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Factors Threatening Central Visual Function of Patients with Advanced Glaucoma

A Prospective Longitudinal Observational Study

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Purpose: To identify risk factors for further deterioration of central visual function in advanced glaucoma eyes.

Design: Prospective, observational 5-year study.

Participants: Advanced glaucoma patients with well-controlled intraocular pressure (IOP), mean deviation (MD) of the Humphrey Field Analyzer (HFA) 24-2 program ≤−20 dB and best-corrected visual acuity (BCVA) of 20/40.

Methods: The HFA 10-2 test and BCVA examination were performed every 6 months, and the HFA 24-2 test was performed every 12 months for 5 years. The Cox proportional hazards model was used to identify risk factors for deterioration of HFA 10-2 and 24-2 results and BCVA.

Main Outcome Measures: Deterioration of HFA 10-2 results was defined by the presence of the same ≥3 points with negative total deviation slope ≤−1 dB/year at $P < 0.01$ on ≥3 consecutive tests, deterioration of HFA 24-2 results by an increase ≥2 in the Advanced Glaucoma Intervention Study score on ≥2 consecutive tests, and deterioration of BCVA by an increase of ≥0.2 logarithm of the minimum angle of resolution (logMAR) on ≥2 consecutive tests.

Results: A total of 175 eyes of 175 patients (mean age, 64.1 years; mean baseline IOP, 13.2 mmHg; mean BCVA, 0.02 logMAR; mean HFA 24-2 and 10-2 MD, −25.9 and -22.9 dB, respectively) were included. The probabilities of deterioration in HFA 10-2 and 24-2 results and BCVA were 0.269 ± 0.043 (standard error), 0.173 ± 0.031, and 0.194 ± 0.033, respectively, at 5 years. Lower BCVA at baseline ($P = 0.012$) was associated significantly with further deterioration of HFA 10-2 results. Better HFA 24-2 MD ($P < 0.001$) and use of systemic antihypertensive agents ($P = 0.009$) were associated significantly with further deterioration of HFA 24-2 results, and a greater β-peripapillary atrophy area-to-disc area ratio ($P < 0.001$), use of systemic antihypertensive agents ($P = 0.025$), and lower BCVA ($P = 0.042$) were associated significantly with further deterioration of BCVA, respectively.

Conclusions: In advanced glaucoma eyes with well-controlled IOP, BCVA, β-peripapillary atrophy area-to-disc area ratio, and use of systemic antihypertensive agents were significant prognostic factors for further deterioration of central visual function. *Ophthalmology 2022;129:488-497 © 2021 by the American Academy of Ophthalmology*

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Glaucoma is one of the leading causes of visual dysfunction and blindness worldwide,[1] with a prevalence rate of 5.0% in the Japanese population older than 40 years.[2] The major risk factors for blindness resulting from glaucoma include high intraocular pressure (IOP) and visual field (VF) defects that already have progressed at the time of diagnosis.[3] Many studies recruiting patients with glaucoma with mild to moderate damage have shown that IOP-lowering therapy is effective in delaying the progression of glaucoma,[4–9] and more strict control of IOP generally is indicated for glaucoma with advanced damage[6]; however, even if the IOP is thought to be controlled, a significant proportion of these patients ultimately lose their vision.[10–12]

The purpose of glaucoma treatment is to maintain lifelong visual function and vision-related quality of life by retarding the progression of glaucoma. Many studies conducted in patients with glaucoma with mild to moderate damage have identified risk factors for progression other than higher IOP.[4–9,13–17] Investigation of risk factors for further deterioration of functional damage in patients with advanced glaucoma who are at higher risk of loss of sight and severe vision-related quality of life impairment is of additional clinical importance; however, information on the risk factors for further deterioration of central visual function in a large cohort of patients with advanced glaucoma is relatively scarce. The mean deviation (MD) value of the

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Humphrey Field Analyzer (HFA) 24-2 test in patients included in the Advanced Glaucoma Intervention Study (AGIS) was approximately −13 dB,[6] and information for patients with more advanced disease, such as those with MD <−20 dB, seems to be inadequate. Gilles et al[18] reported that further deterioration of VF damage and visual acuity (VA) was seen in 37.5% and 9.4% of the patients from a prospective observational cohort, including 32 eyes of 22 patients with glaucoma with an effective VF ≤10° who were followed up over a period of 7.7 years. Much et al[19] retrospectively studied 64 patients with advanced glaucoma (MD of HFA 24-2 or 30-2, <−19 dB) and reported that VA was deteriorated further in approximately 20% of the eyes, whereas the HFA 10-2 MD was decreased by ≥3 dB in approximately 10% of the eyes during an average follow-up period of 8.3 years. Recently, Kim and Sung[20] retrospectively studied 87 eyes with normal-tension glaucoma (NTG) with an MD of −16.6 dB and reported that 62.2% of them showed further deterioration of VF damage and 47.2% showed deterioration of VA over a mean period of 5.4 years. Because the VF close to the fixation is of particular functional importance for vision-related quality of life,[21–23] maintenance of this central VF is of particular importance in advanced glaucoma, and information on the risk factors for its further deterioration is clinically important. Thus, we conducted a 5-year prospective, observational study to identify risk factors for further deterioration of visual function in a sufficient number of patients with advanced glaucoma whose IOP was clinically well controlled, paying particular attention to the changes in the central 10° VF.

