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# Impact of Age and Myopia on the Rate of Visual Field Progression in Glaucoma Patients

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**Abstract:** Myopia is rapidly increasing in young populations and patients with glaucoma associated with myopia are reported to be young aged in East Asia. These young patients have a longer life expectancy, which increases their risk of end-of-life visual disabilities. There is a need to understand the clinical course of myopic glaucoma patients, which may be important for the care of these myopic populations. In this study, we evaluated the relationship between the age at presentation and the rate of glaucoma progression in the visual field (VF) according to the presence of myopia. The study was conducted as a prospective observational study including 179 patients with open-angle glaucoma who had undergone at least 5 VF examinations with a follow-up of at least 5 years. The progression rate of the mean deviation (MD) and the pattern standard deviation (PSD) are expressed as change in decibels (dB) per year. The slopes of the MD and PSD were calculated by linear regression analyses. Factors related to the slope of VF MD changes were analyzed with correlation and regression analyses. The slope of the linear fit line plotted against age at presentation and the rate of change in the VF MD was  $-0.026$  ( $P < 0.001$ ) in the myopic group and  $-0.008$  ( $P = 0.167$ ) in the nonmyopic group; the relationship was more prominent in the myopic group than the nonmyopic group. In the myopic group, age ( $\beta = -0.417$ ; 95% confidence intervals (CI),  $-0.651$  to  $-0.200$ ;  $P = 0.050$ ) and baseline untreated intraocular pressure ( $\beta = -0.179$ ; 95% CI,  $-0.331$  to  $-0.028$ ;  $P = 0.022$ ) were significantly related to the rate of change in the MD, which was only the presence of disc hemorrhage ( $\beta = -0.335$ ; 95% CI,  $-0.568$  to  $-0.018$ ;  $P = 0.022$ ) in the nonmyopic group. Age at presentation was significantly related to the rate of change in the VF in glaucomatous eyes with myopia compared to eyes without myopia.

Older age was significantly related to the rate of change in the VF only in myopic glaucomatous eyes.

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**Abbreviations:** IOP = intraocular pressure, MD = mean deviation, OCT = optical coherence tomography, PSD = pattern standard deviation, RNFL = retinal nerve fiber layer, VF = visual field.

## INTRODUCTION

Myopia, particularly high myopia, is a well-known risk factor for glaucoma.<sup>1-4</sup> A recent meta-analysis from 11 population-based studies reported a pooled odds ratio of 2.46 for high myopia and 1.77 for low myopia, with a cutoff value of  $-3.0$  diopters (D).<sup>5</sup> However, the role of myopia in glaucoma progression is controversial. Many studies have proposed that myopia and high myopia are risk factors for glaucoma progression.<sup>6-9</sup> In the Advanced Glaucoma Intervention Study, myopic eyes with  $> -4.0$  D tended to progress faster.<sup>10</sup> However, other studies have reported that myopia does not contribute to the progression of glaucoma and may act as a protective factor for glaucoma progression.<sup>11-14</sup>

The frequencies of myopia and high myopia are rapidly increasing in young populations.<sup>15</sup> In East Asia, myopic glaucoma patients are significantly younger than nonmyopic glaucoma patients.<sup>16</sup> These young patients have a longer life expectancy, which increases their risk of end-of-life visual disabilities. Older age is an important clinical risk factor for glaucoma prevalence<sup>17,18</sup> and is positively correlated with a faster progression of glaucoma.<sup>19-21</sup> Understanding the clinical course of myopic glaucoma patients according to age may be important to care these myopic populations.

In the present study, we analyzed the visual field (VF) progression of glaucoma according to baseline age, and the comparison was performed between myopic and nonmyopic groups. Additionally, related factors to glaucoma progression and the difference between myopic and nonmyopic groups were evaluated.

## METHODS

### Subjects

This study was based on the Glaucoma Progression Study at Seoul St. Mary's Hospital, an ongoing study that has been conducted since March 2009. The study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, Seoul, South Korea, and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from consecutive patients who met the eligibility criteria and were willing to participate in the study.

