infants with a diagnosis of type 1 retinopathy of prematurity (ROP) and aggressive-ROP (A-ROP) and who had pre-treatment fundus photographs and who had at least one refraction examination result on the patient chart were included in the study.

The exclusion criteria are as follows: (1) Eyes treated with combined IVB and laser treatment as primary treatment were excluded. Eyes that underwent laser treatment for early failure, late recurrence, or persistent avascular retina were composed of the IVB plus delayed laser group and were not excluded. (2) Eyes with an interval of >3 days between the fundus photography and treatment were excluded. (3) Eyes that underwent cataract or vitrectomy surgery during follow-up were excluded.

During clinical practice, included infants were hospitalized in different neonatal intensive care units (NICUs) that were located in northwest Turkey. All ROP examinations, fundus imagings, IVB and laser treatments, and refractive examinations of the included infants were performed by the same clinicians (SEB or NS) in the one tertiary center in which the study was performed. Infants who were still receiving systemic care in the NICU of different hospitals were transferred with an incubator to the tertiary center for examination and treatment. Infants who were discharged from NICUs were examined and treated in the outpatient clinic of the tertiary center.

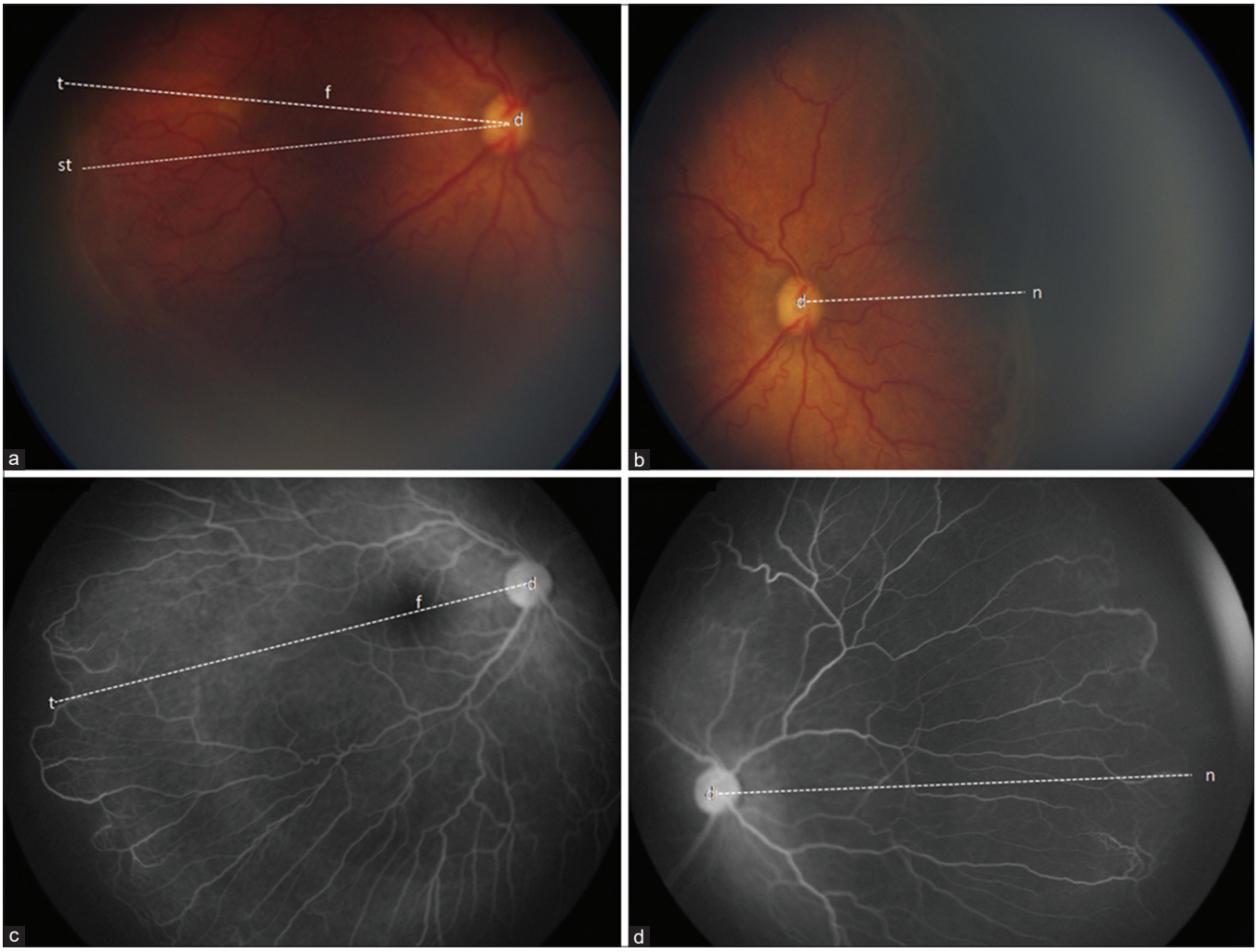

