Factors Associated with Axial Length Elongation in High Myopia

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Research article

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Abstract

Background: To investigate the impact of axial length (AL) and ocular factors on axial length elongation (ALE). Methods: A retrospective chart review of patients who underwent more than two axial length examinations using a single instrument Results: The mean age of the participants was 47.21 ± 7.79 years. Eyes were classified into four groups according to their initial AL measurement. AL remained almost unchanged in the groups with AL < 26mm. On the contrary, AL increased by 0.011mm/year in the group with 26 ≤ AL < 28mm and 0.035mm/year in the group with AL ≥ 28mm (P < .001). In high myopia, ALE increased in eyes with longer axial lengths (r = 0.003, P = .024), females (r = 0.014, P = .019), eyes with larger peripapillary chorioretinal atrophic areas (r = 0.002, P = .019), and smaller vascular arcade angles (r = -0.004, P = .006). The risk of elongation 0.03mm/year in high myopia was increased in females (OR = 2.265, P = .040), and gradually increased in eyes with large peripapillary chorioretinal atrophy area (OR = 5.604, 6.939, and 7.470, respectively; P = .001, < .001, and .008, respectively) Conclusions: AL remained almost unchanged in the group with AL < 26mm. On the contrary, ALE was observed in the group with AL ≥ 26mm. AL elongated significantly in eyes with longer AL, female, and eyes with larger atrophic areas and smaller arcade angles on fundus photographs.

Background

The prevalence of myopia has been steadily rising and myopia has been identified as a leading cause of visual impairment and blindness. [1, 2] Myopic eyes with a spherical equivalent more myopic than -6.0 diopters (D) or an axial length longer than 26 mm are defined as high myopia. [2, 3] High myopia associated with posterior staphyloma and degenerative changes (eg, progressive chorioretinal atrophy) is characterized as pathologic myopia (PM) or degenerative myopia. PM is associated with pathologic features (eg, tessellated fundus, diffuse or patchy chorioretinal atrophy, macular atrophy, lacquer crack, choroidal neovascularization, Fuchs spot, posterior staphyloma. [4]

Continuous elongation of axial length (AL) has been identified in adults—particularly those with high myopia—and many studies have suggested that eyes with longer AL experience a significant axial length elongation (ALE) over time. [5-9] Several studies have suggested that ALE is related to the progression of posterior staphyloma in high myopia [6, 8], while others have reported that no differences in ALE were found between high myopia with and without posterior staphyloma. [5] Ohsugi et al. have reported a significant increase in ALE among females and patients with myopic choroidal neovascularization (CNV) and suggested that there may be a relationship between ALE and collagen abnormalities. [7] Likewise, ALE is significantly related to posterior staphyloma [6], and the progression of posterior staphyloma increases the incidence of myopic maculopathy. [10] Furthermore, high myopia is a serious public health problem because the risk of uncorrectable visual impairment rises drastically with age in highly myopic patients. [11]

The risk of uncorrectable visual impairment and ALE increases steadily with age in highly myopic patients. For this reason, early detection of patients who has high risk of ALE, and appropriately inform of

their prognosis are important. However, no previous studies have investigated the risk of ALE according to AL difference. This study aims to compare the ALE according to AL in middle-aged adults (30-59 years). Additionally, this study investigates ocular factors associate ALE in high myopia (eyes with AL ≥ 26mm).

Methods

Study Subjects

This study involved eyes that were followed up for more than two years (repeated measurements interval more than two years) and examined by optical biometry with the IOL-Master (Carl Zeiss Meditec, Jena, Germany) from April 2007 to September 2016 in a single hospital. We excluded all eyes that underwent an ophthalmologic surgery (eg, refractive surgery, keratoplasty, cataract surgery, glaucoma surgery, retinal surgery) during the period of repeated measurement. Adults aged 30 years or older patients were included in this study. Since AL would be decreased due to phthisis bulbi in older adults, patients aged 60 years or older were excluded. Since both eyes were examined even if only one eye underwent surgery, counter eyes that were not underwent surgery were included in this study. Since repeated axial length examinations were performed in high myopia even without surgery, in this case, only right eyes were included. A total of 324 patients were included in the analysis. To measure AL variation from irregular repeated measurement, we assumed that AL changes linearly. Intercepts (linear change of AL) were calculated using the date of first measurement and dates of repeated measurements (axial length difference, mm / date difference, day). Based on these measures, changes in AL over one year (365 days) were calculated. Eyes were then divided into 4 groups based on the first measurement of AL: i) AL< 24 mm, ii) 24 mm ≤ AL < 26 mm, iii) 26 mm ≤ AL< 28 mm, and iv) AL ≥ 28 mm. To study ocular factors that influence AL elongation in high myopia, an additional investigation was performed on the group with AL ≥ 26mm. ocular factors were identified based on fundus photographs obtained within 6 months from the date of first AL measurement (Figure 1). And mean intraocular pressure (IOP) measured during observation period.

