· Clinical Research ·

Refractive status and ocular characteristics of preschool children with retinopathy of prematurity after different treatments

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Abstract
● **AIM:** To compare the changes in preschool refractive status, ocular biological parameters, and higher-order aberrations in children with retinopathy of prematurity (ROP) after retinal laser photocoagulation or anti-vascular endothelial growth factor (anti-VEGF) treatment and explore their underlying factors.

● **METHODS:** This observational study involved 118 eyes of 59 children, aged 3 to 6y, with ROP followed up between March 2023 and October 2024. They were divided into the laser, anti-VEGF, and anti-VEGF+laser groups. The laser group received a single session of laser photocoagulation. The anti-VEGF group received a single anti-VEGF treatment. The anti-VEGF+laser group received a single anti-VEGF treatment after birth followed by supplementary laser treatment within 2wk to 6mo. Ocular biological parameters were measured using IOL Master 700 and Pentacam HR. Right-eye higher-order aberrations were measured using the OPD-Scan III. Best-corrected visual acuities (BCVA), refractive statuses, ocular biological parameters, and higher-order aberrations were assessed and compared. Multiple linear regression analysis was conducted to evaluate the relationships among ocular biological parameters, higher-order aberrations, spherical equivalent (SE), and treatment methods. Pearson's correlation coefficients were used to assess the relationships between the SE and higher-order aberrations.

● **RESULTS:** The laser group had a higher incidence of myopia and a lower SE than the anti-VEGF group. The incidence of astigmatism and cylindrical power were significantly lower for the anti-VEGF than for the laser and anti-VEGF+laser groups ($P<0.05$). The anterior corneal surface astigmatism was higher for the laser and anti-VEGF+laser groups than for the anti-VEGF group. The anterior corneal surface K_2 and lens thickness were higher for the laser and anti-VEGF+laser groups than for the anti-VEGF group. The whole-eye higher-order aberration root mean square (RMS) values for the right eye were significantly higher for the laser and anti-VEGF+laser groups than for the anti-VEGF group. The whole-eye trefoil RMS values for the right eye were also significantly higher for the laser and anti-VEGF+laser groups than for the anti-VEGF group ($P<0.05$). Laser treatment was significantly associated with SE, anterior corneal surface curvature and astigmatism, lens thickness, whole-eye high-order aberrations, and whole-eye trefoil (all $P<0.05$).

● **CONCLUSION:** Children with ROP who received laser treatment have higher myopia and astigmatism than those who received anti-VEGF treatment. Children treated with laser or supplementary laser treatment have higher anterior corneal astigmatism, anterior corneal curvature, thicker lenses, whole-eye higher-order aberrations, and whole-eye trefoil. The cause of myopia in children with ROP after laser treatment is increased anterior corneal surface curvature and lens thickness.

● **KEYWORDS:** retinopathy of prematurity; refractive status; ocular biological parameters; higher order aberration
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INTRODUCTION

Retinopathy of prematurity (ROP) is a proliferative vascular disease of the retina that commonly occurs in preterm infants born at a gestational age of less than 32wk or with a birth weight of less than 2000 g. It can lead to retinal detachment and significant visual impairment in severe cases[1]. The two conventional treatment modalities for ROP are retinal laser photocoagulation and intravitreal injection of anti-vascular endothelial growth factor (VEGF). Both treatments have been effective in preventing lesion progression[2-3], but may have an impact on the development of the postoperative refractive state in the middle and long term[4].

The refractive state of the eye is primarily determined by the interaction of various biological parameters, with the most important ones being corneal curvature, anterior chamber depth, lens thickness, and axial length. Higher order aberrations can impact the quality of retinal imaging and may also influence the development of refractive errors[5]. This suggests possible connections between the refractive state of children with ROP and ocular biological parameters, as well as higher order aberrations. Previous research reports have indicated that children with ROP who received laser treatment were more myopic than those who received VEGF treatment[6]. However, after receiving anti-VEGF treatment followed by supplementary laser treatment, the degree of myopia in ROP patients significantly decreases[7], indicating that anti-VEGF treatment provides clear refractive advantages. The eye development process in children with ROP may be altered following different treatments, and changes in ocular biological parameters[8] and higher-order aberrations[9] could potentially influence the refractive status of children with ROP. Currently, there are several studies on the refractive status of children with ROP receiving laser or anti-VEGF treatment, but only a few of them have comprehensively compared and analyzed the development of the characteristics of the affected eyes after treatment, especially regarding the development of the affected eye following supplementary laser therapy. In addition, it is not clear whether higher-order aberrations change in affected eyes treated with laser or anti-VEGF treatment and whether these changes are related to the spherical equivalent (SE).