Figure 1: (a) Each image color photo and fluorescein angiogram corresponds to 4160 pixels horizontally and 3120 pixels vertically. The distance from the optic disc-to-fovea (FD) is presented between d and f points. The length of temporal retinal vascularization (LTRV) is between points d and t. The length of the shortest temporal retinal vascularization (LSTRV) is between points d and st. (b) The length of nasal retinal vascularization (LNRV) is between points d and n. (c)There is no significant posterior notching. Therefore, LTRV is equal to LSTRV. (d) LNRV is presented between points d and n

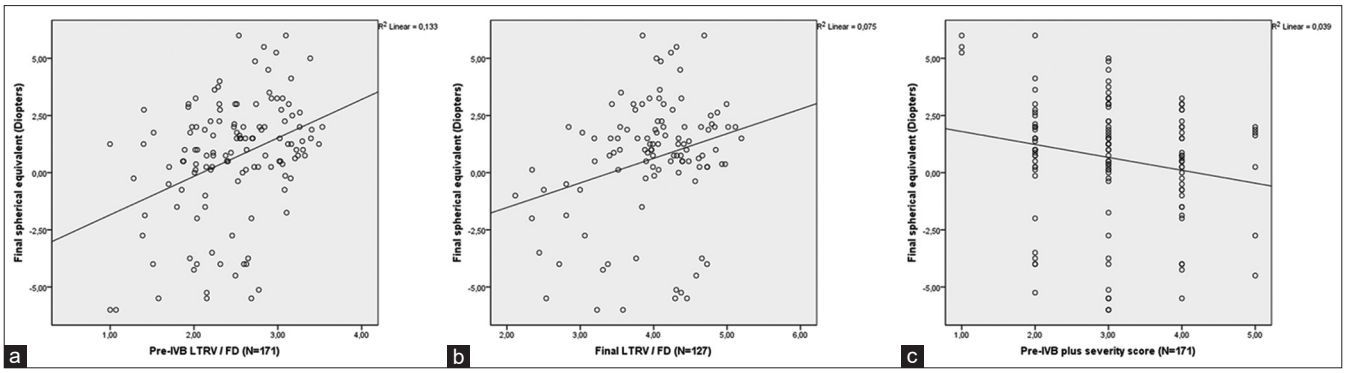

Figure 2: (a-c) The relationship of final spherical equivalent with pre-IVB and final temporal retinal vascularization and plus severity is shown on the scatter plot. Pre-IVB: Before intravitreal bevacizumab; LTRV: The length of the temporal retinal vascularization; FD: The distance from the optic disc-to-fovea

For this manuscript, the "pre-IVB" term was preferred to describe the examination session before IVB treatment. In clinical practice of the infants included in the study, pre-IVB retinal zones (zone I, posterior zone II, and peripheral zone II) were determined by the guide of the International Classification of Retinopathy of Prematurity (ICROP) revisited,[12] and subsequent studies.[5,8] Posterior zone II was defined as the ringed-shaped area between two and three times optic disc-to-fovea distance (FD) away from the optic disc.[5,8] Pre-IVB zone diagnosis was performed by using a binocular indirect ophthalmoscope (BIO) and 28 diopters (D) lens.[12]

