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Original Article

Risk factors for predicting visual field progression in Chinese patients with primary open-angle glaucoma: A retrospective study

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Abstract

Background: Glaucoma is a leading cause of irreversible blindness worldwide. It is characterized by progressive deterioration of the visual field (VF) that results in a complete loss of vision. This study aimed to determine the risk factors associated with VF progression in Chinese patients with primary open-angle glaucoma (POAG).

Methods: We reviewed the charts of POAG patients who visited our clinic between July 2009 and June 2010. We included patients with five or more reliable VF tests using the Humphrey Field Analyzer (Humphrey Instruments, San Leandro, CA, USA) during a period of at least 2 years. The scoring system of the Collaborative Initial Glaucoma Treatment Study (CIGTS) was used to code the VF. Progression was defined as an increasing score ≥ 3, compared to the averaged baseline data. Univariate and multivariate logistic regression analyses were performed to identify the risk factors of VF progression.

Results: There were 92 patients (representing 92 eyes) with an average of 8.9 reliable VFs over a mean follow up of 5.4 years. Multivariate logistic regression showed that eyes with more VF tests [odds ratio (OR) = 1.500, $p < 0.010$] and either increased peak intraocular pressure (IOP) (OR = 1.235, $p = 0.044$) or a wide IOP range (OR = 1.165, $p = 0.041$) favored VF progression. High myopia (less than −6.0 D) was not a risk factor (OR = 1.289, $p = 0.698$) for VF progression in this study.

Conclusion: In addition to a greater number of VF tests, Chinese patients with treated POAG who experienced a high peak IOP or a wide range of IOP during follow up were more likely to have VF deterioration.

Keywords: Chinese; intraocular pressure; myopia; primary open-angle glaucoma; visual field progression

1. Introduction

Primary open-angle glaucoma (POAG) is a leading cause of blindness worldwide.[1] Despite the growing understanding of its pathophysiology and advances in the management armamentarium against glaucoma, the challenges of predicting and halting disease progression remain. The percentage of visual field (VF) progression in open-angle glaucoma have ranged from 12% to 76% in investigations with different study

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designs, populations, treatments, and follow-up periods.[2–9] Candidate factors associated with glaucoma progression include old age,[2–4,6,8] worse baseline mean deviation (MD),[4,6] increased baseline intraocular pressure (IOP), increased mean IOP, increased peak IOP, greater IOP fluctuation during the follow-up period,[2,3,6–10] the presence of disc hemorrhage,[2,6,9] increased number of VF tests,[8] and myopia.[11,12] However, results regarding the role of myopia—a common refractive error and ocular disease in Chinese people—are inconsistent across studies. Debate exists over which IOP-related variable is more closely related to disease progression in treated patients with POAG.

Some studies such as the Advanced Glaucoma Intervention Study (AGIS) show a positive correlation between visit-to-visit IOP fluctuation and VF progression.[3,8,13–15] However, De Moraes et al[9] suggest that the peak IOP rather than IOP fluctuation is a predictor of progression. The latter study is supported by one glaucoma animal study that demonstrated a more predictive role of maximum IOP in structural change, compared to the mean IOP and IOP variability.[16] The role that myopia has in the disease course of POAG similarly remains to be clarified because of its clinical significance and high prevalence in Taiwan. Some studies report that high myopia has an impact on VF exacerbation,[11,12] whereas other studies have found no such correlation.[3,17,18]

Patients with different ethnic backgrounds show variations in the rate of VF deterioration[4]; therefore, they may also differ in the risk factors associated with VF progression. In light of limited data on risk factors for glaucomatous VF progression in Chinese people, we conducted this retrospective study to evaluate the rate of VF progression and determine the associated risk factors in a cohort of Chinese patients with POAG.

2. Methods

We reviewed the medical records of all POAG patients who had regular follow up at our glaucoma service for at least 2 years and maintained their follow-up schedules during the study period between July 2009 and June 2010. The study protocol was approved by the Institutional Review Board of the Taipei Veterans General Hospital (Taipei, Taiwan). The requirement for informed consent was waived (2013-08-010AC).