Methods

This study was a multicenter, prospective, observational, and long-term study of patients with advanced glaucoma by the Japan Glaucoma Society. The institutes participating in the study were as follows: University of Tokyo (Tokyo), Kumamoto University (Kumamoto), Nihon University (Tokyo), Kobe University (Hyogo), Saga University (Saga), Yoshikawa Ophthalmology Clinic (Tokyo), and Tokyo Post and Telecommunications Hospital (Tokyo). The protocol for this study was approved by the ethics committee of each institution, followed the tenets of the Declaration of Helsinki, and was registered in UMIN-Clinical Trials Registry under identifier UMIN000001004. Written informed consent was obtained from all participants.

Japanese patients with advanced glaucoma who met the following criteria and were thought to be eligible for a 5-year observational study were recruited from the outpatient ophthalmology clinics of the above-mentioned institutions between July 2004 and February 2010. The inclusion criteria were as follows: (1) glaucoma with clinically well-controlled IOP and no apparent progression of the HFA 24-2 VF in the past 2 years, (2) no other clinical disease other than glaucoma that affects the VF or VA, (3) age at the time of obtaining consent of 20 to 80 years, (4) reliable results obtained with the HFA Swedish Interactive Threshold Algorithm Standard 24-2 and 10-2 test programs (fixation loss, ≤20%; false-positive results, ≤15%; HFA 24-2 and 10-2 [Carl Zeiss Meditec]), (5) MD with HFA 24-2 ≤−20 dB in at least 1 eye, (6) best-corrected VA (BCVA) of 20/40 or worse (0.5 decimal vision; ≤0.3 logarithm of the minimum angle of resolution [logMAR]), and (7) no clinically significant cataracts that could affect the VF test results. Exclusion criteria included (1) a spherical equivalent refraction ≥+4.0 diopters or ≤−8.0 diopters or an ocular axial length ≥27.0 mm, (2) moderate or severe systemic comorbidities, and (3) a history of ocular surgery other than uncomplicated cataract or glaucoma surgeries. After providing written informed consent, the patients underwent an interview regarding their medical history. Measurements of blood pressure (BP) were followed by assessment of refractive status with an autorefractometer (ARK-730; Topcon), VA measurement with a chart of Landolt rings at a distance of 5 m initially using the data obtained with an autorefkeratometer, central corneal thickness measurement with a specular microscope (SP-2000P; Topcon), axial length measurement with the IOL Master (Carl Zeiss Meditec) or A-scan ultrasound biometry (AL-2000; Tomey), and biomicroscopic examination. Intraocular pressure was measured with Goldmann applanation tonometry, and gonioscopy was performed using a Goldmann 2-mirror gonioscope, which was followed by fundus examinations. Twenty-degree fundus photography or 30° stereo fundus photography of the optic disc was performed and repeated every year thereafter. Visual field tests with the HFA 10-2 and HFA 24-2 test programs were performed within 1 month of enrollment, and HFA 10-2 and 24-2 tests were performed at intervals of 6 months and 1 year, respectively. Ophthalmic examinations, including IOP measurement, were performed every 2 to 3 months, and VA measurement was performed every 6 months after enrollment. Treatment of glaucoma during follow-up was performed as deemed necessary by a glaucoma subspecialist at each facility.

Criteria for Deterioration of VF and VA

Criteria for Deterioration of HFA 10-2 Results. Because no criteria are established for deterioration of HFA 10-2 results in eyes with advanced glaucoma, we referred to the corresponding criteria for HFA 24-2 results in the Low-Pressure Glaucoma Treatment Study (LoGTS),[24] which are summarized herein. First, the total deviation value (TD) of each measurement point on the HFA 24-2 was used as a dependent variable, and the number of years from entry to the time of VF testing was used as the independent variable to calculate linear regression from the first measurement to each measurement point. Linear regression was performed using ≥3 consecutive VF analyses. Second, when the above slope was ≤−1.0 dB/year at $P < 0.05$ at the same 3 points for 3 consecutive VF tests, the first of the 3 tests described above was defined as showing significant deterioration.