The database of patients included in the above-mentioned study was reviewed. Patients who had undergone at least 5 VF examinations with follow-up for at least 5 years were selected.

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Study approval: for the prospective component, ethical approval was obtained from the Institutional Review Board of Seoul St. Mary's Hospital, Seoul, South Korea. The study was conducted according to the principles set out in the Declaration of Helsinki. Written informed consent was obtained from all prospective patients before inclusion in the study, which was conducted according to the tenets of the Declaration of Helsinki.

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Each participant underwent a comprehensive ophthalmic assessment, including detailed glaucoma evaluation. This included measurement of best-corrected visual acuity, refraction, central corneal thickness, axial length measurement, slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, dilated stereoscopic examination, color disc and red-free retinal nerve fiber layer (RNFL) photography (Canon, Tokyo, Japan), Humphrey VF examination (24–2 Swedish Interactive Threshold Algorithm Standard program; Carl Zeiss Meditec), and Cirrus optical coherence tomography (OCT) (Carl Zeiss Meditec). Cataracts were graded using the LOCS III grading system at each visit.<sup>22</sup>

For a glaucoma diagnosis, patients had to fulfill the following criteria: glaucomatous optic disc appearances (such as diffuse or localized rim thinning, a notch in the rim, or a vertical cup-to-disc ratio higher than that of the other eye by > 0.2), VF consistent with glaucoma (a cluster of  $\geq 3$  non-edge points on pattern deviation plot with a probability of < 5% of the normal population, with one of these points having the probability of < 1%, a pattern standard deviation with  $P < 5\%$ , or a Glaucoma Hemifield Test result outside the normal limits in a consistent pattern on 2 qualifying VFs), confirmed by 2 glaucoma specialists (HYP and CKP), and an open angle on gonioscopy.

Patients were required to meet the following inclusion criteria: a best-corrected visual acuity of  $\geq 20/40$ , mean deviation (MD) better than  $-12.00$  decibels (dB), and consistently reliable VFs (defined as a false-negative rate of <15%, a false positive rate of <15%, and fixation losses of <20%). Patients were excluded on the basis of any of the following criteria: an axial length >30 mm; a cataract with LOCS III grade higher than grade 3 at any visit; a history of any retinal disease, including diabetic or hypertensive retinopathy or other retinal complications that accompany myopia; a history of eye trauma or surgery, including cataract surgery during the follow-up period; a glaucoma incisional surgery or laser procedure; another optic nerve disease besides glaucoma; a history of systemic or neurological diseases that might affect the VF; and progression of cataract defined as an increase in LOCS grading by >1 scale. If both eyes were eligible, 1 eye was randomly selected from each patient that met the inclusion and exclusion criteria.

Patients were classified into 2 groups according to axial length. Eyes with axial length < 24.0 mm were classified as nonmyopic and eyes with axial length  $\geq 24.0$  mm were classified as myopic.

### Analysis of Change in the VF

VF testing was performed with optical correction using either trial lenses or disposable hydrophilic contact lenses in eyes with myopia. Only reliable VF test results were included in the analyses. The MD and pattern standard deviation (PSD) progression rate were expressed as change in dB per year. The slopes of the MD and PSD change were calculated by linear regression analyses. We excluded fields that showed an apparent progression because of retinal or neurological pathologies.

### Statistical Analyses

An independent *t*-test was used to compare differences between groups. The *chi*-square test was used where appropriate to compare frequencies. The relationship between age at presentation and the rate of change in the VF was assessed by scatter plots and graphically fitting a linear function. Linear regression

analyses were used to evaluate the influence of several factors on the rate of change in the VF, such as age, axial length, central corneal thickness, baseline untreated intraocular pressure (IOP), mean IOP during the follow-up period, baseline MD, baseline PSD, baseline average RNFL thickness, and the presence of disc hemorrhage. *P* values <0.05 was considered statistically significant. Variables with a significance of  $P < 0.20$  were included in the multivariate regression analyses. Statistical analyses were performed using the SPSS statistical package (SPSS, Chicago, IL).