The diagnosis of POAG was based on normal open angles, glaucomatous optic nerve head changes, and reproducible VF defects of the retinal nerve fiber bundle pattern in at least two consecutive reliable field tests. The Glaucoma Hemifield Test and the pattern standard deviation of VF reports should correspond to outside normal limits and correspond to <5% of the age-matched normal patients, respectively. Patients with a pretreatment IOP ≥22 mmHg were classified as having high-tension POAG (HTG), and patients with a pretreatment IOP <22 mmHg at three or more visits were regarded as having normal-tension glaucoma (NTG). Patients with secondary glaucoma associated with corticosteroid use, trauma, ocular inflammation, or pigment dispersion were excluded. Also excluded were eyes with a patent iridotomy, with a best corrected visual acuity (BCVA) worse than 6/20, or with concomitant ocular disease such as diabetic retinopathy, age-related maculopathy, or neurological diseases that influence VF presentation. Eyes that received cataract extraction or glaucoma surgical intervention during the follow-up period were documented for surgical type and date of intervention.

2.1. VF tests

We retrieved VF tests that were performed using program 24-2 of a Humphrey Field Analyzer 750 (Humphrey Instruments, San Leandro, CA, USA) with the Swedish Interactive Thresholding Algorithm standard. The VF results included in the analysis had to fulfill the reliability criteria that the fixation loss, false-positive results, and false-negative results were all <33%. After excluding the VF tests with inconsistent patterns that reflected a learning effect, the first two reliable consecutive field tests were treated as the baseline fields.

Each VF was then scored, based on the Collaborative Initial Glaucoma Treatment Study (CIGTS) scoring system.[19] In brief, each point with a total deviation probability plot value of ≤5% was considered a depressed location. A weight was administered to each depressed location, depending on the minimum depth of defects among a given point and the neighboring two most defective points. Minimum defects of 0.05, 0.02, 0.01, and 0.005 were administered weights of 1, 2, 3, and 4, respectively. Locations without a probability plot value <0.05 in the two most depressed neighboring locations were given a score of zero. The weight of all 52 points were summed (ranging from 0 to 208), then the sum was scaled (divided by 10.4) to range from 0 (no defect) to 20 (all points show a defect at the $p < 0.005$ level). Eyes with a baseline CIGTS score of ≥18 were excluded from the study. Only eyes that had at least five qualified VF tests over a minimum span of 2 years were included in the analysis. If both eyes of one patient fulfilled the inclusion criteria, the eye with a lower CIGTS score was selected for the final analysis.

2.2. Definition of VF progression

Progression was defined as an increasing CIGTS score of ≥3, compared to the average score of the two baseline fields, and confirmed by two additional tests.[20]

2.3. Statistical analysis

Statistical analyses were performed using statistical software (SPSS, version 17.0; SPSS, Inc., Chicago, IL). A p value < 0.05 was considered statistically significant. Because of the inclusion of 92 patients (13 progressors and 79 non-progressors), the study had 80% of power to detect an OR of 0.4 or 2.5 for progression per one standard deviation change in the covariate ($\alpha = 0.05$).

Age, sex, and variables with $p < 0.2$ in univariate logistic regression analysis were entered stepwise into the multivariate logistic regression analysis. The mean IOP was also

considered in the model for adjustment because it has repeatedly been associated with disease progression. Factors taken into account included demographic data, ocular parameters, and medical conditions. The IOP data were included from the first baseline VF result. The IOP within 1 month after glaucoma surgery or within 1 week after bleb revision were omitted. The standard deviation (SD) of the IOP readings from all other visits throughout the follow-up period was regarded as the long-term IOP fluctuation, whereas the range of IOP was the difference between the highest (i.e., peak) and the lowest IOP readings from visit to visit.

