The biometric parameters of aniso-astigmatism and its risk factor in Chinese preschool children: the Nanjing Eye Study

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Abstract

Backgrounds

To determine the biometric components of aniso-astigmatism and associated maternal risk factors in Chinese preschool children.

Methods

In the population-based, cohort Nanjing Eye Study, children were measured for noncycloplegic refractive error using an autorefractor and for biometric parameters using an optical low-coherent reflectometry. The difference of total astigmatism (TA) between both eyes was calculated using cylinder power (non-vectorial aniso-TA was defined as ≥ 1.00 Dioptre Cylinder [DC] between both eyes) and by vector analysis (vectorial aniso-TA was defined as a difference of ≥ 0.5 in J_0 or J_{45} between both eyes which is equivalent to 1.00 DC). The prevalence of aniso-TA was presented. Interocular biometric parameters were compared between with vs. without aniso-astigmatism group. In addition, risk factors were determined using multivariate logistic regression model.

Results

Of 1131 children (66.90 ± 3.38 months, 53.31% male), the prevalence of non-vectorial aniso-TA was 1.95% (95% Confidence Interval (CI) = 1.14%-2.75%), while the prevalence of vectorial aniso-TA was twice as common as non-vectorial aniso-TA, neither varying with sex or age. With aniso-TA eyes were more asymmetric in axial length and corneal curvature radius than without aniso-TA eyes. In multivariate logistic regression model, 5-min apgar score less than 7 was significantly associated with higher risk of aniso-TA (vectorial aniso-TA: Odds Ratio (OR) = 6.42, 95%CI = 2.63–15.69, $P < 0.001$; non-vectorial aniso-TA: OR = 4.92, 95%CI = 1.41–17.68, $P = 0.01$). Being twin or triple was significantly associated with higher risk of vectorial aniso-CA (OR = 2.43, 95%CI = 1.05–5.60, $P = 0.38$). Pre-term delivery (OR = 2.60, 95%CI = 1.09–6.15, $P = 0.03$) and post-term delivery (OR = 3.61, 95%CI = 1.31–9.96, $P = 0.01$) were significantly associated with higher risk of vectorial aniso-CA.

Conclusions

Both corneal curvature radius and axial length asymmetry were correlated with aniso-TA. Children with 5-min apgar score < 7 were more likely to have aniso-TA, while twin or triple, pre-term or post-term delivery were risk factors for vectorial aniso-CA.

Background

Astigmatism occurs when incident light rays do not converge at a single focal point [1]. It can lead to substantial visual dysfunction due to visual torsion, metamorphosis, asthenopia and reduced accommodation response [2, 3]. Some studies suggest astigmatism may also be associated with myopia progression [4, 5]. Anisometropia is an interocular asymmetry in refraction that can be associated with strabismus, amblyopia, aniseikonia, and reduced stereopsis [6–9]. Vision In Preschoolers Study Group (VIP) has demonstrated that non-vectorial aniso-astigmatism was more related with unilateral amblyopia than isometropia [10]. Thus aniso-astigmatism may bring damage to visual development in preschool children.

Previous studies have been focusing on risk factors for astigmatism [11–13]. Maternal smoking during pregnancy, caesarean section, darker iris colour, Hispanic, African American, and Asian race might be risks factor of astigmatism. Few studies explore the risk factors for aniso-astigmatism except the Sydney Myopia Study and the Shandong Children Eye Study [14, 15]. It remains unclear whether maternal factors are associated with aniso-astigmatism in Chinese preschool children. Furthermore, vectorial feature of astigmatism was rarely considered while analyzing the risk factors for aniso-astigmatism [10, 16, 17]. However, initial oblique astigmatism is easier to cause amblyopia than orthogonal astigmatism, even with a small degree [18, 19]. Thus cylinder axis should not be neglected.

This study was to describe the characteristics of aniso-TA using cylinder power and by vector analysis, to compare the interocular biometric parameters between with aniso-astigmatism group and without aniso-astigmatism group and to determine risk factors for aniso-astigmatism including vectorial aniso-total astigmatism (vectorial aniso-TA), non-vectorial aniso-TA, vectorial aniso-corneal astigmatism (vectorial aniso-CA) and vectorial aniso-residual astigmatism (vectoiral aniso-RA) in a population-based Nanjing Eye Study (NES).