Ocular Examinations

Ocular factors affecting ALE were examined according to the following three categories. First, atrophic area—defined as the ratio of circular area of chorioretinal atrophy to a circle having the longest axis of disc as the radius on fundus photograph—was measured. By doing this, we have resolved individual size differences of fundus photographs. Second, tilted disc ratio—defined as the ratio of maximum to minimum disc diameter—was measured (Hyung et al. 1992; Tay et al. 2005). Third, vascular arcade angle — defined as the angel between two lines parallel to superior and inferior temporal arcades—was measured (Fledelius & Goldschmidt 2010; Jonas et al. 2018). Atrophic area was categorized as follows: i) 0 (area < 2), ii) 1 (2 ≤ area < 3), iii) 2 (3 ≤ area < 4), iv) 3 (4 ≤ area < 6), and v) 4 (area ≥ 6). Arcade angle was rated as 0 (angle > 90°), 1 (angle of 75-90°), 2 (angle of 60-75°), 3 (angle of 45-60°), or 4 (angle ≤ 45°) (Figure 2).

In addition, we recorded mean IOP during the observation period and checked for a history of refractive surgery.

Statistical Analysis

Data for continuous variables are expressed as the means ± standard deviations. Intercepts were calculated from repeated measures of AL using Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA). Atrophic area, tilted disc and arcade angle were measured with ImageJ® (National Institutes of Health, Bethesda, MD, USA) on fundus photographs. ANOVA was used to evaluate differences in AL changes among four groups and a post-hoc analysis was performed using Tukey's HSD. Univariate and multivariate linear regressions were carried out to identify factors having a correlation with the increase of AL in the group with AL ≥ 26mm. Univariate and multivariate binary logistic regressions were conducted to investigate the risk of severe elongation. Two-tailed *P*-values less than 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS ver. 23.0 (IBM Corp., Armonk, NY, USA).

Results

No differences were observed between age, sex, and measurement duration among the 4 groups classified according to AL (*P* = .172, .076, .423, respectively). AL remained almost unchanged in the groups with AL < 24 mm and 24 ≤ AL< 26 mm. AL increased by 0.01 mm/year in the group with 26 ≤ AL< 28 mm, and 0.03 mm/year in the group with AL ≥ 28 mm (*P* < .001; Table 1).

Univariate linear regression was performed to determine factors that may be associated with ALE. A significant AL increase was found in: longer axial length, female, larger chorioretinal atrophic areas, severe tilted disc ratios, and narrower vascular arcade angles (*P* < .001, = .002, < .001, < .001, respectively). Age at initial examination, refractive surgery or not, mean IOP were not correlated with ALE (*P* = .312, .896, .125, respectively). Multivariate linear regression analyses revealed that longer axial length, female, larger chorioretinal atrophy and narrower vascular arcade angle were significantly associated with ALE (Table 2).

For assessing risk of severe ALE (defined as ≥ 0.03 mm per year, that was mean axial elongation per year on the group with AL ≥ 28mm), univariate binary logistic regression was conducted in high myopia. Compared to AL 26-26.99 mm, the odds ratio (OR) for AL ≥ 29 mm was 6.905 (CI = 2.823 to 16.890, *P* = .013). Females had an OR 2.583 higher when compared to male (CI = 1.278 to 5.253, *P* < .001). Compared to peripapillary atrophic area of less than 2 disc area, the OR for atrophic area between 2-2.99 was 5.750 (CI = 2.004 to 16.173, *P* = .002), 7.187 (CI = 2.637 to 19.590, *P* < .001) for atrophic area between 3-5.99, and 8.944 (CI = 2.101 to 38.077, *P* = .003) for atrophic area ≥ 6. Compared to vascular arcade angle > 90°, the OR for eyes with angle between 60-75° was 3.750 (CI = 1.476 to 9.529, *P* = .005), and OR for narrower angle than 60° was 4.167 (0.963 to 18.023, *P* = .056). Multivariate logistic regression analyses

revealed that female and larger chorioretinal atrophic area were significantly increased the risk of severe ALE (Table 3).