3. Results

Based on our inclusion and exclusion criteria, we included 96 patients (representing 96 eyes) for chart review. Ninety-two patients (representing 92 eyes) were included for final analysis, which included 45 NTG and 47 HTG patients. Table 1 lists the clinical characteristics. There were significant differences in the distribution of central corneal thickness, various IOP-related parameters, and the number of VF tests between NTG and HTG, although the slope of the VF mean deviation and CIGTS score over time were comparable between the two groups. Therefore, the data from the NTG and HTG patients were grouped together as open-angle glaucoma for further analysis.

In all, 8.85 reliable fields were available for each patient after a mean follow up of 5.4 years. The average MD declined from −8.87 dB to −9.52 dB ($p = 0.130$), the mean pattern SD increased from 7.56 dB to 8.14 dB ($p = 0.030$), and the CIGTS score increased from 9.86 to 10.08 ($p = 0.630$) throughout the follow-up period. Thirteen eyes of 13 patients (14%) showed VF progression during the follow-up period.

In univariate logistic regression analyses, we found the following were associated with VF progression: disc hemorrhage, glaucoma family history, visit-to-visit IOP fluctuation, duration of follow-up period, range of IOP and peak IOP during follow up, and number of VF tests ($p < 0.2$; Table 2). Owing to high correlations among three IOP parameters with $p < 0.2$ in univariate analysis (IOP fluctuation vs. range of IOP, $r = 0.94$, $p < 0.001$; range of IOP vs. peak IOP, $r = 0.82$, $p < 0.001$; and peak IOP vs. IOP fluctuation, $r = 0.76$, $p < 0.001$), different models that included only one of these variables were established. Model 1 showed that eyes with a greater IOP range and more VF tests during follow up were more likely to be progressors, after adjusting for age, sex, disc hemorrhage, mean IOP, family history of glaucoma, and follow-up period (Table 3), and Model 2 showed that eyes with an increased peak IOP and more VF tests during the follow-up period were more likely to progress (Table 4). The results remained similar after excluding the data of patients ($n = 8$) who had received cataract surgery during the follow-up period.

Univariate logistic regression analysis did not identify high myopia (i.e., a spherical equivalent of −6.0 D or less) as a potential risk factor for disease progression (OR = 1.289, $p = 0.698$). In addition, by estimating the slope of the VF mean deviation or the CIGTS score, we did not find a correlation between the VF change and axial length or spherical equivalent by linear regression analysis.

4. Discussion

The aim of glaucoma treatment is to maintain the quality of life by preserving patients' visual function througout their lifetime. Because VF loss has substantially negative impacts on visual function in glaucoma patients,[21] the detection of VF progression is important in disease management and therapeutic decisions. To date, no gold standard has been established to define clinically relevant VF progression, but the consensus is to use event-based methods in the first few years of follow up when few VFs are available for an authentic trend analysis.

Table 1
Baseline and follow-up data of all patients.

	All ($n = 92$)	HTG ($n = 47$)	NTG ($n = 45$)	p
Baseline				
Age (y)	57.98 ± 15.54	55.62 ± 17.13	60.44 ± 13.43	0.240
Female, *n* (%)	26 (28)	16 (34)	10 (22)	
BCVA	0.83 ± 0.20	0.83 ± 0.21	0.83 ± 0.19	0.946
Spherical equivalent (D)	−3.10 ± 4.40	−4.02 ± 4.51	−2.18 ± 4.14	0.058
Axial length (mm)	25.07 ± 1.78	25.26 ± 1.83	24.85 ± 1.72	0.313
IOP (mmHg)	20.71 ± 3.98	23.54 ± 3.18	17.36 ± 1.23	<0.001*
CCT (μm)	553 ± 30	562 ± 31	544 ± 25	0.003*
No. of glaucoma medications	1.31 ± 0.60	1.49 ± 0.74	1.12 ± 0.33	0.022*
Mean deviation (dB)	−8.87 ± 5.93	−9.08 ± 6.21	−8.66 ± 5.68	0.916
PSD (dB)	7.56 ± 3.94	7.55 ± 4.15	7.58 ± 3.74	0.888
Disc hemorrhage, *n* (%)	6 (7)	3 (6)	3 (7)	
Glaucoma family history, *n* (%)	14 (15)	7 (15)	7 (16)	
Hypertension, *n* (%)	24 (26)	8 (17)	16 (38)	
Cardiovascular disease, *n* (%)	19 (21)	5 (11)	14 (31)	
Diabetes mellitus, *n* (%)	15 (16)	7 (15)	8 (18)	
Follow up				
IOP (mmHg)				
Mean	14.54 ± 2.59	15.87 ± 2.58	13.15 ± 1.74	<0.001*
Fluctuation	2.14 ± 0.92	2.36 ± 1.04	1.91 ± 0.70	0.023*
Range	8.41 ± 4.50	9.48 ± 5.57	7.30 ± 2.65	0.129
Peak	19.29 ± 4.44	21.4 ± 5.01	17.1 ± 2.24	<0.001*
Period (y)	5.41 ± 2.3	5.05 ± 2.32	5.80 ± 2.23	0.097
Qualified VF tests per person	8.85 ± 3.52	7.64 ± 2.52	10.11 ± 3.97	0.002*
Surgical intervention, *n* (%)	20 (22)	12 (26)	8 (18)	
Progressor, *n* (%)	13 (14)	7 (15)	6 (13)	