Methods

Study design

The NES is an ongoing population-based open cohort study, designed to longitudinally observe the onset and progression of childhood ocular diseases in eastern China. All study procedures were approved by the institutional review board in The First Affiliated Hospital with Nanjing Medical University and were conducted according to the tenets of the Declaration of Helsinki. Written consent was obtained from the parents or guardians of all children. This study comprised 61- to 72-month-old children enrolled in kindergarten in the Yuhuatai District of Nanjing City in East China. Data from eye examinations and questionnaire presented in this paper were collected in 2017.

Ocular Examinations And Questionnaires

All children underwent comprehensive eye examinations, including noncycloplegic autorefraction of both eyes of each participant and measurement of biometric parameters by the optic low-coherent reflectometer. Biometric parameters refer to central corneal thickness (CCT), corneal radius (CR), anterior chamber depth (ACD), lens thickness (LT) and axial length (AL). A comprehensive questionnaire was distributed to legal guardians of each child. The examining procedures and content of the questionnaire have been described in detail previously [20, 21].

Definition

Definition and calculations of TA, CA and RA were described in previous publications. To decompose vectorial aniso-astigmatism, the vector method modified by Thibos was used for the following calculations [22]:

SE = S + C/2

$J_0 = (-C/2) \times (\cos 2A)$

$J_{45} = (-C/2) \times (\sin 2A)$

where SE is the spherical equivalent, S is sphere, C is the cylinder in minus format, A is the cylinder axis, J_0 and J_{45} are the horizontal or vertical and oblique vectors of the cylinder, respectively. The magnitude of vectorial aniso-RA was calculated as the vectorial difference between vectorial aniso-TA and vectorial aniso-CA.

The difference of TA between both eyes was calculated using cylinder power (non-vectorial aniso-TA was defined as ≥ 1.00 Dioptre Cylinder [DC] between both eyes) and by vector analysis (vectorial aniso-TA was defined as a difference of ≥ 0.5 in J_0 or J_{45} between both eyes which is equivalent to 1.00 DC). Similar definition applied to aniso-CA and aniso-RA. Group A included children with vectorial aniso-TA, and the others belonged to group B. Group C included children with vectorial aniso-CA, and the others belonged to group D. Group E included children with vectorial aniso-RA, and the others belonged to group F. Group G included children with non-vectorial aniso-TA, and the others belonged to group H.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS V.13.0; IBM, Chicago, IL, USA) was used for all statistical analyses. Characteristics of children included in the analysis were compared to those excluded due to missing data in questionnaire using two-sample t-test for comparisons of means and chi-square test for comparison of proportions. Prevalence variations by sex and age were assessed using chi-square test. Spearman correlation coefficient (ρ) was used to evaluate the relationships between the components of aniso-astigmatism. Comparisons of interocular difference in biometric parameters were performed between children with vs. without vectorial aniso-astigmatism (Mann-Whitney U test). Comparisons of distribution of each candidate risk factor were performed between groups using two-sample t-tests for continuous variables and chi-square tests for categorical variables. Multivariate logistic regression models using forward variable selection were performed to determine statistically significant risk factors for each type of aniso-astigmatism. Odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated from multivariate logistic regression models. All statistical tests were two-sided and P less than 0.05 was considered statistically significant.

Results

Prevalence of aniso-TA

Among 2300 eligible preschoolers, 1920 (participation rate 83.48%) children were examined,404 children were uncooperative and no refraction measurements or biometric parameters from right or left eyes were obtained after several attempts. Guardians of 385 children did

not complete the questionnaires, leaving 1131 children (58.90% of eligible participants) included in this study.

There were no significant differences in characteristics of children (including age, gender, prevalence rate of aniso-TA) between children included in the analysis and those excluded from analysis due to missing data in questionnaire.

The mean (± SD) age was 66.90 ± 3.38 months and 53.31% of participants were boys. Han nationality children (1117, 98.76%) constituted the majority of the population. The prevalence of TA ≥ 1.00 DC was 12.56% (95% CI = 10.62–14.49%) in right eye and 12.73% (95% CI = 10.79–14.68%) in left eye. Table 1 shows the prevalence of aniso-TA stratified by sex and age. The prevalence of non-vectorial aniso-TA was 1.95%, while the prevalence of vectorial aniso-TA was 3.89%. Neither non-vectorial aniso-TA nor vectorial aniso-TA varied with sex or age (all $P > 0.05$). Forty-four children had vectorial aniso-TA. Of them, twenty-six children had aniso-$J_{0t} \geq 0.5$, twenty-four children had aniso-$J_{45t} \geq 0.5$, and six children had both.