The objective of this study was to compare the preschool refractive statuses, ocular biological parameters, and higher-order aberrations in children treated with laser therapy and anti-VEGF therapy. Additionally, the study aimed to evaluate factors influencing the refractive status of children with ROP who received different treatments. The goal was to provide insights into the personalized selection of clinical treatment methods and prevention and management of refractive errors in children with ROP.

PARTICIPANTS AND METHODS

Ethical Approval This observational study adhered to the principles of the Helsinki Declaration and was approved by the Ethics Committee of the Hospital (approval: KY20232305-C-1), the legal guardians of the children voluntarily signed the informed consent.

Study Population and Grouping It involved infants who were born premature and underwent fundus examination at the hospital between January 2018 and December 2020; were diagnosed with ROP; and received treatment. The inclusion criteria were as follows: 1) meeting the international classification criteria for ROP and the diagnostic criteria for threshold ROP, type 1 prethreshold ROP or aggressive retinopathy of prematurity (A-ROP) as outlined in the Chinese ROP screening guidelines[1,10]; 2) having received laser therapy or anti-VEGF treatment at our hospital and having been followed up until the lesion subsided or was stabilized; 3) having undergone regular follow-up examinations with complete data. The exclusion criteria were: 1) unclear refractive media; 2) presence of other eye diseases or prior eye surgeries; 3) family history of high myopia; 4) history of retinal detachment or prior vitrectomy or other surgical treatments.

The infants were divided into the following three groups according to the treatments they received during the neonatal period: laser group, anti-VEGF group, and anti-VEGF+laser group. Infants in the laser group received a single session of retinal laser photocoagulation after the diagnosis of ROP. The ridge and peripheral retinal avascular areas were treated with 810 nm laser photocoagulation. Infants in the anti-VEGF group received a single anti-VEGF treatment after the diagnosis of ROP, with intravitreal injection of 0.25 mg of conbercept (Chengdu Kanghong Biotechnology Co., Ltd., China) or 0.25 mg of ranibizumab (Novartis, Switzerland). Infants in the anti-VEGF+laser group were treated with supplementary retinal laser photocoagulation within 2wk to 6mo after receiving the first anti-VEGF treatment. Both retinal laser photocoagulation and intravitreal injection of anti-VEGF were performed by the same senior doctor under general anesthesia. These children with ROP were followed from March 2023 to October 2024 for best-corrected visual acuities (BCVA), refractive status, ocular biological parameters, and high-order aberrations.

Measurement of Best-Corrected Visual Acuity and Refractive Status All children received treatment with compound tropicamide eye drops (Shenyang Xingqi Eye Drug Co., Ltd., China) for mydriasis, with 0.1 mL of eye drops administered at 5min intervals for four times. The automatic optometer (KR800; Topcon, Japan) was used to measure the refractive error. Retinoscopy with a banded light lens was also performed when the pupil diameter reached ≥6 mm, and there was no light reflection. The optometric assessments

Table 1 Comparison of demographic data of the laser, anti-VEGF, and anti-VEGF+laser groups *n*, mean±SD

Groups	Age (y)	Gestational week of birth (wk)	Birth weight (g)	Time of last treatment (wk)	Sex (male/female)
Laser	4.30±1.22	29.02±1.76	1261.25±305.33	41.42±2.99	12/8
Anti-VEGF	4.26±1.15	28.64±2.79	1126.84±284.04	41.59±3.12	11/8
Anti-VEGF+laser	4.30±1.26	29.18±1.80	1206.25±229.78	51.22±7.18[a,b]	10/10
F/χ^2	0.006	0.319	1.176	26.339	0.450
P	0.994	0.728	0.316	>0.001	0.799

P<0.05 statistically significant difference. [a]P<0.05 *vs* laser group; [b]P<0.05 *vs* anti-VEGF group. VEGF: Vascular endothelial growth factor.

were performed by the same optometrist, and the spherical and cylindrical power for each group of patients were recorded. BCVA was assessed using a standard logarithmic eye chart (GB11533-89) and converted to logMAR.