## RESULTS

A total of 101 eyes with myopia and 78 eyes without myopia that met the inclusion and exclusion criteria were analyzed. Baseline characteristics, except for spherical equivalent and axial length, were similar between groups, as shown in Table 1. The total follow-up period and the number of VFs evaluated were similar between groups.

The mean rate of MD change was  $-0.41 \pm 1.20$  dB/year in the nonmyopic group and  $-0.18 \pm 1.55$  dB/year in the myopic group, which did not show statistical difference ( $P = 0.336$ ). The mean rate of PSD change was  $0.92 \pm 1.37$  dB/year in the nonmyopic group and  $0.71 \pm 1.39$  dB/year in the myopic group, which did not show statistical difference ( $P = 0.354$ ). According to subgroup analyses, the rates of MD change for the age groups 40 to 60, 60 to 80, and >80 were  $-0.07 \pm 1.71$  dB/year,  $-0.05 \pm 0.93$  dB/year, and  $-0.49 \pm 1.77$  dB/year, respectively, in the myopic group. The respective values were  $-0.24 \pm 0.14$  dB/year,  $-0.38 \pm 0.93$  dB/year, and  $-0.52 \pm 1.42$  dB/year in the nonmyopic group. Figure 1 shows a scatter plot of the rates of change in the MD and PSD as a function of axial length. The slope of the linear fit line was positive for MD change and axial length and negative for PSD change and axial length.

The relationship between age and the rates of change in MD and PSD is shown in Figure 2. The slope of the linear fit line was negative for MD but positive for PSD against age. These relationships were more prominent in the myopic group than in the nonmyopic group. The negative slope for MD and age was  $-0.026$  ( $P < 0.001$ ) in the myopic group and  $-0.008$  ( $P = 0.167$ ) in the nonmyopic group. The positive slope for PSD and age was  $0.013$  ( $P < 0.001$ ) in the myopic group and  $0.002$  ( $P = 0.487$ ) in the nonmyopic group.

Parameters related to the rate of MD change were evaluated by regression analyses. For the entire group, the presence of disc hemorrhage ( $\beta = -0.231$ ; 95% confidence intervals (CI),  $-0.373$  to  $-0.089$ ;  $P = 0.026$ ) was the only related parameter (Table 2). In the myopic group, age ( $\beta = -0.417$ ; 95% CI,  $-0.651$  to  $-0.200$ ;  $P = 0.050$ ) and baseline untreated IOP during the follow-up period ( $\beta = -0.179$ ; 95% CI,  $-0.331$  to  $-0.028$ ;  $P = 0.022$ ) were significantly related to the rate of MD change, based on multivariate analyses (Table 3). In the nonmyopic group, only disc hemorrhage ( $\beta = -0.335$ ; 95% CI,  $-0.568$  to  $-0.018$ ;  $P = 0.022$ ) was related to the rate of MD change in the multivariate analysis (Table 4).

## DISCUSSION

Age at presentation was significantly related to the rates of change in MD and PSD in glaucomatous eyes with myopia, and patients with older age at presentation progressed faster which was greater in myopic eyes than in nonmyopic eyes. Regarding the relationship between the rate of change in the VF and axial length (Figure 1), the rate of change decreased as axial length increased. Previous studies have reported that glaucoma in both myopic and high myopic glaucoma patients do not progress, and