Table 1
Prevalence of aniso- total astigmatism stratified by sex and age.

Characteristics	N (%)	Vectorial aniso-TA * N (%, 95% CI)	*P*	Non-vectorial aniso-TA # N (%, 95% CI)	*P*
Sex			0.77		0.74
Boys	603 (53.3%)	22 (3.65%, 2.15–5.15)		13 (2.16%, 0.99–3.32)	
Girls	528 (46.7%)	22 (4.17%, 2.46–5.88)		9 (1.70%, 0.60–2.81)	
Age (month)			0.82		0.71
61–66	546 (48.3%)	20 (3.66%, 2.08–5.24)		12 (2.20%, 0.95–3.43)	
67–72	685 (51.7%)	24 (3.50%, 2.12–4.88)		10 (1.71%, 0.66–2.76)	
Total	1131 (100%)	44 (3.89%, 2.76–5.02)		22 (1.95%, 1.14–2.75)	

* Vectorial aniso-TA was defined as a difference of ≥ 0.5 in J_0 or J_{45} between the two eyes.

Non-vectoral aniso-TA was defined as the difference of ≥ 1.0 diopter cylinder in absolute cylinder between the two eyes regardless of axis.

N, number; CI, confidence interval.

The Components Of Vectorial Aniso-astigmatism

There was a statistically significant association between aniso-J_{0t} and aniso-J_{0c} (ρ = 0.15, $P < 0.001$), and also between aniso-J_{45t} and aniso-J_{45c} (ρ = 0.11, $P < 0.001$). There was a statistically significant association between aniso-J_{0t} and aniso-J_{0r} (ρ = 0.22, $P < 0.001$), and also between aniso-J_{45t} and aniso- J_{45r} (ρ = 0.11, $P < 0.001$).

Comparison Between Groups Towards Interocular Biometric Parameters

Table 2 shows comparisons of interocular differences in ocular biometric parameters between groups with vs. without aniso-astigmatism. Absolute value of interocular differences in AL, mean CR, AL/CR, CCT, ACD, LT were calculated. The absolute value of interocular differences in AL, CR and AL/CR, ACD were significantly different between group A and group B ($P = 0.001$, $P < 0.001$, $P = 0.001$, and $P = 0.01$ respectively). The absolute value of interocular differences in CR and AL/CR were significantly different between group C and group D (both $P < 0.001$), which were also significantly different between group E and group F (both $P < 0.001$). The absolute value of interocular differences in AL, CR and AL/CR were significantly different between group G and group H ($P < 0.001$, $P = 0.001$, and $P < 0.001$ respectively).

Table 2
Comparisons of interocular differences in ocular biometric parameters between groups with vs. without aniso-astigmatism.

	AL (mm)		MCR (mm)		AL/CR		CCT (mm)		ACD (mm)		LT (mm)	
	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P
Vectorial aniso-TA group (N)		0.001		< 0.001		0.001		0.19		0.01		0.09
Group A (44)	0.19 ± 0.24		0.12 ± 0.09		0.05 ± 0.05		9.50 ± 17.17		0.09 ± 0.09		0.10 ± 0.10	
Group B (1087)	0.11 ± 0.14		0.07 ± 0.07		0.03 ± 0.03		7.59 ± 14.27		0.06 ± 0.08		0.07 ± 0.09	
Vectorial aniso-CA group (N)		0.89		< 0.001		< 0.001		0.30		0.79		0.78
Group C (278)	0.11 ± 0.14		0.11 ± 0.09		0.04 ± 0.04		7.54 ± 14.74		0.06 ± 0.07		0.08 ± 0.09	
Group D (853)	0.11 ± 0.14		0.06 ± 0.06		0.03 ± 0.03		7.70 ± 14.29		0.06 ± 0.08		0.07 ± 0.10	
Vectorial aniso-RA group (N)		0.48		< 0.001		< 0.001		0.36		0.42		0.87
Group E (273)	0.12 ± 0.15		0.11 ± 0.09		0.04 ± 0.04		7.95 ± 15.18		0.06 ± 0.07		0.07 ± 0.08	
Group F (858)	0.11 ± 0.14		0.06 ± 0.06		0.03 ± 0.03		7.57 ± 14.14		0.06 ± 0.08		0.08 ± 0.10	
Non-vectorial aniso-TA group (N)		< 0.001		0.001		< 0.001		0.97		0.81		0.68
Group G (22)	0.28 ± 0.30		0.13 ± 0.09		0.06 ± 0.06		8.95 ± 17.20		0.06 ± 0.06		0.07 ± 0.09	
Group H(1109)	0.10 ± 0.14		0.07 ± 0.07		0.03 ± 0.03		7.63 ± 14.34		0.06 ± 0.08		0.07 ± 0.09	