Pre-IVB fundus images (PFIs) and final fundus images (FFIs) were captured with a 130° Panocam PRO (Visunex, Fremon CA, USA) device. While all PFIs consisted of color fundus photographs, FFIs consisted of color fundus photographs and fluorescein angiograms. Each image (color photographs or fluorescein angiograms) corresponds to 4160 pixels horizontally and 3120 pixels vertically. For each eye treated with IVB, the latest fundus images recorded on the Panocam PRO device were accepted as FFI. If the interval between the FFI and PFI was smaller than eight weeks, FFIs of that eye were excluded from further analyses except for eyes that underwent laser treatment. If the age at the final fundus imaging session was equal to or greater than the age at the laser treatment, these FFIs were included for further analyses.

In all treated eyes, 0.625 mg or 0.3125 mg Altuzan (Roche, Basel, Switzerland) was injected into the vitreous cavity, 1.5 mm away from the limbus with a 30G 4 or 6 mm needle. The injection was performed in the operating room and under topical anesthesia.

All quantitative measurements and subjective plus scoring were performed by one clinician (SEB) with Image J (National Institutes of Health, Bethesda, MD, USA) software as described in previous studies.[13-15] In our previous study, we reported that this quantitative measurement method is reproducible.[14] The length of the temporal retinal vascularization (LTRV), the length of the shortest temporal retinal vascularization (LSTRV), and the length of the nasal retinal vascularization (LNRV), and FD were measured on PFIs and FFIs [Fig. 1]. All results were outputted as pixels in the Image J software. LSTRV/FD, LTRV/FD, and LNRV/FD ratios were calculated for PFIs and FFIs.

Table 1: Quantitative extent of retinal vascularization and refractive outcomes of the study eyes

	n	Unit	Mean±Std
Age at IVB treatment	171	w, PMA	36.5±2.5
Pre-IVB treatment LSTRV	171	FD	2.5±0.5
Pre-IVB treatment LTRV	171	FD	2.5±0.5
Pre-IVB treatment LNRV	45†	FD	1.6±0.6
Age at final imaging	127‡	w, PMA	66.1±16.0
Final LSTRV	127‡	FD	3.9±0.7
Final LTRV	127‡	FD	4.0±0.7
Final LNRV	20†‡	FD	2.9±0.8
Final SE	171	D	0.5±2.6
Age at final refraction	171	m	18.2±5.8

IVB=Intravitreal bevacizumab; LSTRV=The length of the shortest temporal retinal vascularization; LTRV=The length of the temporal retinal vascularization; LNRV=The length of the nasal retinal vascularization; SE=Spherical equivalent; w=week; PMA=postmenstrual age; FD=The distance from optic disc-to-fovea; D=Diopters; m=Month† = LNRV distance couldn't be measured precisely in all eyes, only measured eyes are presented;‡= If the interval between the final and pre-IVB images was smaller than 8 weeks, final images of these eyes were excluded from further analyses except eyes that underwent laser treatment

Plus disease was graded according to a previously recommended scoring scale.[11] The severity of venous dilatation and arterial tortuosity was graded in five levels as normal, pre-plus, mild plus, moderate plus, and severe plus.[11]

The cycloplegic refractive error was measured by using the Plusoptix A09 (Plusoptix GmbH, Nuremberg, Germany) device. Streak retinoscopy was performed in eyes with measurements that were out of range or excessive pupil dilation that prevented the device from measuring. The spherical equivalent (SE) was calculated by this formula (*SE = sphere + ½ cylinder*). The final SE measurement in the patient's chart was designated as the final refractive error. Cycloplegia was obtained with two drops of tropicamide 0.5% (infants that were <1 year of age) or 1.0%.