Ocular Biological Parameters and Higher Order Aberration Measurements The eye parameters of the children were measured using the IOL Master 700 (Zeiss, Germany), Pentacam HR (OCULUS, Germany), and OPD-Scan III (Nidek, Japan). The IOL Master 700 was used to measure central corneal thickness, anterior chamber depth, lens thickness, and axial length. The Pentacam HR was employed to measure the astigmatism of the anterior and posterior corneal surfaces, average curvature (K_m) of the anterior and posterior corneal surfaces, flat curvature (K_1) of the anterior and posterior corneal surfaces, and the steep curvature (K_2) of the anterior and posterior corneal surfaces. The OPD-Scan III was used to measure the high-order aberrations of the right eyes of the children. The root mean square (RMS) value was used to record the high-order aberrations of the entire eye, corneal high-order aberrations, and intraocular high-order aberrations of the child through a 4-mm pupil.

Evaluation Method The SE was used to evaluate refractive status. It was given as follows: SE=sphere+1/2cylinder. Myopia was defined as SE of ≤-0.50 D after pupil dilation[11], and astigmatism was defined as cylindrical power of ≥1.00 D after pupil dilation[12].

Statistical Analysis SPSS 27.0 was used for the statistical analysis. The Kolmogorov-Smirnov test revealed that all data conformed to the normal distribution, and they were summarized as mean±standard deviation. Continuous variables were compared using one-way ANOVA. Data with differences in the one-way ANOVA results were variance-aligned using LSD multiple comparisons for post-hoc tests, variance-inconsistency was post-hoc tested using Tamhane's T2, and categorical data were analyzed using the Chi-squared test. Multiple linear regression analysis was conducted to evaluate the relationships among ocular biological parameters, higher-order aberrations, SEs, and treatment methods. Pearson's correlation coefficients were used to assess the relationships between the SE and higher-order aberrations. Differences were considered statistically significant at P<0.05.

Table 2 Comparison of severity of ROP in the laser, anti-VEGF, and anti-VEGF+laser groups

Groups	ROP typing (number of eyes)		
	A-ROP	Type-1 prethreshold ROP	Threshold ROP
Laser	0	27	13
Anti-VEGF	2	20	16
Anti-VEGF+laser	2	22	16
χ^2		3.444	
P		0.487	

P<0.05 Statistically significant difference. ROP: Retinopathy of prematurity; VEGF: Vascular endothelial growth factor; A-ROP: Aggressive retinopathy of prematurity.

RESULTS

General Information of Children in Each Group A total of 118 eyes of 59 children with ROP who were treated with laser or anti-VEGF therapy were included in this study. The laser group comprised 20 children (12 males and 8 females; mean age of 4.30±1.22y) with a total of 40 eyes. The anti-VEGF group comprised 19 children (11 males and 8 females; mean age of 4.26±1.15y) with a total of 38 eyes. The anti-VEGF+laser group comprised 20 children (10 males and 10 females; mean age of 4.30±1.26y) with a total of 40 eyes. The ages, gender distributions, gestational weeks of birth, birth weights, and disease severity of the groups did not differ significantly (P>0.05). The corrected gestational age at the last treatment time in the anti-VEGF+laser treatment group was 51.22±7.18wk, which was significantly higher than that in the laser treatment group (41.42±2.99wk) and the anti-VEGF treatment group (41.59±3.12wk; P<0.05; Tables 1 and 2).

Comparison of the BCVAs and Refractive Statuses of the Treatment Groups The BCVAs of the children in the laser, anti-VEGF, and anti-VEGF+laser groups were not significantly different (P>0.05). However, their refractive statuses were significantly different. The prevalence of myopia was 45.00% in the laser group, which was significantly higher than 13.16% in the anti-VEGF group (P<0.05). SE of laser group was -0.39±2.02 D, significantly lower than that of anti-VEGF group 0.55±1.41 D (P<0.05). The laser and anti-VEGF+laser groups had significantly higher prevalence of astigmatism than the anti-VEGF group (55.00%, 62.50% *vs* 26.23%; P<0.05). The laser and anti-VEGF+laser groups had significantly higher