Three criteria obtained by partial modification of the LoGTS criteria listed above were defined using the TD of each measurement point in HFA 10-2 instead of those in HFA 24-2. Criterion A was defined as the P value of the TD slope ≤−1.0 dB/year being set at $P < 0.01$ instead of $P < 0.05$. The number of VF tests needed to confirm the deterioration was 3 consecutive VF tests. Criterion B was defined as the P value of the TD slope ≤−1.0 dB/year being set at $P < 0.05$. The number of VF tests needed to confirm the deterioration was 3 consecutive VF tests. This criterion was applied directly from the LoGTS criteria for HFA 24-2 to HFA 10-2. Criterion C was defined as the P value of the TD slope ≤−1.0 dB/year being set at $P < 0.05$, as in criterion B, but the number of VF tests needed to confirm the deterioration was changed from 3 to 2 consecutive VF tests.

To assess the specificity of the above criteria, nonprogressive HFA 10-2 results for advanced glaucoma were simulated using a method used by Mayama et al[25] to simulate nonprogressive HFA 24-2 results for moderately advanced glaucoma. A covariance matrix was created on the basis of the measured VF of the first and second HFA 10-2 results obtained at an interval ≤6 months in 219 eyes screened for this study. The IOPs were clinically

well controlled, and the MDs of HFA 24-2 <−20 dB and HFA 24-2 results showed no significant changes over the previous 2 years. Based on the above covariance matrix, noise was generated using a noise generator according to a 68-dimensional normal distribution and was added to TD at each test point of the 219 eyes' initial HFA 10-2 VF. This task was repeated 10 times to create a time series of HFA 10-2 VFs 1 through 10. The same processes were repeated 100 times per eye to generate 100 series of nonprogressing HFA 10-2 VF series per eye, yielding a total of 21 900 nonprogressive HVF 10-2 VF series. The specificity of these 3 criteria was assessed by counting the number of HFA 10-2 VF series that met the current criteria.

Criteria for Deterioration of HFA 24-2 Results. One of the ways to manage a large variation of measured threshold values of test points of HF 24-2 with very low sensitivities in eyes with advanced glaucoma is to calculate a score representing the measurement results of the all test points over the entire HFA 24-2 VF. We adopted the AGIS score developed for estimating VF performance in eyes with advanced glaucomatous damage.[26] The HFA 24-2 results were considered to have deteriorated when the AGIS score increased ≥2 levels from baseline at ≥2 consecutive VF examinations.[26] Although the AGIS criteria state an increase ≥4, 75% of the patients in this study showed an AGIS score ≥17, making it impossible to determine progression in many of the participant eyes in the current study. Therefore, in this study, progression of HFA 24-2 results was suspected when the AGIS score increased ≥2 levels from baseline.

Criteria for VA Deterioration. When BCVA decreased by ≥0.2 logMAR at ≥2 consecutive VA tests from baseline and the decrease could not be explained by nonglaucomatous changes such as ocular media changes, cataract progression, changes in fundus including hypotonic changes attributable to intraocular surgeries before enrollment, or other ocular or systemic comorbidities, VA deterioration was considered to have occurred as a result of progression of glaucoma. Based on the World Health Organization criteria, BCVA of worse than 3/60 (0.05 decimal vision) was defined as blindness.

Method of Data Analysis

If both eyes of a patient met the inclusion criteria, the eye with the worse HFA 24-2 MD was included in the study after confirming its VA of 20/40 or worse, and the data from this eye were used for analysis. Kaplan−Meier survival curve analysis was used to assess the probability of VF or VA deterioration. Patients who no longer could be followed up during the course of the study were included in the analysis as censored patients. Patients who underwent glaucoma surgery during the course of the study were included in the analysis until the time of surgery, whereas those who underwent cataract surgery were censored at the time when cataract-caused VA deterioration was suspected. A Cox proportional hazards model was used to identify risk factors for further VF or VA deterioration. The explanatory variables used for the Cox proportional hazard model were age, sex, MD of HFA 24-2 and mean of TD values of HFA 10-2, central corneal thickness, axial length, VA (logMAR), glaucoma type, β-peripapillary atrophy (PPA) area-to-disc area ratio, systolic and diastolic BP, absence or presence of systemic antihypertensive agents, absence or presence of diabetes mellitus at baseline, and mean IOP and long-term IOP fluctuation defined as the standard deviation of the measured IOP during the follow-up period. The β-PPA-to-disc area ratio was calculated from the number of pixels of the clinical optic disc and photographically defined β-PPA area[27] from the photographs using the image analysis software ImageJ (National Institutes of Health, Bethesda, MD). Glaucoma types were categorized into 4 groups: primary open-angle glaucoma with elevated IOP, primary open-angle glaucoma with normal IOP (NTG), primary angle-closure glaucoma, and secondary glaucoma and developmental glaucoma (others). The minimum Akaike's information criterion method was used to select variables for the multivariate Cox proportional hazards model analysis. All statistical analyses were performed using JMP software version 14.0 (SAS Institute, Inc).