**TABLE 1.** Baseline Demographics of Glaucoma Patients With and Without Myopia Classified as an Axial Length of 24.0 mm

	Myopic Group (n = 101)	Nonmyopic Group (n = 78)	P Value
Total follow-up period (years)	6.19 ± 1.11	6.73 ± 0.86	0.742*
Total number of visits (n)	12.44 ± 2.38	12.56 ± 2.04	0.820*
Number of VFs evaluated (n)	8.50 ± 0.96	8.52 ± 0.78	0.610*
Age (years)	67.92 ± 16.35	73.24 ± 15.13	0.172*
Gender, male:female (n)	44:57	38:40	0.269†
BCVA (log MAR)	0.12 ± 0.05	0.10 ± 0.04	0.634*
Spherical equivalent (diopters)	-3.82 ± 3.46	0.19 ± 1.26	<0.001*
Axial length (mm)	25.67 ± 1.22	23.11 ± 0.52	<0.001*
Central corneal thickness (µm)	532.52 ± 38.24	542.30 ± 40.22	0.916*
Baseline untreated IOP (mm Hg)	19.82 ± 2.24	18.32 ± 2.01	0.704*
Mean treated IOP (mm Hg)	14.21 ± 2.22	14.35 ± 2.38	0.736*
Baseline visual field MD (dB)	-4.18 ± 4.97	-4.06 ± 5.22	0.746*
Baseline visual field PSD (dB)	4.63 ± 3.90	3.96 ± 3.46	0.274*
Average RNFL thickness (µm)	76.32 ± 9.23	78.24 ± 7.96	0.308*

BCVA = best-corrected visual acuity, dB = decibels, IOP = intraocular pressure, log MAR = logarithm of the minimum angle of resolution, MD = mean deviation, N = number, PSD = pattern standard deviation, RNFL = retinal nerve fiber layer, VFs = visual fields.

Data are mean ± standard deviation unless otherwise indicated.

\*Student's *t*-test.

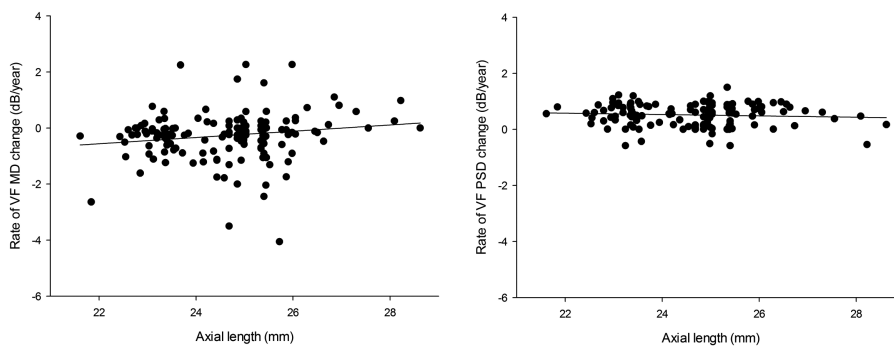
†Chi-square test.

that might even be protective against glaucoma progression, which was also for high myopic glaucomatous eyes.<sup>9,11,14</sup> However, all of these studies involved relatively young subjects (mean age 40–60 years) and follow-up periods of ~4 to 7 years. In additions, none of these studies characterized the progression rate according to age in myopic glaucomatous eyes. As shown in Figure 2, myopic eyes tended to progress faster according to age at diagnosis compared to nonmyopic eyes. This means that myopic glaucomatous eyes tend to progress faster at an older age than nonmyopic eyes, implying that glaucoma in young myopic glaucoma patients may progress faster in their later life.