Table 3 Comparison of BCVAs and refractive statuses of the laser, anti-VEGF, and anti-VEGF+laser groups *n* (%), mean±SD

Parameters	Laser	Anti-VEGF	Anti-VEGF+laser	F/χ^2	P
Number of cases/eyes	20/40	19/38	20/40		
BCVA	0.24±0.21	0.20±0.18	0.20±0.16	0.489	0.615
SE (D)	-0.39±2.02	0.55±1.41[a]	0.06±1.41	3.134	0.047
Mean cylindrical power (D)	1.20±1.02	0.70±0.74[a]	1.24±0.95[b]	4.232	0.017
Prevalence of myopia (%)	18 (45.00)	5 (13.16)[a]	12 (30.00)	9.474	0.009
Prevalence of astigmatism (%)	22 (55.00)	10 (26.23)[a]	25 (62.50)[b]	11.304	0.004

BCVA: Best-corrected visual acuity; SE: Spherical equivalent; VEGF: Vascular endothelial growth factor. [a]P<0.05 *vs* laser group; [b]P<0.05 *vs* anti-VEGF group.

Table 4 Comparison of ocular biological parameters of the laser, anti-VEGF, and anti-VEGF+laser groups mean±SD

Parameters	Laser	Anti-VEGF	Anti-VEGF+laser	F	P
Axis length (mm)	21.88±1.12	21.96±0.72	21.64±0.86	1.326	0.270
Central corneal thickness (μm)	527.33±31.82	543.16±43.47	533.52±27.83	2.009	0.140
Anterior chamber depth (mm)	3.34±0.18	3.35±0.23	3.29±0.20	0.824	0.441
Lens thickness (mm)	3.73±0.14	3.62±0.19[a]	3.73±0.15[b]	5.905	0.004
Anterior corneal surface astigmatism (D)	-1.85±1.03	-1.20±0.57[a]	-1.92±1.08[b]	7.207	0.001
Posterior corneal surface astigmatism (D)	0.45±0.21	0.43±0.24	0.40±0.24	0.383	0.683
Anterior corneal surface K_m (D)	44.77±1.22	44.03±1.63	44.63±1.58	2.729	0.069
Anterior corneal surface K_1 (D)	43.87±1.18	43.46±1.56	43.71±1.56	0.783	0.459
Anterior corneal surface K_2 (D)	45.77±1.53	44.62±1.73[a]	45.64±1.80[b]	5.387	0.006
Posterior corneal surface K_m (D)	-6.47±0.29	-6.47±0.24	-6.48±0.37	0.005	0.995
Posterior corneal surface K_1 (D)	-6.26±0.29	-6.29±0.25	-6.30±0.33	0.150	0.861
Posterior corneal surface K_2 (D)	-6.71±0.34	-6.69±0.27	-6.65±0.45	0.314	0.732

K_m: Mean curvature; K_1: Flat curvature; K_2: Steep curvature; VEGF: Vascular endothelial growth factor. [a]P<0.05 *vs* laser group; [b]P<0.05 *vs* anti-VEGF group.

cylindrical powers than the anti-VEGF group (1.20±1.02 D, 1.24±0.95 *vs* 0.70±0.74 D; P<0.05). The choice of treatment did not have a significant effect on BCVA. However, the laser group had higher prevalence of myopia and astigmatism and cylindrical lens power and lower SE (Table 3).

Comparison of Ocular Biological Parameters of the Different Treatment Groups The ocular biological parameters differed significantly across the laser, anti-VEGF+laser, and anti-VEGF groups. The anterior corneal surface astigmatism (-1.85±1.03 D, -1.92±1.08 D) in laser group and anti-VEGF+laser group was significantly higher than that in anti-VEGF group (-1.20±0.57 D; P<0.05). The anterior corneal surface K_2 (45.77±1.53, 45.64±1.80 D) in the laser and anti-VEGF+laser groups was significantly higher than that in the anti-VEGF group (44.62±1.73 D; P<0.05). The lens thickness (3.73±0.14 mm, 3.73±0.15 mm) in the laser group and the anti-VEGF+laser group was significantly higher than that in the anti-VEGF group (3.62±0.19 mm; P<0.05). There were no statistically significant differences in the ocular axis length and anterior chamber depth between the laser, anti-VEGF, and anti-VEGF+laser groups (P>0.05). Astigmatism on the anterior surface of the cornea, K_2 on the anterior surface of the cornea, and lens thickness increased in children following single laser treatment or supplemental laser treatment (Table 4).