Results

A total of 219 patients were screened as candidates meeting the inclusion and exclusion criteria at each institution in this study. After excluding the eyes that were found to show a small deviation from the inclusion criteria and excluding patients who withdrew informed consent before the first follow-up measurement of HFA 10-2 VF because of unexpected personal or familiar matters or relocation, 175 eyes of 175 patients (mean ± standard deviation age, IOP, and MD values of HFA 24-2 and 10-2 MD at baseline: 64.1 ± 12.3 years, 13.2 ± 2.9 mmHg, −25.9 ± 3.1 dB, and −22.9 ± 5.8 dB, respectively) were included in the prospective follow-up study. The demographic and clinical characteristics of the patients are shown in Table 1. Figure 1 shows the average TD values for each test point of the HFA 10-2 and 24-2 test programs at baseline. During the 5-year follow-up, 5 patients died or were lost to follow-up because of poor general condition, 2 relocated, and 3 declined further testing during the follow-up period. Eighteen patients underwent cataract surgeries, 16 patients underwent glaucoma surgeries (3 combined cataract and glaucoma surgeries and 5 after cataract surgeries), and 149 patients did not undergo surgical treatment during the course of the study.

To confirm the validity of simulated stable HFA 10-2 VF series in eyes with advanced glaucomatous damage, the distribution of the mean TD slope of HFA 10-2 results on the basis of 21 900 simulated stable HFA 10-2 VF series was studied and is shown in Figure S1 (available at www.aaojournal.org). The curve followed a normal distribution, with 5.0% of the simulated HFA 10-2 VF series showing a significant positive or negative trend at $P < 0.05$. According to criteria A, B, and C, 2 series, 613 series, and 3262 series were judged to have deteriorated, with simulated specificities of 99.99%, 97.20%, and 85.11%, respectively. Thus, criterion A (TD slope ≤−1.0 dB/year at $P < 0.01$ at the same 3 points for 3 consecutive VF tests, in which the first of the 3 tests was defined as significantly deteriorated), which was thought to be the most conservative among the examined, was adopted as the current criterion for significant deterioration of HFA 10-2 VF of advanced glaucoma.

The mean ± standard deviation HFA 10-2 and 24-2 MD slopes averaged −0.44 ± 0.78 and −0.22 ± 0.45 dB/year (n = 175), respectively. According to the current criteria, 36 of 175 eyes were judged to have deteriorated HFA 10-2 results, and 26 of 175 eyes were judged to have deteriorated HFA 24-2 results, of which 11 eyes were judged to show deterioration in both HFA 10-2 and 24-2 results. Visual acuity was judged to have deteriorated in 28 of the 175 eyes. During the follow-up period, 6 eyes experienced blindness. The mean ± standard error probabilities of HFA 10-2 and HFA 24-2 VF deterioration at 5 years were 0.269 ± 0.043

Table 1. Participant Characteristics

Characteristic	Data
Age (yrs)	64.1 ± 12.3
Sex	
Male	111
Female	64
Eye	
Right	80
Left	95
Type of glaucoma (no. of eyes)	
POAG	62
NTG	64
PACG	19
Others	30
Axial length (mm)	24.29 ± 1.42
Central corneal thickness (μm)	516.4 ± 36.8
BCVA at baseline (logMAR)	0 .02 (−0.079 to 0.097)
IOP (mmHg)	
Baseline	13.19 ± 2.94
During follow-up	12.96 ± 3.00
SD of IOP during follow-up	1.87 ± 1.41
HFA MD (dB)	
24-2	−25.85 ± 3.10
10-2	−22.93 ± 5.77
β-PPA-to-disc area ratio	0.12 (0.066–0.18)
BP (mmHg)	
Systolic	131 ± 18
Diastolic	79 ± 11
Diabetes mellitus	13
Antihypertensive medications	36

BCVA = best-corrected visual acuity; BP = blood pressure; HFA = Humphrey Field Analyzer; IOP = intraocular pressure; logMAR = logarithm of the minimum angle resolution; MD = mean deviation; NTG = normal-tension glaucoma; PACG = primary angle-closure glaucoma; POAG = primary open-angle glaucoma; PPA = peripapillary atrophy area; SD = standard deviation.
Data are presented as number (no.), mean ± standard deviation, or median (interquartile range).

and 0.173 ± 0.031, respectively; the probability of VA deterioration at 5 years was 0.194 ± 0.033 (Figs 2, 3, and 4); and the probability of becoming blind in the study eye based on the World Health Organization VA criterion at 5 years was 0.046 ± 0.019.