Statistical analysis used the SPSS (SPSS Inc, PASW Statistics for Windows, Version, 18.0, Chicago, USA). Normality analysis of the data was performed using the Kolmogorov–Smirnov test. Normally distributed data were analyzed with parametric tests, and other parameters were analyzed by nonparametric tests.

Table 2: Comparison of eyes treated with IVB and IVB plus delayed laser

	Eyes treated with IVB monotherapy			Eyes treated with primary IVB plus delayed laser			*P*
	n	Unit	Mean+Std	*n*	Unit	Mean±Std	
Age at IVB treatment	131	w, PMA	36.6±2.2	40	w, PMA	36.5±3.1	0.624[m]
Pre-IVB LSTRV	131	FD	2.5±0.5	40	FD	2.4±0.5	0.323[m]
Pre-IVB LTRV	131	FD	2.6±0.6	40	FD	2.4±0.5	0.195[m]
Pre-IVB LNRV	34	FD	1.6±0.5	11	FD	1.8±0.8	0.335[t]
Age at laser treatment	N/A	w, PMA		40	w, PMA	53.1±14.0	
Age at final imaging	87	w, PMA	71±13.9	40	w, PMA	55.2±15.1	0.000[m]
Final LSTRV	87	FD	4.2±0.6	40	FD	3.4±0.7	0.000[t]
Final LTRV	87	FD	4.2±0.5	40	FD	3.5±0.6	0.000[t]
Final LNRV	9	FD	3.2±0.8	11	FD	2.7±0.9	0.130[t]
Final SE	131	D	0.6±2.6	40	D	0.2±2.5	0.301[m]
Age at final refraction	131	m	18.6±6.0	40	m	16.9±4.9	0.133[m]

IVB=Intravitreal bevacizumab; LSTRV=The length of the shortest temporal retinal vascularization; LTRV=The length of the temporal retinal vascularization; LNRV=The length of the nasal retinal vascularization; FD=The distance from optic disc-to-fovea; D=Diopters; m=Month; [m]=Mann-Whitney *U* test; [t]=Independent samples *t* test

Table 3: Correlation of the variables with the final refractive outcome (Spherical equivalent, D)

	n	Unit	*r*	*P*[†]
Gestational age	171	w, PMA	-0.088	0.251
Birth weight	171	g	-0.018	0.814
Pre-treatment LNRV	45	FD	0.429	0.003
Pre-treatment LSTRV	171	FD	0.282	0.000
Pre-treatment LTRV	171	FD	0.267	0.000
Pre-treatment plus severity score	171	ordinal variable	-0.192	0.012
Pre-treatment retinal zone	171	categoric variable	0.190	0.013
The presence of additional IVB	171	categoric variable	0.057	0.456
The presence of additional laser	171	categoric variable	-0.079	0.302
The presence of A-ROP	171	categoric variable	0.122	0.112
Age at laser treatment	40	w, PMA	0.319	0.045
Final LNRV	20	FD	0.588	0.006
Final LSTRV	127	FD	0.286	0.001
Final LTRV	127	FD	0.274	0.002

D=Diopters; LNRV=The length of nasal retinal vascularization; LSTRV=The length of shortest temporal retinal vascularization; LTRV=The length of temporal retinal vascularization; IVB=Intravitreal bevacizumab; A-ROP=Aggressive retinopathy of prematurity; FD=Optic disc-to-fovea distance; w=Weeks; PMA=Postmenstrual age; [†] = Spearman test

Comparison between groups was made using independent-t or Mann–Whitney-*U* tests. Correlation analyses were performed with the Spearman test. Univariate logistic regression analyses were performed to evaluate the relationship between >1 D myopia and potential risk factors. A *P* value of <0.05 was considered significant.

Results

One hundred seventy-one eyes of 93 infants met all study criteria. Before IVB treatment, infants had been hospitalized in the NICUs of 35 different hospitals. The mean gestational age (GA) was 28.9 ± 2.5 weeks. The mean birth weight (BW) was 1282 ± 393 g. The mean treatment age was 36.6 ± 2.5 weeks PMA. One hundred thirty eyes were treated for type 1 ROP, and 41 eyes were treated for A-ROP. Before treatment, 83 eyes had zone I, 86 eyes had posterior zone II, and two eyes had peripheral zone II ROP.