All numbers showed in this table were calculated as absolute values of interocular deviation with a form of mean ± standard deviation.

AL, axial length; MCR,mean coreal curvature radius; CCT, central corneal thickness; ACD, anterior chamber depth; LT, lens thickness; SD, standard deviation; N, number.

Risk Factors For Aniso-astigmatism

Comparisons for each risk factor between group A and group B were shown in sTable **1**. Children in group A were more likely to have abnormal 5 min-apgar score ($P < 0.001$) and parental astigmatism ($P = 0.03$) than those in group B. In the multivariate analysis, two variables remained significantly associated with vectorial aniso-TA: 5 min-apgar score and parental astigmatism. Children with 5 min-apgar score lower than 7 were 6.42 times as likely to have vectorial aniso-TA as children with normal apgar score (95%CI = 2.63–15.69, $P < 0.001$).

Children with parental astigmatism were 2.03 times as likely to have vectorial aniso-TA as children without parental astigmatism (95%CI = 1.09–3.79, *P* = 0.03).

Comparisons for each risk factor between group C and group D were shown in sTable **2**. Children in group C were more likely to have older father at child birth (*P* = 0.047), pre-term delivery (*P* = 0.01), more outdoor activity (*P* = 0.03) and being twin or triple (*P* = 0.03) than those in group D. In the multivariate logistic regression analysis, two variables remained significantly associated with vectorial aniso-CA: being twin or triple and term delivery (Table 3). Children being twin or triple were 2.43 times as likely to have vectorial aniso-CA as those being monotocous (95%CI = 1.05–5.60, *P* = 0.38). Pre-term delivery (OR = 2.60, 95%CI = 1.09–6.15, *P* = 0.03) and post-term delivery (OR = 3.61, 95%CI = 1.31–9.96, *P* = 0.01) were more likely to have vectorial aniso-CA than full-term delivery.

Table 3
Independent Risk Factors for vectorial aniso-CA from Multivariate Logistic Regression

	Multivariate analysis		
Risk factors	Adjusted OR	95% CI	*P*
Twin or triple (Yes vs No)	2.43	1.05–5.60	0.04
Term delivery			
Full-term	Reference		
Pre-term	2.60	1.09–6.15	0.03
Post-term	3.61	1.31–9.96	0.01
OR, odds ratio; CI, confidence interval.			

Comparisons for each risk factor between group E and group F were shown in sTable **3** and no statistically significant difference was found. Likewise, no statistically significant variable was found to be associated with vectorial aniso-RA in the multivariate logistic regression analysis. Comparisons for each risk factor between group G and group H were shown in sTable **4**. Children in group G were more likely to have abnormal 5 min-apgar score (*P* = 0.03) than those in group H. In the multivariate logistic regression analysis, only 5 min-apgar score remained significantly associated with non-vectorial aniso-TA. Children with 5 min-apgar score lower than 7 were 4.92 times as likely to have non-vectorial aniso-TA as children with normal apgar score (95%CI = 1.41–17.68, *P* = 0.01).

Discussion

This study describes, for the first time to our knowledge, the prevalence of aniso-TA using both non-vectorial aniso-TA and vectorial aniso-TA in Chinese preschool children. The prevalence of vectorial aniso-TA was twice as common as non-vectorial aniso-TA, which did not vary with sex and age. The prevalence of aniso-TA was much lower than that of TA.