Continuous variables are presented as the mean ± the standard deviation.
* Indicates statistical significance.
BCVA = best corrected visual acuity; CCT = central corneal thickness; HTG = high-tension glaucoma; IOP = intraocular pressure; NTG = normal-tension glaucoma; PSD = pattern standard deviation; VF = visual field.

Table 2
Univariate logistic regression analysis of risk factors for glaucoma progression ($n = 92$).

	Odds ratio	*beta* value	SE	*p*	95% confidence interval
Baseline					
Age (y)	0.995	−0.005	0.019	0.791	0.958–1.033
Female	1.152	0.141	0.651	0.828	0.321–4.127
NTG	0.879	−0.129	0.600	0.830	0.271–2.850
BCVA	7.720	2.044	1.840	0.267	0.210–284.1
Spherical equivalent (D)	0.993	−0.007	0.068	0.923	0.869–1.135
Axial length (mm)	1.096	0.091	0.182	0.616	0.767–1.565
IOP (mmHg)	3.002	1.099	0.968	0.256	0.450–20.03
CCT (μm)	1.001	0.001	0.010	0.919	0.981–1.021
Glaucoma medication	1.691	0.525	0.492	0.286	0.644–4.440
Mean deviation (dB)	1.053	0.052	0.058	0.374	0.940–1.180
PSD (dB)	0.991	−0.009	0.077	0.902	0.852–1.152
Disc hemorrhage	3.409	1.226	0.924	0.185 *	0.557–20.86
Glaucoma family history	3.067	1.121	0.690	0.104 *	0.794–11.84
Hypertension	0.829	−0.188	0.706	0.790	0.208–3.305
Cardiovascular disease	1.896	0.640	0.666	0.337	0.514–6.994
Diabetes mellitus	0.387	−0.950	1.082	0.380	0.046–3.224
Follow up					
IOP (mmHg)					
Mean	1.005	0.005	0.116	0.966	0.800–1.262
Fluctuation	1.673	0.515	0.283	0.069 *	0.962–2.912
Range	1.137	0.128	0.058	0.027 *	1.015–1.274
Peak	1.085	0.082	0.061	0.181 *	0.963–1.224
Period (y)	1.195	0.179	0.134	0.183 *	0.919–1.554
Number of VF tests	1.303	0.264	0.083	0.001 *	1.108–1.531

* This value ($p < 0.2$) was entered into multivariate logistic regression analysis.
BCVA = best corrected visual acuity; CCT = central corneal thickness; IOP = intraocular pressure; NTG = normal-tension glaucoma; PSD = pattern standard deviation; SE = standard error; VF = visual field.