For HFA 10-2 VF deterioration, univariate Cox proportional hazard model analysis suggested contribution of lower VA at baseline, higher mean IOP during follow-up, greater long-term IOP fluctuation, and lower diastolic BP ($P = 0.025$, $P = 0.036$, $P = 0.033$, and $P = 0.022$, respectively; Table S1, available at www.aaojournal.org). Multivariate Cox proportional hazard model analysis indicated that lower VA at baseline ($P = 0.012$ adjusted for the number of variables) significantly contributed to HFA 10-2 VF deterioration and higher MD value of HFA 24-2 at baseline ($P = 0.070$) and lower diastolic BP ($P = 0.066$) tended to be associated with HFA 10-2 VF deterioration (Table 2). For HFA 24-2 VF deterioration, univariate Cox analysis suggested contribution of higher MD value of HFA 24-2 at baseline, the same of HFA 10-2 at baseline, and use of systemic antihypertensive agents ($P < 0.001$, $P = 0.052$, and $P = 0.012$, respectively; Table S2, available at www.aaojournal.org), and multivariate Cox analysis showed significant contribution of higher MD value of HFA 24-2 at baseline ($P < 0.001$) and use of systemic antihypertensive agents ($P = 0.009$) to HFA 24-2 VF deterioration (Table 3). For VA deterioration, univariate Cox analysis suggested contribution of male gender, lower VA at baseline, greater long-term IOP fluctuation, a larger β-PPA area-to-disc area ratio, and use of systemic antihypertensive agents ($P = 0.046$, $P = 0.017$, $P = 0.053$, $P = 0.014$, and $P = 0.033$, respectively; Table S3, available at www.aaojournal.org), and multivariate Cox analysis showed significant contribution of lower VA at baseline ($P = 0.042$), a larger β-PPA area-to-disc area ratio ($P < 0.001$), and use of systemic antihypertensive agents ($P = 0.025$) to VA deterioration (Table 4). Further, we evaluated risk factors for NTG and non-NTG glaucoma eyes separately. In non-NTG glaucoma eyes, multivariate Cox proportional hazard model analysis indicated that older age ($P = 0.045$ adjusted for the number of variables) was associated significantly with HFA 10-2 VF deterioration, use of systemic antihypertensive agents was associated significantly with HFA 24-2 VF and VA deterioration ($P = 0.001$ and $P = 0.042$, respectively), and better MD of HFA 24-2 at baseline was associated significantly with HFA 24-2 VF deterioration ($P = 0.008$; Tables S4, S5, and S6, available at www.aaojournal.org). In NTG eyes, multivariate Cox proportional hazard model analysis indicated that lower VA at baseline was associated significantly with HFA 10-2 VF deterioration ($P = 0.010$) and that larger β-PPA area-to-disc area ratio was associated significantly with VA deterioration ($P = 0.009$; Tables S7, S8, and S9, available at www.aaojournal.org).

Discussion

The main goal of treatment of patients with advanced glaucoma is the maintenance of vision-related quality of life over the course of a lifetime. In glaucoma, the central VF generally is maintained until late in life,[28,29] and the VF within 5° of the center and the central VA are thought to be especially important for vision-related quality of life in patients with glaucoma.[21–23] In the present study, we focused on further deterioration of the central 10° VF and central VA in eyes with advanced glaucoma with a mean HFA 24-2 MD of approximately −25.9 dB and examined the associated factors. The patients in the study were all receiving outpatient IOP-lowering therapy by a glaucoma subspecialist, and all showed no apparent deterioration of HFA 24-2 results in at least the 2 years before enrollment and were not likely to need further aggressive therapy in the near future. In fact, the mean IOP during follow-up was 13.0 mmHg; over the course of 5 years, 26.9% of the eyes showed deterioration of VF within the central 10°, and 19.4% of the eyes showed VA deterioration attributable to glaucoma progression, which resulted in blindness in 4.6% of eyes.