Comparison of Higher-Order Aberrations in the Different Treatment Groups Some of the higher order aberration values differed for the various treatment groups. The whole-eye higher-order aberration RMS values of the right eyes of the children in the laser and the anti-VEGF+laser groups were significantly higher than those of the children in the anti-VEGF group (0.255±0.094, 0.267±0.120 *vs* 0.185±0.067; P<0.05). The whole-eye trefoil RMS values of the right eyes of the children in the laser and the anti-VEGF+laser groups were significantly higher than those of the children in the anti-VEGF group (0.195±0.086, 0.201±0.088 *vs* 0.134±0.068; P<0.05). Except for the whole-eye higher order aberration and whole-eye trefoil, no significant differences were observed in the higher-order aberrations in the right eyes across the treatment groups (Table 5).

Effects of Different Treatment Methods on Spherical Equivalents, Ocular Biological Parameters, and Higher Order Aberrations in Children with ROP Anti-VEGF treatment was used as reference to set dummy variables, and the age and gender of the children with ROP were corrected.

Table 5 Comparison of higher-order aberrations in the laser, anti-VEGF, and anti-VEGF+laser groups mean±SD

Parameters	Laser	Anti-VEGF	Anti-VEGF+laser	*F*	*P*
Higher-order aberration (μm)	0.255±0.094	0.185±0.067[a]	0.267±0.120[b]	4.078	0.022
Coma (μm)	0.061±0.024	0.058±0.030	0.066±0.033	0.361	0.699
Trefoil (μm)	0.195±0.086	0.134±0.068[a]	0.201±0.088[b]	3.991	0.024
Spherical aberration (μm)	0.024±0.016	0.029±0.019	0.035±0.028	1.263	0.291
Corneal high-order aberration (μm)	0.243±0.117	0.237±0.138	0.232±0.120	0.041	0.960
Intraocular high-order aberration (μm)	0.290±0.142	0.252±0.122	0.310±0.170	0.773	0.466

[a]*P*<0.05 vs laser group; [b]*P*<0.05 *vs* anti-VEGF group. VEGF: Vascular endothelial growth factor.

Table 6 Multiple linear regression analysis of spherical equivalents, ocular biological parameters, and higher order aberrations

Parameters	Laser	Anti-VEGF+laser
SE	*B*=-0.943, *P*=0.012	*B*=-0.484, *P*=0.195
Axial length	*B*=-0.096, *P*=0.617	*B*=-0.301, *P*=0.119
Central corneal thickness	*B*=-16.186, *P*=0.039	*B*=-8.366, *P*=0.283
Anterior chamber depth	*B*=-0.014, *P*=0.755	*B*=-0.052, *P*=0.257
Lens thickness	*B*=0.106, *P*=0.004	*B*=0.108, *P*=0.003
Anterior corneal surface astigmatism (D)	*B*=-0.667, *P*=0.001	*B*=-0.688, *P*=0.001
Posterior corneal surface astigmatism (D)	*B*=0.022, *P*=0.667	*B*=-0.026, *P*=0.623
Anterior corneal surface K_m	*B*=0.753, *P*=0.027	*B*=0.582, *P*=0.087
Anterior corneal surface K_1	*B*=0.409, *P*=0.217	*B*=0.254, *P*=0.443
Anterior corneal surface K_2	*B*=1.166, *P*=0.003	*B*=0.988, *P*=0.011
Posterior corneal surface K_m	*B*=-0.003, *P*=0.970	*B*=-0.008, *P*=0.906
Posterior corneal surface K_1	*B*=0.023, *P*=0.727	*B*=-0.013, *P*=0.846
Posterior corneal surface K_2	*B*=-0.022, *P*=0.785	*B*=0.045, *P*=0.587
Higher-order aberration	*B*=0.073, *P*=0.001	*B*=0.078, *P*>0.001
Coma	*B*=-0.000, *P*=0.980	*B*=0.003, *P*=0.650
Trefoil	*B*=0.073, *P*>0.001	*B*=0.076, *P*>0.001
Spherical aberration	*B*=-0.002, *P*=0.589	*B*=0.005, *P*=0.266
Corneal high-order aberration	*B*=0.030, *P*=0.285	*B*=0.006, *P*=0.828
Intraocular high-order aberration	*B*=0.035, *P*=0.257	*B*=0.048, *P*=0.119

P<0.05 statistically significant difference. SE: Spherical equivalent.