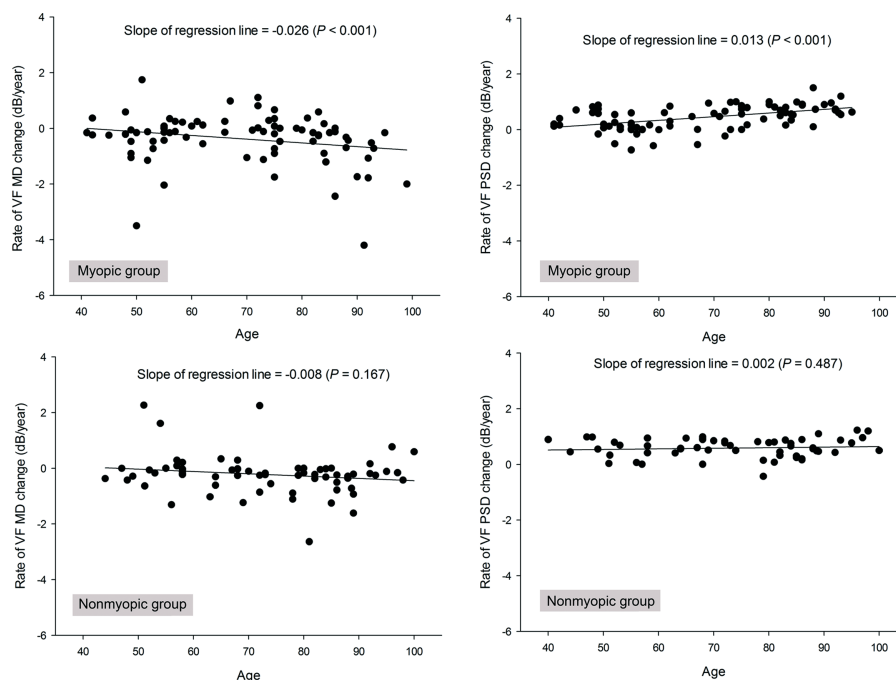
Many studies have reported that increasing age is associated with the rate of progression.<sup>23–26</sup> Many clinical trials, including the Early Manifest Glaucoma Trial, the Advanced Glaucoma Intervention Study, and the Collaborative Initial Glaucoma Treatment Study, have also reported that older age is a significant clinical predictor for glaucoma progression. The estimated average rate of change in the VF, defined as the MD rate, has reported MD rates of 0 to -1.1 dB/year in glaucoma

patients. For glaucoma patients undergoing routine care, mean MD rates of -0.35 to -0.62 dB/year have been reported after adjusting for age. In our study, the mean rate of MD change was -0.41 ± 1.20 dB/year in the nonmyopic group and -0.18 ± 1.55 dB/year in the myopic group, indicating that the myopic group had a slower MD rate. This rate is also slower than those reported in previous studies. However, the mean rate of changes was -0.49 ± 1.77 dB/year in the myopic group in the >80 years age group showing a distinct increase in the MD change rate in this age group.

Loss of retinal ganglion cells is part of the normal aging process, which causes reduced visual sensitivity across the VF and thinning of the RNFL.<sup>27,28</sup> The MD is an adjusted value according to age, because it compares the sensitivity of the VF of patients in similar age-matched groups at each location of the VF. However, changes in MD values have been consistently reported to be associated with older age. The reason for this is not well understood; however, it is possible that aging affects neuronal function, making older patients more vulnerable to



**FIGURE 1.** Scatter plot showing the relationships between the rate of change in visual field parameters (mean deviation [MD] and pattern standard deviation [PSD]) and axial length. MD = mean deviation, PSD = pattern standard deviation.



**FIGURE 2.** Scatter plot showing the relationships between the rate of visual field parameters (mean deviation [MD] and pattern standard deviation [PSD]) and age in myopic and nonmyopic groups classified by axial length of 24.0 mm. MD = mean deviation, PSD = pattern standard deviation.

glaucomatous changes. Alternatively, older patients may have a smaller neuronal reserve, allowing progressive changes to be detected earlier.<sup>29–31</sup> Myopic changes in older patients increase their vulnerability to glaucoma. Myopic changes are usually stable after adolescence; however, they can impact glaucoma throughout life. Myopic eyes have myopic changes in the posterior pole during eyeball elongation. We hypothesize that this may stretch and deform the axons of the retinal ganglion cells, resulting in changes in neuronal function, making eyes

more vulnerable to additional insults.<sup>32</sup> In addition, myopic changes may result in weakness of the supporting tissues around the optic nerve head. Furthermore, peripapillary atrophy could result in structural weakness of the supporting tissues of the optic nerve head, and thinning of the choriocapillaris and choroidal vessels may disturb the blood supply to the optic disc.<sup>33,34</sup>