The criteria for judging VF deterioration using HFA have been reported in the literature, but most are based on the

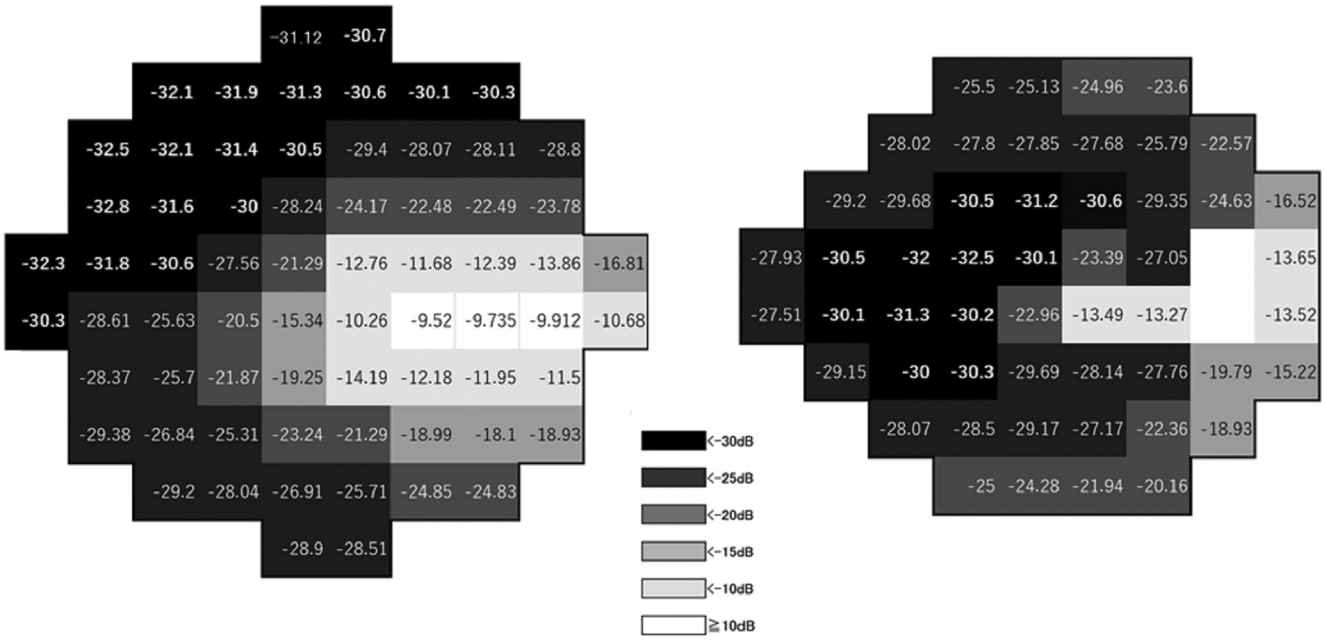

Figure 1. Mean total deviation values at each test location in the Humphrey Field Analyzer 10-2 and 24-2 test programs at baseline: (**A**) Humphrey Field Analyzer 10-2 visual field and (**B**) Humphrey Field Analyzer 24-2 visual field.

results of HFA 24-2 or 30-2 tests in eyes with mild or moderate glaucomatous damage[30–34]; however, in an eye with severely advanced damage, such as the eyes of the present participants, the accuracy of the evaluation of thresholds of test points with very low sensitivities is likely to be low.[35] The central 10° VF covered by HFA 10-2 is more related to vision-related quality of life,[21–23] and quite a few test points are relatively well spared in this subfield, even at the advancement of glaucomatous damage[28,29]; however, no criteria have been established for judging significant deterioration of the HFA 10-2 VF in eyes with advanced glaucoma. The specificity of the current criteria (the same 3 points with TD slope ≤ -1.0 dB/year at $P < 0.01$ at 3 consecutive HFA 10-2 tests) was assessed in the simulated nonprogressing HFA 10-2 VF series, whose mean MD was very similar to that of the participants of the current study, and the assessed specificity was 99.99%. An advantage exists in adopting *P* values of TD slopes as one of the criteria in VF series where many of the test points showed a large measurement variation. That is, the greater the variation of measured thresholds at each test point, the greater the *P* value for the calculated slopes or the less statistically significant the coefficient for time change. De Moraes et al[36] examined the criteria for deterioration of HFA 10-2 VF using pointwise linear regression based on the HFA 10-2 VF series with a mean MD of −12 dB. Although the criterion that was the same as the current criterion A was found to be the second best among those tested,[36] we did not test the criteria yielding the best performance in their analyses[36] because the assessed specificity of the current criteria was sufficiently high (99.99%) for the simulated stable HFA 10-2 VF series of eyes with advanced glaucoma. According to the current criteria, lower VA at baseline was a significant risk factor for further deterioration of HFA 10-2 VF in eyes with advanced glaucoma, and higher MD of HFA 24-2 and lower diastolic BP tended to be associated with further deterioration of VA. Because the identified risk factors depend on the criteria adopted, we also applied the most liberal criteria (criterion C with an assessed specificity of 85.1%) to the current HFA 10-2 results. These factors still tended to be associated with HFA 10-2 deterioration as