Prevalence of aniso-TA from previous studies on similar age population was shown in Table 4. These studies reported different prevalence rate, which might be due to different ethnicity, age, and whether vectorial analysis was used. We compared the prevalence of non-vectorial aniso-TA with previous studies defined as ≥ 1.0DC. The prevalence of non-vectorial aniso-TA in the present study was lower than that found in the Tohono O'odham Native American children, in the Northern Ireland Childhood Errors of Refraction (NICER) study and in the rural area of southwestern Japan [23–25]. However, it was higher than that in the Sydney Myopia Study, and similar to that in the Sydney Paediatric Eye Disease Study [14, 26]. Among these studies, the prevalence of non-vectorial aniso-TA found in the Tohono O'odham Native American children was the highest, in accordance with the population's high TA prevalence [23, 27]. When compared with the Shandong Children Eye Study, which was also carried out among Chinese children, the prevalence in this study was lower [15]. Our previous study also showed the TA prevalence was lower than that from The Shandong Children Eye Study [20, 28]. Few studies revealed the prevalence of vectorial aniso-TA. The prevalence of vectorial aniso-TA in the present study was lower than that found in the Multi-Ethnic Pediatric Eye Disease Study (MEPEDS) [16]. In their study, vectorial aniso-TA was twice as common as non-vectorial aniso-TA,similar with our results. Children in MEDPEDS were African American and Hispanic, who also showed higher TA prevalence. The difference between non-vectorial aniso-TA prevalence and vectorial aniso-TA prevalence was reasonable as the later one took astigmatic axis into consideration

Table 4
Studies of aniso-stigmatism among young children.

Author	Year	Location	Age	Sample size	Definition	Prevalence
The Sydney Myopia Study	2006	Sydney, Australia	6 years	1765	≥ 1.0DC	1.60%
Dobson et al.	2008	Tohono O'odham, American	4–13 years	1041	≥ 1.0DC	15%
The Northern Ireland Childhood Errors of Refraction Study	2013	Northern Ireland, England	6–7 years	661	≥ 1.0DC	7.70%
			12–13 years	389		5.60%
The Sydney Paediatric Eye Disease Study	2013	Sydney, Australia	6–72 months	2090	≥ 1.0DC	Overall 3%
						European-Caucasian 1.9%
						East-Asian 5.2%
						South-Asian 3.6%
						Middle-Eastern 3.3%
The Multi-Ethnic Pediatric Eye Disease Study	2010	California, America	6–72 months	Hispanic American, 3030	≥ 1.0DC	5.60%
					≥ 0.50 in J_0/J_{45}	10.40%
				African American, 2994	≥ 1.0DC	4.50%
					≥ 0.50 in J_0/J_{45}	11.90%
The Shandong Children Eye Study	2015	Shandong, China	4–18 years	6025	≥ 1.0DC	3.70%
Yamashita et al.	1997	Rural area of southwestern Japan	6 years	350	≥ 1.0DC	2.6%
			7 years			2.3%
			8 years			2.0%
			9 years			3.4%
			10 years			3.7%
			11 years			4.3%

Whatever definition was used, aniso-TA was associated not only with increased interocular differences in CR, but also with AL, possibly due to the relationship among aniso-TA and anisometropia. A similar correlation was reported by Huynh et al [14], O'Donoghue et al [24], Singh et al [29], and Hameshi et al [30]. These studies showed non-vectorial aniso-CA was associated with non-vectorial aniso-TA. This finding is in agreement with our knowledge that most aniso-TA of the eyes is due to corneal issues. Interestingly, we found interocular differences in ACD were associated with vectorial aniso-TA. The finding is in accordance with Hameshi et al, but contradicts with the results of the NICER Study [24, 30]. Vectorial aniso-CA and vectorial aniso-RA can only be explained by interocular differences in CR.

Genetic factor plays an important role in the development of astigmatism. Accordingly, this study revealed that parental astigmatism was a risk factor for vectorial aniso-TA. Previous genetic studies on astigmatism provided contradicting results on the genetic contribution to astigmatism. Wixson concluded that both parents seemed to play roles in determining the corneal power characteristics of the child. Early twin studies showed that the correlations between monozygotic twins and those between dizygotic twins for astigmatism were not significantly different, which indicated low genetic contribution to astigmatism. However, some other twin studies drew different conclusions, with the estimated heritability ranging from 30–60%. A meta-analysis of five Asian cohorts identifies PDGFRA as a susceptibility locus for CA [21]. Similarly, previous studies have obtained contradicting results on genetic contribution to aniso-astigmatism. Recently, a population-based twin study showed that the correlation between monozygotic twins for aniso-CA were significantly different from dizygotic twins [31]. A study in Korea found that intraclass correlation coefficients for spherical equivalent and ocular biometrics were

significantly higher in monozygotic twins compared with singleton, with greater consistency and conformity [32]. However, another study did not find any significantly difference between children being twin or siblings in refractive error, corneal curvature, ACD and CCT [33].