Ten eyes underwent additional IVB treatment. The mean age at additional IVB treatment was 40.0 ± 4.6 weeks PMA. Forty eyes underwent laser treatment during follow-up. The mean age at laser treatment was 53.1 ± 14.0 weeks PMA. On final examination, the retinal zone was noted as zone I in 7 eyes, posterior zone II in 33 eyes, peripheral zone II in 72 eyes, and zone III in 59 eyes. The mean age at the final refraction examination was 18.2 ± 5.8 months postnatal. The final SE was 0.5 ± 2.6 D.

The detailed analyses of the quantitative extent of retinal vascularization of the eyes are presented in Table 1. The mean of pre-IVB and final LTRV/FD ratios were 2.5 ± 0.6 (n = 171), and 4.0 ± 0.7 (n = 127), respectively. LNRV/LTRV ratio was 0.74 ± 0.18 and 0.85 ± 0.11 on PFIs (n = 45) and FFIs (n = 20), respectively. The pre-IVB quantitative extent of retinal vascularization was similar between the eyes treated with IVB monotherapy and IVB plus delayed laser [Table 2]. LTRV improved 1.6 FD and 1.1

Table 4: Logistic regression analyses of covariates for > 1 D myopia development

	n	Unit (coding method of categorical and ordinal data)	Univariate model			Multivariate logistic regression model*		
			P	OR	95% confidence interval	*P*	OR	95% confidence interval
Gestational age	171	Week	0.659	0.968	0.837-1.119			
Birth weight	171	g	0.411	1.000	0.999-1.001			
Presence of A-ROP	171	(1: Type 1 ROP; 2: A-ROP)	0.962	0.980	0.420-2.285			
Pre-IVB retinal zone	171	(1: zone I ; 2: posterior zone II; 3: peripheral zone II	0.002	0.298	0.138-0.644			
IVB dose	171	(1: 0.625 mg; 2: 0.3125 mg)	0.488	0.774	0.375-1.596			
Presence of additional IVB	171	1: none; 2: present	0.545	1.543	0.379-6.278			
Presence of additional laser	171	1: none; 2: present	0.630	1.226	0.535-2.808			
Age at laser treatment	40	Week	0.120	0.935	0.860-1.018			
Pre-treatment plus severity score	171	1: no plus; 2: pre-plus; 3: mild plus; 4: moderate plus; 5: severe plus	0.015	1.677	1.106-2.544			
Pre-IVB LTRV/FD	171	Ratio	0.000	0.281	0.138-0.570	0.000	0.281	0.138-0.570
Final LTRV/FD	127	Ratio	0.001	0.317	0.160-0.630			

A-ROP=Aggressive-ROP; OR: odds ratio IVB=Intravitreal bevacizumab; ROP=Retinopathy of prematurity; D=Diopters; FD=The distance from optic disc-to-fovea; LTRV=The length of the temporal retinal vascularization;*=Logistic regression performed with forward LR method with the variables of pre-IVB retinal zone, pre-treatment plus severity score, and pre-IVB LTRV/FD ratio

FD in eyes treated with IVB monotherapy and IVB plus delayed laser, respectively. The final extent of retinal vascularization was more posterior in the eyes treated with primary IVB with delayed laser. Final SE was similar between groups.

There was no significant correlation between final SE with GA, BW, presence of type 1 ROP or ARPOP, IVB dose, and presence of additional IVB or laser treatments [Table 3]. There was a low positive correlation between final SE (hyperopic refraction) with pre-treatment and final LTRV/FD, LSTRV/FD, and LNRV/FD. There was a low negative correlation between final SE (hyperopic refraction) and pre-IVB plus severity. Scatter plots showing the relationship between refractive outcomes with pre-IVB and final LTRV/FD ratios, and plus severity score are presented in Fig. 2.