Table 7 Correlation analysis of higher-order aberrations and spherical equivalents of the laser, anti-VEGF, and anti-VEGF+laser groups

Parameters	laser	Anti-VEGF	Anti-VEGF+laser
Higher-order aberration	*r*=-0.138, *P*=0.560	*r*=-0.560, *P*=0.013	*r*=0.023, *P*=0.925
Coma	*r*=-0.214, *P*=0.365	*r*=-0.107, *P*=0.661	*r*=-0.477, *P*=0.003
Trefoil	*r*=-0.161, *P*=0.498	*r*=-0.591, *P*=0.008	*r*=0.056, *P*=0.814
Spherical aberration	*r*=-0.252, *P*=0.285	*r*=0.356, *P*=0.134	*r*=-0.538, *P*=0.014
Corneal high-order aberration	*r*=0.099, *P*=0.678	*r*=-0.598, *P*=0.007	*r*=0.015, *P*=0.951
Intraocular high-order aberration	*r*=0.158, *P*=0.506	*r*=-0.566, *P*=0.012	*r*=0.197, *P*=0.406

P<0.05 Statistically significant difference. VEGF: Vascular endothelial growth factor.

The results showed that laser treatment was negatively associated with SE, central corneal thickness, and anterior corneal surface astigmatism in children with ROP (*P*<0.05). However, it was positively associated with lens thickness, anterior corneal surface curvature (K_2, K_m), whole-eye high-order aberration, and whole-eye trefoil (*P*<0.05). Anti-VEGF+laser treatment was negatively associated with anterior corneal surface astigmatism in children with ROP (*P*<0.05) but positively associated with lens thickness, anterior corneal surface curvature K_2, whole-eye high-order aberration, and whole-eye trefoil in children with ROP (*P*<0.05; Table 6).

Correlation Analysis of High-order Aberration and Spherical Equivalents For the laser group, there was no correlation between higher-order aberrations and SE (Table 7). For the anti-VEGF group, the SE was negatively correlated with whole-eye higher-order aberration (*r*=-0.560, *P*=0.013), whole-eye trefoil (*r*=-0.591, *P*=0.008), corneal higher-order aberration (*r*=-0.598, *P*=0.007), and intraocular higher-order aberrations (r=-0.566, P=0.012; Table 7).

For the anti-VEGF+laser group, the SE was negatively correlated with whole-eye coma (r=-0.477, P=0.003) and whole-eye spherical aberration (r=-0.538, P=0.014; Table 7).

DISCUSSION

In recent years, there has been significant interest in comparing the medium- and long-term prognoses of ROP after laser therapy and anti-VEGF therapy. The preschool age is critical for the development of ocular structure and visual function in children. Understanding the characteristics of ocular development in children with ROP is of great significance for preventing and controlling the development of refractive errors. In our study, we conducted follow-up assessments of preschool children with ROP who were treated with laser therapy or anti-VEGF therapy. We compared their refractive statuses, ocular biological parameters, and higher-order aberrations after receiving their treatments. The children with ROP who received laser therapy alone had a higher prevalence of myopia and a lower SE than those who received anti-VEGF therapy alone. Further, children who received laser therapy alone or in combination with laser-assisted therapy showed a higher prevalence of astigmatism and had higher cylindrical lens power than those who received anti-VEGF therapy alone. Additionally, children treated with laser therapy had higher anterior corneal astigmatism, anterior corneal K_2 values, thicker lenses, whole-eye higher-order aberrations, and whole-eye trefoil.