Discussion

Pathologic myopia (PM) is distinguished from myopia in that it may cause a decrease in best-corrected visual acuity, while visual acuity can be maintained with correction in myopia. [16] PM is one of the leading causes for the loss of visual acuity and prevalence rates are considerably high, especially in East Asian countries. [16-20] PM is defined as high myopia associated with degenerative changes (eg, myopic maculopathy that included diffuse or patchy chorioretinal atrophy, lacquer cracks, myopic choroidal neovascularization). [21] For simple classification of PM, an international panel of myopia researchers developed a new classification of myopia maculopathy (META-PM classification). [4] Based on the META-PM classification, PM is classified into 4 categories including “tessellated fundus” (category 1), “diffuse chorioretinal atrophy” (category 2), “patchy chorioretinal atrophy” (category 3), and “macular atrophy” (category 4). Three additional features defined as “plus” lesions include lacquer cracks, Fuchs spot, and posterior staphyloma.

Several studies were performed to explore the relationship between ALE and ocular factors. A previous study reported that AL was significantly correlated with tilted disc ratio, and eyes with a longer AL had more severe disc tilt. [12, 13] In this study, ALE was correlated with tilted disc ratio before adjusting for AL, age, sex and other variables, but no significance was found between ALE and tilted disc ratio after adjustment. While some studies had found a significant link between posterior staphyloma and ALE [6, 8], other study obtained contradictory findings. [5] We did not analyze the correlation between ALE and posterior staphyloma, because it was challenging to assess posterior staphyloma based on fundus photography alone. Instead, we analyzed the correlation between ALE and chorioretinal atrophy area that had a significant relationship with posterior staphyloma. ALE was correlated with chorioretinal atrophy area, and this correlation was maintained after adjusting for several variables. Fledelius et al. suggested that myopia progression was correlated with both vascular arcade angle and angle peaking, also defined as change in vascular arcade angle. [14] In the current study, a significant correlation was found between ALE and vascular arcade angle, and this correlation was maintained after adjustment for all variables.

The recent widespread application of optical coherence tomography (OCT) has facilitated studies aimed at investigating high myopia and choroidal thickness. Many studies addressed that choroidal thickness was lower in the high myopia group. [2, 6, 22-24] Wang et al. suggested that macular choroidal thickness had a more profound relationship with myopic maculopathy than AL. [25, 26] If macular choroidal thickness is strongly associated with myopic maculopathy, there is a strong possibility that it will also be related with ALE. However, we were unable to confirm this because OCT data was not included. There are contradictory findings regarding ALE and intraocular pressure. Some authors stated that AL increased significantly in groups with higher IOP [22, 23], while others reported no relationship between them. [5, 7] It has been recognized that normal tension glaucoma prevalence is higher in myopic eyes [24], and high-teen IOP increases the risk of normal tension glaucoma in highly myopic eyes. Therefore, we supposed

that IOP would be associated with ALE in highly myopic eyes, but any relationship was found in our study.

Several studies intended to explore the association between ALE and age and sex. There are some contradictory studies that identified that ALE was more likely to be severe in older patients, while others revealed no association between ALE and age. [5, 7] In the studies that showed a significant correlation between ALE and age, AL was not adjusted for age and this had probably caused greater axial elongation in older individuals. Since AL is relatively longer in older individuals, ALE may be more severe as age increases without adjusting for AL. It is possible that there is no association between ALE and age, if they had adjusted for AL. With respect to the relationship between ALE and sex, Ohsugi et al. suggested that AL significantly increased in female. [7] In our study, there was a significant correlation between ALE and female sex, and this correlation remained significant even after adjusting for all variables.

There are some limitations to the present study. First, we assumed linear elongation of AL. It would be thought that there were some critical point associated AL elongation, nevertheless we assume that the AL change constantly. Second, this study has relatively short follow-up period. Since AL increases gradually, follow-up for more than 10 years was meaningful. However, observation of AL using a single biometry instrument over a long period of time was challenging. Third, corneal thickness was not taken into consideration. Since IOP measure was deeply influenced by corneal thickness, we could not completely reveal the relationship between mean IOP and ALE, even though relationship was not observed in this study. Fourth, OCT data was not reviewed in this study. As the importance of choroidal thickness has been recently described, additional studies need to be carried out using OCT data. Last, we could not analyze the relationship between ALE and systemic diseases. Based on the finding that AL elongated more significantly in females, it can be inferred that ALE is related with systemic conditions such as collagen abnormalities. [7] An additional study is currently in progress to clearly elucidate this relationship.