Our study found that being twin or triple was a risk factor for vectorial aniso-CA. Silventoinen et al. found that differences between singletons and twins can persist into adult life with twins being shorter, lighter. In addition, twins demonstrate lower muscle strength than singletons [34]. Another study showed that twins had higher prevalence of prematurity or low birth weight and presented difference in gross motor, fine motor, language and social development [35]. A systematic review showed that twins tend to have worse academic outcomes and lower ratings in arithmetic, language, and reading than singleton children [36]. These studies all suggested being twin had a side effect on neurodevelopment, cognitive development and whole body development. As for ocular development, a study using optical coherence tomography showed twins had thicker RNFL [37]. Further investigations are needed to clarify the ocualr developmental difference between twin and singleton.

Our study demonstrated that children with a 5-min Apgar score < 7 had a higher likelihood of developing aniso-TA at 5- to 6- years compared to those with an Apgar score of 7–10 (within the normal range), while pre-term or post-term delivery were risk factors for vectorial aniso-CA. A previous study found asymmetrical growth restriction in perterm-born children [38]. Dubois reported structural asymmetries of perisylvian regions in the preterm newborn [39]. Additionally, several studies have revealed abnormal nervous system function in preterm born children. Michalczuk suggested that Apgar score seemed to be a predicting factor for developmental rate of brain function in children with history of prematurity [40]. Teli found that low 5-minute Apgar score in very perterm infants hindered corpus callosum microstructural development [41]. Moreover, eye growth is parellel to neurodevelopment. White matter changes were found in children with anisometropic amblyopia [42]. It has also been reported that low 5-minute Apgar score increased the risk of reduced vision in children [43]. The Sydney Myopia Study found that paternal age > 35 years was accociated with non-vectorial aniso-TA in unadjusted analyses. After multivariable adjustment, breast feeding had a significant protective association ($P = 0.02$) with non-vectorial aniso-TA. In our study, neither paternal age > 35 years or breast feeding was a risk factor for non-vectorial aniso-TA. To sum up, intrauterine hypoplasia and poor birth condition may be associated with asymmeric whole body development, neurodevelopment, and asymmeric visual and refractive development such as aniso-astigmatism. Further work is required to clarify the developmental mechanism behind these associations.

The strengths of this study include its population-based design, large sample size, and standardized examination protocols performed by an expert team, risk factors during pregnancy and early childhood. Our analyses are different from most previous studies by considering vectorial features of aniso-astigmatism. The limitation of this study is that some eligible children were not included into the anaysis due to missing data in questionnaire or refractive error measures. In addition, the risk factor data collected through questionnaire may be subjective and biased.

Conclusions

In summary, in the 61- to 72-month-old children in the Yuhuatai District, the prevalence of non-vectorial aniso-TA was 1.95%, while the prevalence of vectorial aniso-TA was twice as common as non-vectorial aniso-TA. Both CR and AL asymmetry were correlated with aniso-TA. Children with 5-min apgar score < 7 were more likely to have aniso-TA, while twin or triple, pre-term or post-term delivery were risk factors for vectorial aniso-CA.

Abbreviations

TA: Total Astigmatism; CA: Corneal Astigmatism; RA: Resiual Astigmatism; DC: Dioptre Cylinder; CCT: Central Corneal Thickness; CR: Corneal Radiu; ACD: Anterior Chamber Depth; LT: Lens Thickness; AL: Axial Length.

Declarations

Ethics approval and consent to participate

This study followed the tenets of the Declaration of Helsinki and was approved by the ethics committee of the Nanjiing Medical University. Informed consent was obtained from all participants.

Consent to publish

Not Applicable.

Availability of data and materials

Data can be shared upon request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

Study concept and design (DH, HZ, XC); data collection (HT, QH, YW, RL, XZ, QS); analysis and interpretation of data (HT, QH, ZW); drafting of the manuscript (HT, QH, ZW); critical revision of the manuscript (HL); supervision (HL). All authors read and approved the final manuscript.

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