Out of 171 eyes, 38 eyes had >1 D myopia. In the univariate logistic analyses, pre-IVB retinal zone, pre-treatment plus severity score, pre-IVB LTRV/FD, and final LTRV/FD ratios were related to the development of >1 D myopia [Table 4]. GA, BW, presence of A-ROP, IVB dose, presence of additional IVB, and the presence of additional laser treatment were not related to the >1 D myopia. According to the multivariate logistic regression analysis that was performed with forward likelihood ratio (LR) method with the variables of the pre-IVB retinal zone, pre-treatment plus severity score, and pre-IVB LTRV/FD ratio, increased pre-IVB LTRV/FD ratio was found to be as an independent predictive variable for a lower likelihood of having >1D myopia myopia (Odds ratio (OR): 0.281; $P = 0.000$).

Discussion

GA, BW, IVB dose, presence of additional IVB, or laser treatments were not associated with the final refractive outcome. Our study demonstrated a linear and weak positive relationship between pre-IVB retinal vascularization and hyperopic refraction. In addition, the present study reports a weak positive relationship between the plus severity score and myopic refraction.

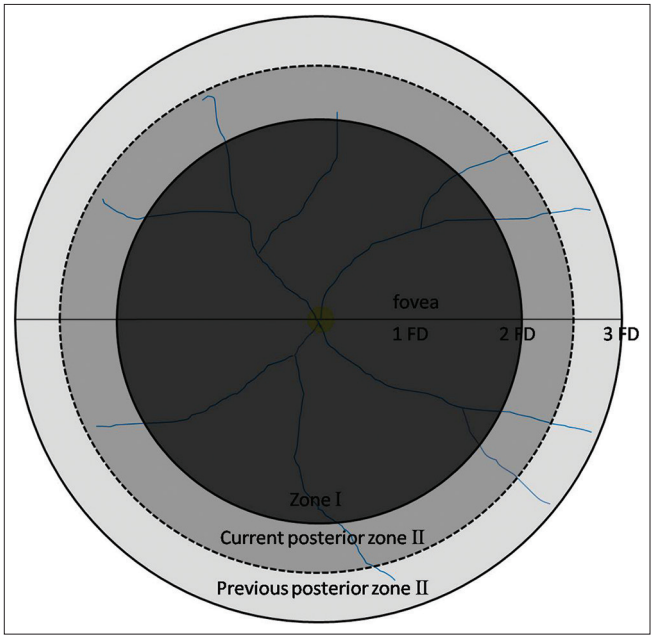

Figure 3: The posterior zone II that we used in the presented study encompasses the current posterior zone II described in the International Classification of Retinopathy of Prematurity Third Edition 2021. FD: The distance from the optic disc-to-fovea

The developmental process of the ocular structures may be affected by the prematurity, concomitant systemic abnormalities, presence and severity of ROP, and treatment type of ROP disease.[16-18] Steepening of the cornea, decreased anterior chamber depth, and increased lenticular thickness

were the probable alterations that induce more myopia in prematurely born infants.[16,19-22] All these changes may conclude with nonaxial myopia in the eyes of prematurely born infants. We consider that the pre-IVB extent of retinal vascularization, duration of arrested retinal vascularization, and progression of retinal vascularization may affect these prematurity-related myopic factors. But this topic should be investigated with further studies.

In a recent study investigating the relationship between the laser-treated area and refractive outcomes, it has been shown that myopia was higher in the eyes with a larger proportion of the retina treated with laser.[23] In addition, a greater number of laser burns was found to be accountable for high myopia.[23,24] Our study indicates that not only in laser-treated eyes but also in IVB-treated eyes, pre-treatment and final extent of retinal vascularization affect the final refractive outcome.