This study revealed differences in refractive status between the treatment groups. The laser group had a higher prevalence of myopia and lower SE than the anti-VEGF group. This suggested that the refractive status of children with ROP treated with laser therapy was more inclined toward myopia, a result consistent with that of BEAT-ROP[4]. This study also found that the prevalence of myopia and SE for the anti-VEGF+laser group did not differ from those for the laser group, suggesting that children with ROP receiving supplementary laser treatment may also have myopia. However, the results of the study by Anand *et al*[7] were not consistent with those of the present study, which showed that the degree of myopia in children in the anti-VEGF+laser group was significantly lower than that in those treated with laser alone. In this study, the mean corrected gestational age of children with ROP receiving supplementary laser therapy was 51.22wk, whereas in the study by Anand *et al*[7], the corrected gestational age of children with ROP receiving supplementary laser therapy exceeded 60wk. We speculate that the inconsistency of the results is attributable to the time of receiving supplementary laser therapy and the difference between the degrees of retinal vascularization in children with ROP in this study and the study by Anand *et al*[7]. Continued growth of retinal blood vessels towards the periphery of the retina after anti-VEGF treatment and the higher degree of retinal vascularization may be beneficial for optimizing the refractive status[13]. However, supplementary laser treatment prevents the continued growth of retinal blood vessels and damages the peripheral retina, which may lead to interruption of the normalization process[14]. Therefore, further comparative studies are needed to confirm how laser treatment, as supplementary treatment, influences the inclination of the refractive status towards myopia. In this study, we also compared the astigmatism of children who had received different treatments. The prevalence of astigmatism and the cylindrical powers were higher for the children treated with laser alone or laser supplementation than for those treated with anti-VEGF therapy alone. This suggests that children with ROP treated with laser have more severe astigmatism, which is consistent with the conclusion of Tan *et al*[15]. These results indicate differences in the mid- and long-term refractive status of children with ROP treated with laser or anti-VEGF therapy, and children with ROP treated with laser are more likely to develop myopia and astigmatism.

Changes in the ocular biological parameters are the direct cause of the altered refractive status in children. The cornea, as an important component of the refractive system, accounts for approximately 75% of the total refractive power of the human eye[16]. This study showed that the astigmatism and K_2 value of the anterior surface of the cornea significantly increased after laser treatment relative to anti-VEGF treatment. The K_m value of the anterior surface of the cornea showed a tendency to increase, but no significant difference was observed. The increased corneal curvature led to an increase in corneal refractive power, and the refractive status of the children treated with laser was more inclined toward myopia. Wu *et al*[17] studied and compared the anterior and posterior corneal surface parameters in children with ROP after different treatments, revealing that laser treatment was associated with higher corneal curvature and corneal astigmatism. This was further supported by the findings of the present study. The increase in corneal curvature and corneal astigmatism observed in children undergoing laser treatment may be attributed to oxidative stress induced within the cornea during the laser treatment process. This oxidative stress triggers apoptosis of corneal cells and corneal tissue remodeling[18]. Additionally, scattered laser energy may cause damage to the corneal nerves[19], altering the production of trophic factors by these nerves and thereby affecting the normal development of the cornea[20]. Furthermore, laser treatment can induce irreversible damage to the surrounding retina and compromise its integrity, potentially disrupting the normal development of the anterior segment of the eye[21-22]. The refractive status of children with ROP is also related to the anterior chamber depth and lens thickness[23]. In this study, the lens thicknesses of children with ROP in the laser and anti-VEGF+laser groups were higher than those of the children in the anti-VEGF group. The depth of the anterior chamber did not differ significantly across the three groups of children with ROP, indicating that thickening of the lens may increase the refractive power of the lens. The refractive state of children with ROP who received laser treatment was more inclined toward myopia. It has been suggested that myopia in children with ROP treated with laser may be due to increased narrowing of the anterior chamber and increased lens thickness[24], which are partially different from the results of the present study. The anterior chamber depth did not differ across the groups in the present study, and this may be attributed to changes in the relative position of the lens to affect the anterior chamber depth. However, the relative positions of the lens during eye development in the children with ROP in the groups did not differ. Only a difference in lens morphologic development was observed, which may be related to the integrity of the peripheral retina[21]. After a single laser treatment or supplemental laser therapy, the peripheral retina of the child may sustain permanent damage, which subsequently impairs the image perception capabilities of the peripheral retina. The resulting retinal neural conduction abnormalities may also transmit aberrant electrical signals to the ciliary muscle, inducing ciliary muscle contraction. This contraction activates signaling pathways that regulate the morphological development of lens fiber cells, ultimately leading to remodeling of the lens shape[25]. Following laser treatment, the increased lens thickness observed in children with ROP may potentially affect their long-term ocular accommodation ability. Children with ROP may therefore be more susceptible to developing accommodative myopia. Previous studies have confirmed that the development of refractive status in children is closely related to changes in the length of the ocular axis[26], which is an important factor affecting the refractive status of children. In this study, we observed no significant differences among the ocular axis lengths of the children in the laser, the anti-VEGF, and anti-VEGF+laser groups. This was consistent with the results reported by other studies[8,17]. The differences in refractive status among children with ROP treated with different modalities were not due to differences in axial length but differences in the curvature of the anterior surface of the cornea and the thickness of the lens.