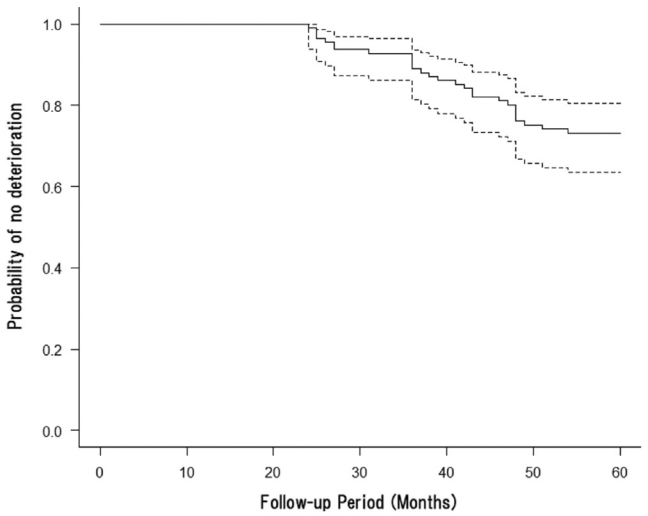

Figure 2. Kaplan–Meier analysis of deterioration in Humphrey Field Analyzer 10-2 test results. The dotted line indicates the 95% confidence interval of the cumulative rate of no deterioration.

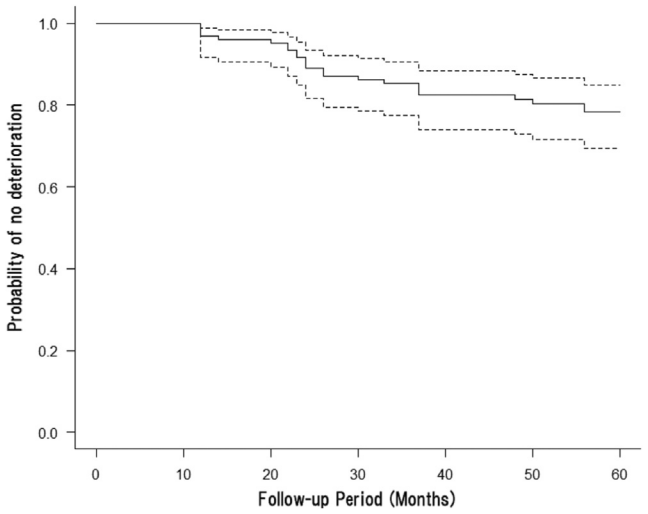

Figure 3. Kaplan–Meier analysis of deterioration in Humphrey Field Analyzer 24-2 test results. The dotted line indicates the 95% confidence interval of the cumulative rate of no deterioration.

determined with criterion C, confirming the validity of the results obtained using the criteria currently adopted.

A lower VA indicates that the most central VF already was severely damaged. The low VA in advanced glaucoma may be used as a simple indicator for further deterioration of the severely damaged central 10° VF in clinical practice. Regarding the HFA 24-2 MD value at baseline as a risk factor for further deterioration of the disease, previous studies yielded conflicting results.[11,13] As discussed above, a higher baseline HFA 24-2 MD simply may have made detection of further worsening of the HFA 24-2 VF possible. Such worsening may not be detectable in eyes with nearly extinguished HFA 24-2 VFs at baseline, resulting in poor sensitivity for detecting further change. The association between BP and progression of glaucoma has been reported by various studies.[37–41] In other tissues, diastolic BP is a major determinant of the hemodynamics, and excessive lowering of diastolic BP results in increased cardiovascular events and mortality.[42] Low diastolic BP, especially at night, has been reported as a significant risk for progression of NTG,[40,41] which is compatible with the current results showing that eyes with advanced glaucoma with a mean treated IOP of 13.0 mmHg tended to show HFA 10-2 VF deterioration if associated with lower diastolic BP.