In the ICROP 2005, zone II had not been divided into subgroups.[12] In 2007, Hittner *et al*.[8] identified the ringed-shaped area between two and three times FD away from the optic disc as posterior zone II. Although the recently published ICROP 2021 report advises posterior zone II and peripheral zone II terms, the committee defined a region of 2 disc diameters peripheral to the zone I border as posterior zone II.[10] Therefore, the posterior zone II that we used in the presented study encompasses the current posterior zone II described in the ICROP 2021[Fig. 3]. Eyes that were grouped as posterior zone II during clinical practice may be grouped as peripheral zone II according to the current classification. In addition, zone determination, which is performed with an indirect ophthalmoscope, may vary according to the experience of the practitioner. The naso-temporal asymmetry is a confounding factor while determining the zone with BIO. In addition, practitioners may tend to bias in terms of detecting the more posterior zone, especially when determining the pre-treatment zone. Therefore, we performed the quantitative measurements to depict the real extent of retinal vascularization to prevent variabilities of examinations conducted by different practitioners.

Even in eyes diagnosed with the plus disease by the same expert, the severity of the plus disease may vary between the eyes. Our study shows that pre-IVB plus severity may affect the final refractive outcome.

In our recently published study with larger sample size, we reported that the pre-treatment retinal zone was the main indicator for the final refractive outcome.[9] Our present study adds that the reporting of pre-IVB temporal retinal vascularization as an independent predictor for the development of >1D myopia, suggests that quantitative assessment may be superior to categorical assessment such as for zone I or posterior zone II. In this presented and previous study, BW and GA were not related to the refractive outcome. We predict that two factors might affect our results. In our region, severe ROP may develop even in larger preterm infants, and our study population consists of heterogeneous infants hospitalized in the different levels of NICUs. Therefore, posterior-severe ROP and high myopia can be detected in a 2000 g born infant in a center where NICU conditions are not sufficient, while ROP may not develop in a 1000 g born infant in a center where adequate intensive care support is provided, or it may be peripherally located even if type 1 ROP develops. Our study indicates that the main factors determining refractive outcome in infants treated with IVB are pre-treatment retinal vascularization and the severity of plus, which are the main factors that show the severity of the disease during the first treatment.

In the analyses that compare the eyes with and without laser, although final refractive outcomes were similar, the mean LTRV was 0.7 FD higher in the without laser eyes. On the other hand, in eyes with a delayed laser, we observed 1.1 FD improvement on the LTRV, and the final LTRV was 3.5 ± 0.6 FD. This finding may suggest that the progression of LTRV from 3.5 FD to 4.2 FD is not very critical for refractive outcomes. Late recurrences and persistent avascular retina are frequent and challenging conditions after IVB treatment.[25,26] Delayed or prophylactic laser is a preferable treatment modality in eyes that underwent primary IVB.[27,28] Due to the fact that the final SE was similar between groups, we consider that delayed, or prophylactic laser treatment is refractively safe in eyes in which the LTRV/FD ratio reaches 3.5.

There are several limitations of the study. The vascular-avascular ridge border was not assessable in all eyes in all quadrants. Although the temporal ridge border was assessable in all eyes, the nasal, superior, and inferior ridge border was assessable only in a small portion of the eyes. Therefore, we could be able to evaluate only the temporal extent of retinal vascularization in all eyes. Although retinal vascularization shows naso-temporal asymmetry, this asymmetry is generally at a predictable rate. To minimalize this limitation, we presented the LNRV/LTRV ratio in eyes whose ridge border was assessable both on the temporal and nasal periphery.

Conclusion

In conclusion, our study revealed that in our cohort that consisted of IVB-treated eyes, there was a weak positive correlation between the development of myopia with the severity of the plus disease and a weak negative correlation between the extent of retinal vascularization with myopic refraction. Although our study provides important data in terms of showing the linear relationship, it is known that the refractive process in infants and children is multifactorial, independent of ROP and prematurity. Corneal curvature, anterior chamber depth, lens thickness, axial length, genetic, environmental, and other factors may affect the refractive outcome in prematurely born infants. Our findings suggest that the extent of retinal vascularization and plus severity should be considered along with other factors in further comprehensive studies that investigate the refractive outcomes of eyes treated with anti-VEGF.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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