Conclusions

This study was meaningful in that it better elucidated differences in ALE according to AL. ALE was minimal or no observation in the group with AL < 26mm, however, it significantly progressed in the group with AL ≥ 28mm. Furthermore, this study determined prognostic factors associated with ALE in high myopia. When encountering high myopic patients, it is necessary to detect the risk of ALE and carefully explained to patients with AL ≥ 28mm, females, and those with large chorioretinal atrophic areas and narrowing vascular arcade angle, even in middle-aged adult patients.

Abbreviations

AL: Axial lengthALE: Axial length elongation

PM: Pathologic myopiaCNV: choroidal neovascularization

IOP: Intraocular pressureOCT: Optical coherence tomography

Declarations

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No conflicting relationships or competing interests exist for any author.

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Availability of data and materials

The datasets used and/or analyzed during the current study available from the first author on reasonable request.

Authors' contributions

Design of the study (SSK); conduct of the study (HKK, THR); collection and management of date (JYY, SHK); Preparation, review, or approval of the manuscript (HKK, SSK). All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study adhered to the tenets of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Severance Hospital, Yonsei University (4-2018-0985), which waived the requirement for informed patient consent because of the retrospective study design.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Tables

Table 1. Difference among four groups classified by axial length (AL): i) AL < 24 mm, ii) 24 mm ≤ AL < 26 mm, iii) 26 mm ≤ AL < 28 mm, iv) AL ≥ 28mm.

Parameter	AL < 24 mm	24 ≤AL < 26 mm	26 ≤AL < 28 mm	AL ≥ 28 mm	*P*-value*
	(N = 105)	(N = 81)	(N = 70)	(N = 68)	
Age at 1st exam, year	48.28 ± 7.52	47.43 ± 7.77	45.63 ± 7.86	46.94 ± 8.06	.172
Sex, male, %	45 (42.9)	50 (61.7)	38 (54.3)	37 (54.4)	.076
Observation duration, month	46.17 ± 18.72	47.32 ± 17.03	46.91 ± 16.20	50.81 ± 21.48	.423
AL change per year, mm	0.000 ± 0.03	0.000 ± 0.03	0.011 ± 0.03	0.035 ± 0.04	< .001

*Analysis of variance with post-hoc Turkey HSD; different letters are significantly different (0.05)

Table 2. Factors related to axial length elongation per year.

Parameter	Unadjusted regression coefficient*				Adjusted regression coefficient†			
	B	95% CI	Beta	*P*-value	B	95% CI	Beta	*P*-value
Axial length, mm	0.012	(0.006 to 0.018)	0.351	< .001	0.003	(0.001 to 0.006)	0.177	.024
Age, y	0.000	(0.000 to 0.001)	0.086	.312				
Sex	0.019	(0.007 to 0.031)	0.255	.002	0.014	(0.003 to 0.026)	0.161	.019
Refractive surgery	-0.001	(-0.015 to 0.013)	-0.011	.896				
Mean IOP, mmHg	-0.002	(-0.004 to 0.001)	-0.130	.125				
Atrophy ratio	0.004	(0.002 to 0.006)	0.349	< .001	0.002	(0.000 to 0.004)	0.195	.019
Tilt ratio	0.037	(0.013 to 0.060)	0.253	.003				
Arcade angle, 10 degrees	-0.007	(-0.011 to -0.004)	-0.353	< .001	-0.004	(-0.008 to -0.001)	-0.220	.006

* Linear regression of “each variable”, †Linear regression of “all variables” with backward elimination variable selection.

CI = confidence interval; IOP = intraocular pressure

Table 3. Factors related to axial length elongation ≥ 0.03mm per year.