In the present study, we adopted the CIGTS criterion to define VF progression because it has good specificity and the best sustainability, compared to other proposed criteria such as the Early Manifest Glaucoma Trial (EMGT) criteria and the AGIS score.[22] We detected VF progression in 14% of POAG patients with Chinese ethnicity during a mean follow-up time of 5.4 years. The result was comparable with that of the interim outcome of the CIGTS, a prospective study in which Asians constitued <5% of the participants; during 5 years of follow up, a substantial VF loss occurred in 10.7% of medically treated patients and 13.5% of surgically treated patients.[23]

Reducing the IOP is beneficial for glaucoma patients to maintain visual function, but uncertainty exists regarding which IOP variable has the most significant impact on disease progression for patients under treatment. We found that an increased peak IOP was accompanied by a wide IOP range; both findings were risk factors for VF deterioration, after adjusting for the mean IOP and other potential risk factors; however, the peak IOP seemed to have slightly more weight than the IOP range. Each 1-mmHg increase in the peak IOP increased the risk of VF progression by 23.5%, whereas each 1-mmHg increase (wider) in the IOP range increased the risk of VF progression by 16.5% during our average follow up of 5.4 years. In a retrospective study, which enrolled 587 eyes with a mean follow up of 6.4 years, De Moraes et al[9] also concluded that the peak IOP was a better predictor of progression than the mean IOP or fluctuation in the IOP. In another study that assessed the association between IOP parameters and VF loss in participants of the CIGTS, Musch et al[10] found that the peak IOP, fluctuation in IOP, and the range of the IOP were all significantly associated with worse VF over a 3–9-year period in the medication group.

As our correlation study shows, IOP variables may interact with each other and lead to subsequent VF deterioration,[10] even when the mean IOP has been controlled at an acceptable level.[8] In clinical practice, it may take years for clinicians to better estimate the intervisit IOP fluctuation of a particular patient. Our results indicated that an IOP measure that is higher than those usually obtained during follow up, once confirmed, should not be regarded as an insignificant outlier, but regarded as an alarm indicating suboptimal control of the patient's diurnal or long-term IOP. Because of recent evidence that peak circadian IOP in glaucoma patients usually occurs during off-office hours,[24,25] the expectation is that an even higher IOP probably occurs at nighttime and strict control of the IOP is required.

Table 3
Multivariate logistic regression analysis of risk factors for glaucoma progression, including and excluding patients with cataract extraction: Model 1.

	All patients ($n = 92$)				Excluding patients with cataract extraction ($n = 84$)			
	Odds ratio	*beta* value	SE	*p*	Odds ratio	*beta* value	SE	*p*
Age (y)	1.047	0.046	0.032	0.150	1.056	0.054	0.032	0.090
Female	1.733	0.550	0.820	0.502	2.505	0.918	0.909	0.312
Range of IOP (mmHg)	1.165	0.153	0.075	0.041 *	1.172	0.159	0.076	0.035 *
Mean IOP (mmHg)	1.083	0.080	0.161	0.619	1.056	0.055	0.166	0.742
Period of follow up (y)	0.823	−0.194	0.231	0.399	0.831	−0.186	0.237	0.434
No. of VF tests	1.461	0.379	0.134	0.005 *	1.517	0.417	0.145	0.004 *
Disc hemorrhage	3.823	1.341	1.079	0.214	2.995	1.097	1.094	0.316
Glaucoma family history	5.630	1.728	0.984	0.079	4.711	1.550	0.987	0.117

* Indicates statistical significance.
IOP = intraocular pressure; SE = standard error; VF = visual field.

Table 4
Multivariate logistic regression analysis of risk factors for glaucoma progression, including and excluding patients with cataract extraction: Model 2.

	All patients (n = 92)				Excluding patients with cataract extraction (n = 84)			
	Odds ratio	*beta* value	SE	p	Odds ratio	*beta* value	SE	p
Age (y)	1.048	0.047	0.032	0.144	1.056	0.054	0.032	0.090
Female	1.794	0.584	0.830	0.481	2.383	0.868	0.906	0.338
Peak IOP (mmHg)	1.235	0.211	4.222	0.044 *	1.236	0.212	0.105	0.044 *
Mean IOP (mmHg)	0.896	−0.110	0.206	0.593	0.879	−0.130	0.211	0.539
Period of follow up (y)	0.802	−0.221	0.229	0.335	0.802	−0.221	0.235	0.347
No. of VF tests	1.500	0.405	0.136	0.003 *	1.557	0.443	0.148	0.003 *
Disc hemorrhage	3.958	1.376	1.084	0.205	3.113	1.136	1.099	0.302
Glaucoma family history	5.994	1.791	0.986	0.069	5.063	1.622	0.986	0.100

* Indicates statistical significance.
IOP = intraocular pressure; SE = standard error; VF = visual field.