We characterized the risk factors related to the rate of change in the MD in myopic and nonmyopic groups separately,

**TABLE 2.** Factors Associated With the Rate of Visual Field Mean Deviation Slope in all Glaucoma Patients

	Univariate Analysis			Multivariate Analysis		
	$\beta$	95% CI	P Value	$\beta$	95% CI	P Value
Age per 1 year older	-0.018	-0.029 to 0.002	0.683			
Axial length per 1 mm longer	0.139	-0.018 to 0.296	0.082	0.193	-0.063 to 0.319	0.185
Central corneal thickness per 1 $\mu$ m thicker	0.055	-0.006 to 0.009	0.661			
Baseline untreated IOP per 1 mm Hg higher	-0.140	-0.188 to -0.018	0.164	0.031	-0.095 to 0.117	0.831
Mean IOP during follow-up period per 1 mm Hg higher	-0.103	-0.174 to 0.040	0.554			
IOP fluctuation during follow-up period per 1 mm Hg higher	-0.150	-0.286 to 0.114	0.390			
Visual field MD per 1 dB higher	0.086	-0.017 to 0.152	0.354			
Visual field PSD per 1 dB higher	-0.067	-0.158 to 0.031	0.467			
Disc hemorrhage	-0.186	-0.354 to -0.006	0.042	-0.231	-0.373 to -0.089	0.026
Average RNFL thickness per 1 $\mu$ m thicker	-0.017	-0.019 to 0.016	0.855			
Follow-up period per 1 year longer	-0.163	-0.421 to 0.153	0.349			
Number of visual field exams	-0.027	-0.261 to 0.224	0.876			

$\beta$  = regression coefficient, CI = confidence interval, dB = decibels, IOP = intraocular pressure, MD = mean deviation, PSD = pattern standard deviation, RNFL = retinal nerve fiber layer.

**TABLE 3.** Factors Associated With the Rate of Visual Field Mean Deviation Slope in Glaucoma Patients With Myopia Defined as an Axial Length  $\geq 24.0$  mm

	Univariate Analysis			Multivariate Analysis		
	$\beta$	95% CI	P Value	$\beta$	95% CI	P Value
Age per 1 year older	-0.026	-0.104 to 0.051	0.032	-0.417	-0.651 to -0.200	0.050
Axial length per 1 mm longer	0.129	-0.062 to 0.319	0.177	0.233	-0.096 to 0.368	0.233
Central corneal thickness per 1 $\mu\text{m}$ thicker	0.001	-0.007 to 0.009	0.774			
Baseline untreated IOP per 1 mm Hg higher	-0.144	-0.265 to -0.022	0.022	-0.179	-0.331 to -0.028	0.022
Mean IOP during follow-up period per 1 mm Hg higher	-0.018	-0.230 to 0.193	0.838			
IOP fluctuation during follow-up period per 1 mm Hg higher	-0.081	-0.943 to 0.780	0.826			
Visual field MD per 1 dB higher	0.055	-0.018 to 0.128	0.134	0.028	-0.065 to 0.121	0.535
Visual field PSD per 1 dB higher	-0.066	-0.163 to 0.030	0.173	-0.018	-0.106 to 0.142	0.763
Disc hemorrhage	-0.138	-0.521 to 0.244	0.468			
Average RNFL thickness per 1 $\mu\text{m}$ thicker	-0.026	-0.061 to 0.010	0.152	-0.027	-0.061 to -0.007	0.072
Follow-up period per 1 year longer	-0.753	-2.291 to 0.786	0.276			
Number of visual field exams	0.075	-0.872 to 1.022	0.853			

$\beta$  = regression coefficient, CI = confidence interval, dB = decibels, IOP = intraocular pressure, MD = mean deviation, PSD = pattern standard deviation, RNFL = retinal nerve fiber layer.

with the assumption that the characteristics of glaucoma may differ. Other than age, few related factors have been differentially associated with the rate of change in the MD between myopic and nonmyopic glaucomatous eyes. Higher baseline untreated IOP was related to the rate of MD change in myopic eyes, whereas the presence of disc hemorrhage was related to it in nonmyopic eyes. Many studies have reported that disc hemorrhage is a risk factor for glaucoma progression.<sup>35,36</sup> IOP has also been reported as a risk factor for glaucoma progression.<sup>25,37</sup> However, whether the difference in significant risk factors for progression between myopic and nonmyopic eyes has important clinical implications will need further investigation.