Parameter		Unadjusted OR*		Adjusted OR†	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Axial length, mm	26 – 26.99	(reference)			
	27 – 27.99	1.640 (0.508-5.296)	.408		
	28 – 28.99	1.262 (0.338-4.707)	.729		
	≥ 29	6.905 (2.823-16.890)	< .001		
Age, y	30 – 39	(reference)			
	40 – 49	1.926 (0.748-4.959)	.174		
	50 – 59	2.076 (0.821-5.253)	.123		
Sex	male	(reference)		(reference)	
	female	2.583 (1.278-5.223)	.008	2.265 (1.039-4.934)	.040
Refractive surgery	no	(reference)			
	yes	0.982 (0.454-2.126)	.964		
Mean IOP, mmHg	< 15	(reference)			
	15 – 20.99	0.928 (0.431-2.002)	.850		
Atrophy ratio	< 2	(reference)		(reference)	
	2 – 2.99	5.750 (2.044-16.173)	.001	5.604 (1.953-16.076)	.001
	3 – 5.99	7.187 (2.637-19.590)	<.001	6.939 (2.500-19.263)	< .001
	≥ 6	8.944 (2.101-38.077)	.003	7.470 (1.708-32.670)	.008
Tilt ratio	< 1.30	(reference)			
	1.30 – 1.39	1.467 (0.588-3.657)	.411		
	1.40 – 1.49	3.048 (0.965-9.625)	.058		
	≥ 1.50	3.077 (1.227-7.715)	.017		
Arcade angle, °	> 90	(reference)			
	75.01 – 90	2.024 (0.937-4.893)	.118		
	60.01 – 75	3.750 (1.476-9.529)	.005		
	≤ 60	4.167 (0.963-18.023)	.056		

* binary logistic regression of “each variable”, †binary logistic regression of “all variables” with backward elimination variable selection