We found the number of VF tests was the most significant parameter associated with VF progression, which is in line with the findings of the AGIS.[8] Our study was retrospective and VF tests were not performed at a scheduled interval; however, as part of our clinical strategy, we routinely performed three to four tests during the first year of follow up to identify patients with rapid progression. In the real world, clinicians tend to repeat VF tests within a shorter interval when they are managing patients with more advanced glaucoma or with a VF defect that is threatening central vision, even before VF progression has been detected. In our study, the average MD and the percentage of eyes with central VF involvement at baseline were not significantly different between eyes with and without VF progression. A greater number of VF tests in our patients with progression, compared to the number of VF tests in patients without progression, were likely to be associated with a clinical judgment of possible disease progression in the first place. To improve the detection of early VF progression in glaucoma, the preferred practice pattern recommends repeating VF testing sooner than glaucoma patients with regular follow-up and regular VF examinations when likely progression is detected.[26]

We did not find a correlation between the spherical equivalent or axial length and VF progression by using logistic or linear regression analysis. However, myopia was a risk factor of glaucoma formation. The findings are coherent with several studies that found that neither axial length nor myopia was associated with VF progression in open-angle glaucoma.[3,8,18] By contrast, Chihara et al[11] found that glaucomatous eyes with high myopia (average spherical equivalent, −9.3 D) were at high risk of VF progression, and Lee et al[12] found that POAG patients with myopia greater than −6.0 D had greater VF exacerbation. We compared our study with Lee's work, and adopted different criteria to define progression in Chinese patients with POAG. We found that our population was older (58.0 ± 15.5 years vs. 48.6 ± 14.2 years), less myopic (−3.1 ± 4.4 D vs. −5.1 ± 4.2 D), had worse initial MD (−8.9 ± 5.9 dB vs. −5.0 ± 4.5 dB), and lower mean IOP during follow up (14.5 ± 2.6 mmHg vs. 15.9 ± 2.9 mmHg). These differences may have contributed to the disparity in results between our study and Lee's work. Based on these paradoxical results, whether myopia is a risk factor for glaucomatous VF progression awaits further study for clarification. In light of existing literature and our findings, the role of myopia in VF progression can be overcome, at least in part, by aggressive IOP reduction.

Our study is limited by its small sample size, relatively short-term follow up, and shortcomings inherent in retrospective studies. The various follow-up periods and inconsistent intervals between VF tests may have prohibited us from detecting progression in some patients. However, our inclusion criteria of five or more qualified tests over a minimum span of 2 years makes this occurrence less likely. Another issue that may be argued is that a postintervention low IOP may contribute to the IOP variation, which in fact results from the intervention rather than leads to progression. To minimize the impact of IOP variation after glaucoma surgical intervention in our study results, we excluded the early postintervention IOP from our analysis. The findings that peak IOP is a significant factor associated with VF progression and that it is highly correlated with IOP fluctuation and the range of IOP indicate that the variation in IOP leading to disease progression is a more likely explanation. The patients with high myopia may have been too few in number (n = 24, 26%) in this study to detect a correlation between VF progression and myopic refraction, although refractive error is only one aspect of disease presentation in myopia.

In conclusion, we found the proportion of eyes reaching the progression endpoint after a mean follow up of 5.4 years was quite similar to that reported in the CIGTS after 5 years of follow up. Eyes with a greater number of VF tests, an increased peak IOP, and a wide range in IOP were more likely to have VF progression, based on the CIGTS criteria, in this cohort of Chinese patients with POAG.

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