Our study had several limitations. First, only modest sample size were included in this study and this means small effects of different variables could have not been fully apparent

in the present analysis. Second, only glaucoma patients from a single ethnic group were included. Thus, these results may not be applicable to all patients with glaucoma. Third, the follow-up period was relatively short. Further investigation is needed to determine the long-term influence of age on glaucoma progression in eyes with myopia. Fourth, statistically multiple testing was not considered in the analysis. Fifth, cataract formation in the older age group may have affected the results. Cataract is a well-known factor that decreases VF sensitivities.<sup>38</sup> However, its development may not differ between myopic and nonmyopic eyes, and comparisons between these eyes may have only minimal influence. In addition, cataract has minimal effects on the fast component of the VF rate and on the deepest part of the scotoma where progression usually occurs.<sup>39,40</sup> To minimize the effect of cataracts, we excluded

**TABLE 4.** Factors Associated With the Rate of Visual Field Mean Deviation Slope in Glaucoma Patients Without Myopia Defined as an Axial Length  $< 24.0$  mm

	Univariate Analysis			Multivariate Analysis		
	$\beta$	95% CI	P Value	$\beta$	95% CI	P Value
Age per 1 year older	-0.008	-0.039 to 0.027	0.930			
Axial length per 1 mm longer	0.902	-0.009 to 1.027	0.241			
Central corneal thickness per 1 $\mu\text{m}$ thicker	0.002	-0.010 to 0.014	0.738			
Baseline untreated IOP per 1 mm Hg higher	-0.031	-0.155 to 0.093	0.615			
Mean IOP during follow-up period per 1 mm Hg higher	-0.044	-0.133 to 0.045	0.288			
IOP fluctuation during follow-up period per 1 mm Hg higher	-0.181	-0.607 to 0.244	0.355			
Visual field MD per 1 dB higher	0.045	-0.072 to 0.197	0.124	0.138	-0.240 to 0.522	0.278
Visual field PSD per 1 dB higher	-0.024	-0.126 to 0.079	0.644			
Disc hemorrhage	-0.246	-0.596 to 0.104	0.163	-0.335	-0.568 to -0.018	0.022
Average RNFL thickness per 1 $\mu\text{m}$ thicker	0.007	-0.027 to 0.041	0.676			
Follow-up period per 1 year longer	-0.502	-1.175 to 0.172	0.224			
Number of visual field exams	-0.071	-0.417 to 0.274	0.648			

$\beta$  = regression coefficient, CI = confidence interval, dB = decibels, IOP = intraocular pressure, MD = mean deviation, PSD = pattern standard deviation, RNFL = retinal nerve fiber layer.

patients with a LOCS III grade higher than 3 at all visits, as well as patients who underwent cataract surgery during the follow-up period. Finally, we only included patients with typical VF defects located in the Bjerrum area in myopic eyes. Myopic eyes present with variety of stationary VF defects and sometime difficult to be differentiated with glaucomatous VF damage and there are possibilities of misclassification. We excluded all temporal field loss or others not in the Bjerrum area, which did not seem to be typical for glaucoma. Also, myopic eyes with retinal lesions were excluded with the assistance of retinal specialists.

In conclusion, age at presentation was significantly related to the rate of change in the VF in glaucomatous eyes with myopia but not in eyes without myopia. Older age and baseline untreated IOP were significant factors related to the rate of VF change in myopic glaucomatous eyes. When managing myopic glaucoma patients, it is important to consider that glaucoma in these patients may progress faster in their later life.

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