OR = odds ratio; IOP = intraocular pressure

Figures

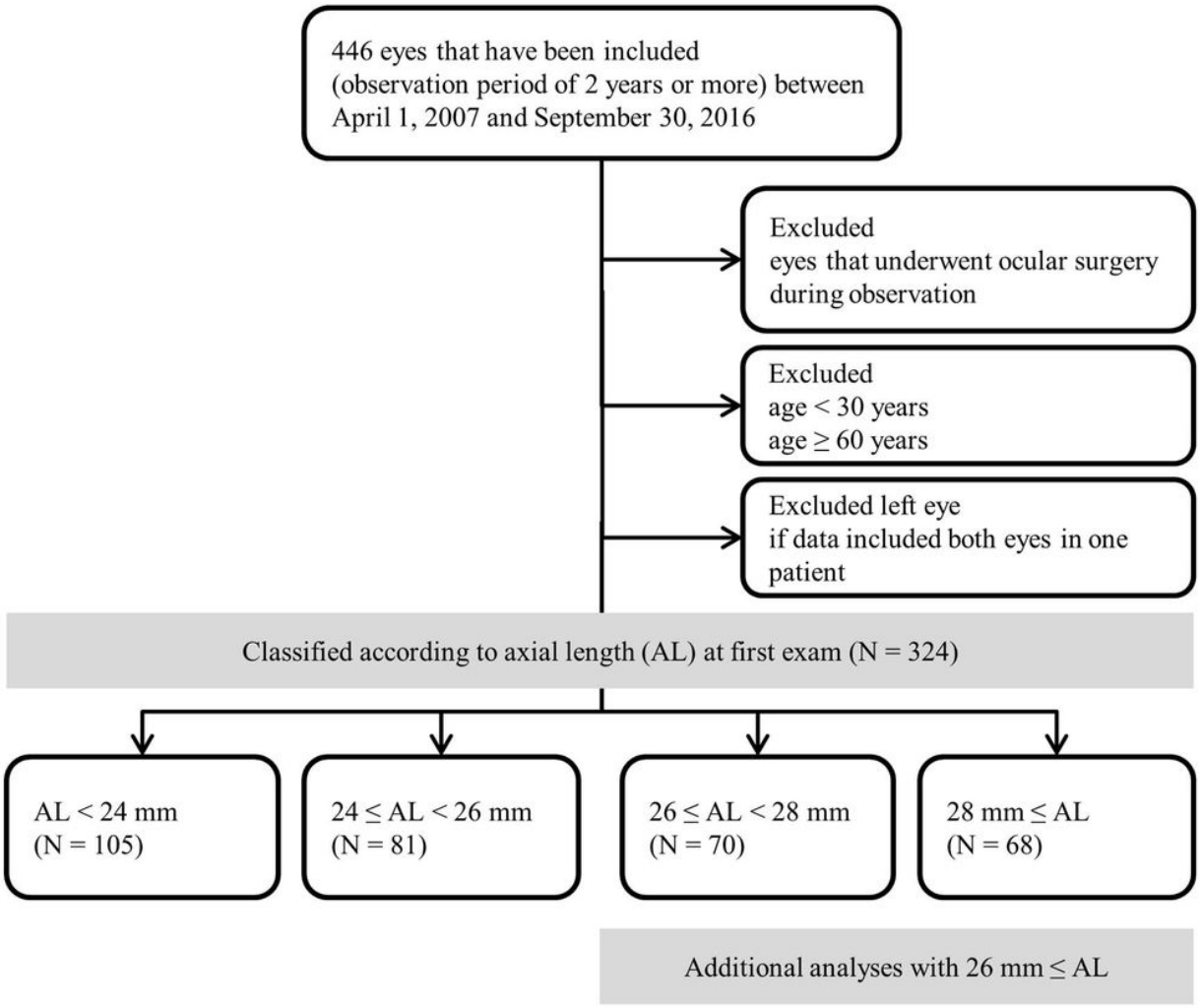

Figure 1

Flow chart of study population. This study included comparative analysis of 324 eyes after dividing them into 4 groups according to AL. Additional analyses were performed to elucidate factors that may affect axial length elongation in eyes with an AL ≥ 26mm.

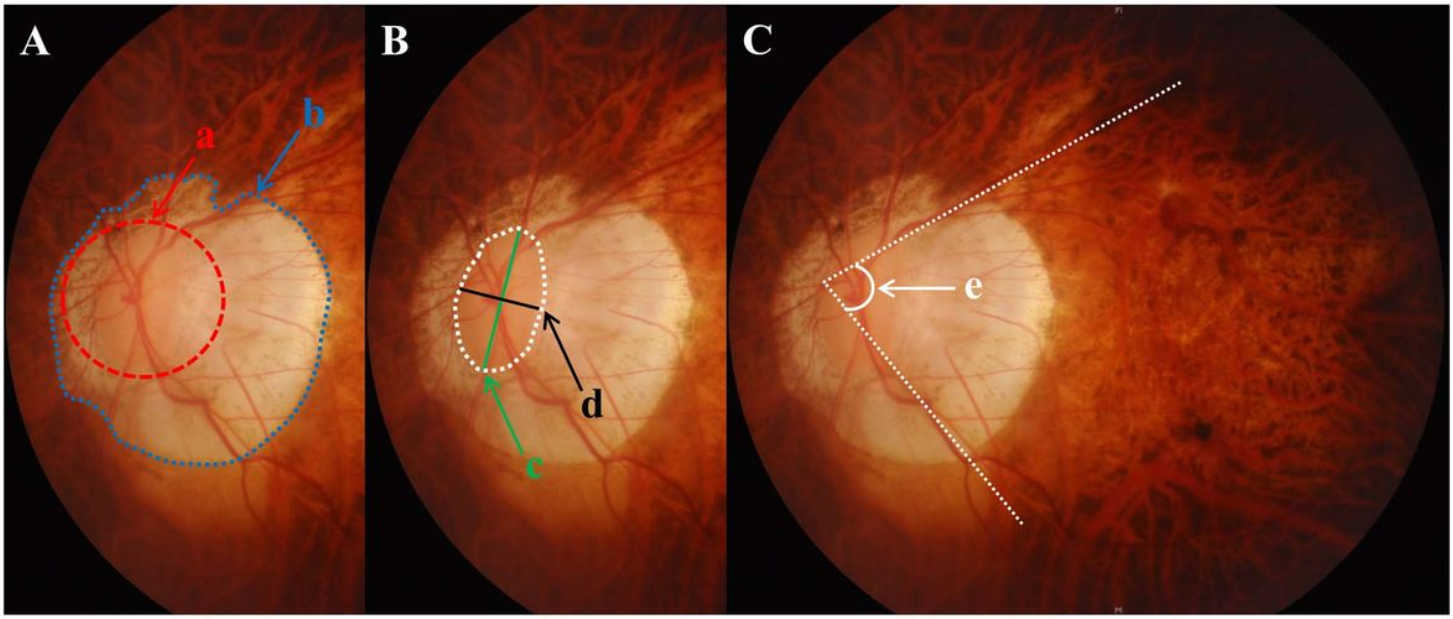

Figure 2

Ocular factors determined from fundus photographs. Atrophic area = “b” area/ “a” area (A); Tilted disc ratio = “c” length/ “d” length (B); Vascular arcade angle = “e” angle (C).