The refractive status and ocular development in children with ROP are directly influenced by age. Therefore, this study employed linear regression analysis after adjusting for age and gender to investigate the specific effects of different treatment modalities on the refractive status and ocular development of children with ROP. The results demonstrated that, compared with anti-VEGF therapy, laser therapy was associated with increased anterior corneal astigmatism, anterior corneal surface curvature, and lens thickening in children with ROP. These findings further confirm that laser treatment can induce changes in ocular biological parameters in children with ROP, potentially contributing to myopia and astigmatism.

The refractive status of children with ROP is not only related to ocular biological parameters such as corneal curvature and lens thickness but may also be related to higher order aberrations. High order aberrations represent optical defects of the eye. Among these aberrations, coma, trefoil, and spherical aberration have the greatest influence on the quality of retinal imaging. A reduction in retinal imaging quality may alter the regulatory signal for eye growth and refractive state development[27]. Whole-eye higher-order aberrations and whole-eye trefoil were observed after laser treatment. We speculate that the cause may be energy absorption during the laser treatment process that altered the metabolism and proliferation of the refractive medium cells. This affected the morphology and optical properties of the peripheral part of the refractive medium, thereby leading to the elevation of the whole-eye trefoil. Damage to the peripheral retina may impact neural conduction and biological signal regulation within the eye, causing changes in structures like the lens and axial length. This indirectly worsened the whole-eye higher-order aberrations. Asymmetric changes occurred during the growth and development of the affected eye after the laser treatment. This led to changes in retinal imaging quality, which potentially affected the refractive status. The correlation between higher-order aberrations and refractive status is still debated. Some studies have shown a significant correlation between myopia progression in school-aged children and higher-order aberrations[28]. However, other scholars, such as Kalikivayi *et al*[29], have found no significant difference in higher order aberrations among different refractive error groups. They hypothesized that higher order aberrations do not significantly impact retinal imaging in eyes with regular refractive surfaces. The current study revealed no significant correlations between whole-eye higher order aberrations, whole-eye trefoil, and SE in the laser and anti-VEGF+laser groups. This suggests that worsening higher order aberrations after laser treatment may not be a crucial factor affecting the refractive status of children with ROP. However, further longitudinal studies are essential to explore the relationship between changes in high-order aberrations and ametropia subsequent to either laser or anti-VEGF treatments. Such investigations will enhance our understanding of the potential role that high-order aberrations play in ametropia development among children with ROP.

This study has the following limitations. First, this study was observational and information and selection biases were inevitable at the time of follow-up. Further prospective, randomized, controlled studies are needed to demonstrate this. Second, the patients in this study were from the same medical institution, which limits the generalizability of the findings of this study to other populations. Finally, since all children with ROP in this study underwent refractive examination at preschool age, the follow-up of study participants was relatively challenging, leading to a smaller sample size.

In conclusion, the refractive statuses of children who received anti-VEGF therapy were better than those of the children who received laser therapy. Compared with the children who only received anti-VEGF treatment, those who received laser treatment or laser supplementation were more myopic and astigmatism. Children treated with laser therapy or laser supplementation had higher anterior corneal astigmatism and anterior corneal curvature, thicker lenses, higher-order aberrations, and trefoil. Corneal anterior surface curvature and lens thickness were closely related to the refractive status of children with ROP after laser treatment. It is essential to conduct long-term monitoring of the refractive status and ocular development in children with ROP after laser treatment, particularly focusing on corneal and lens development. Myopia prevention and control may be achieved by regulating or adjusting corneal curvature. In the future, a refractive risk classification system for children with ROP could be developed, incorporating parameters such as corneal curvature and lens thickness, in conjunction with artificial intelligence systems, to facilitate the prevention and management of abnormal refractive states.

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