In the eyes assessed in the present study, baseline HFA 24-2 MD averaged −26.0 dB, and 47% of the eyes showed a baseline HFA 24-2 AGIS score of 19 or 20, probably making it rather difficult to detect further HFA 24-2 VF deterioration. In fact, the probability of deterioration of HFA 24-2 VF at 5 years was much lower than that of HFA 10-2 VF in the same participant's eyes (27% vs. 17%). Despite these limitations, 2 factors, higher MD of HFA 24-2 VF and use of systemic antihypertensive agents, could be identified as significant risk factors for further HFA 24-2 VF deterioration. As discussed above, a higher baseline HFA 24-2 MD might have resulted in a better sensitivity of detecting change, especially in eyes with advanced glaucoma. The LoGTS identified the use of systemic antihypertensive agents as an independent risk factor for progression in patients with mild to moderate NTG,[39] and the current results suggest that this also was the case in the HFA 24-2 VF of eyes with advanced glaucoma, which will be discussed later in more detail. Although the mechanism by which systemic antihypertensive agents are involved in glaucoma progression is not clear, the use of systemic antihypertensive agents as a risk factor for HFA 24-2 VF deterioration is compatible with a tendency of association of lower diastolic BP with HFA 10-2 VF deterioration because the use of systemic antihypertensive agents should lower diastolic BP, and several investigations have reported compromised autoregulation of ocular blood flow in glaucomatous eyes.[43,44]

In the present study, the probability for further VA deterioration was 0.194 and for blindness was 0.046 at 5 years, respectively, which was not far from the results reported previously.[18–20,45,46] Previously reported risk factors for severe VA deterioration in treated patients with glaucoma included the extent of VF damage at diagnosis,[45,46] long-term IOP fluctuation,[46] low compliance,[45] and presence of exfoliation.[46] If we adopted the criteria of blindness of the previous studies (VA, ≤20/200),[45,46] the probability of blindness was 0.046 ± 0.018% at 5 years. The somewhat lower rate of blindness of a participant's eye currently found by including only eyes with very advanced glaucoma (4.6% vs. 7.1% or 8.0%) may be attributable to the shorter follow-up of the current study compared with that of previous studies (approximately 10 years).

In the current study, a larger β-PPA-to-disc area ratio, use of systemic antihypertensive agents, and lower baseline VA were identified as significant risk factors for further VA deterioration in eyes with advanced glaucoma. Lower baseline VA was indicative with the greater extent of damage at diagnosis.[45,46] The contribution of a larger β-PPA-to-disc area ratio and use of systemic

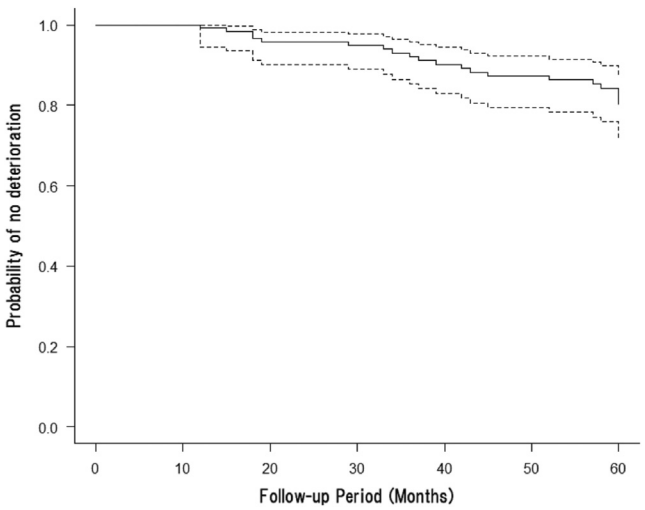

Figure 4. Kaplan–Meier analysis of visual acuity deterioration. The dotted line indicates the 95% confidence interval of the cumulative rate of no deterioration.

Table 2. Risk Factors for Further Deterioration of the Humphrey Field Analyzer 10-2 Test Results

Variables	Multivariate Risk Ratio	95% Confidence Interval	P Value*
SD of IOP during follow-up (per 1 mmHg higher)	2.18	1.18–4.03	0.103
HFA 24-2 MD (per 1.0 dB lower)	1.19	1.03–1.38	0.070
BCVA at baseline (per 0.1 logMAR lower)	1.73	1.21–2.46	0.012
Diastolic BP at baseline (per 1 mmHg higher)	0.95	0.90–0.99	0.066
Glaucoma type (normal-tension glaucoma)	2.57	1.12–5.89	0.138

BCVA = best-corrected visual acuity; BP = blood pressure; HFA = Humphrey Field Analyzer; IOP = intraocular pressure; logMAR = logarithm of the minimum angle resolution; MD = mean deviation; SD = standard deviation.
*Adjusted for the total number of variables included using Bonferroni's method.

antihypertensive agents, which were identified first as risk factors for VA deterioration in the eyes with advanced glaucoma in the current study, is interesting. Involvement of β-PPA in the development or progression of glaucoma, or both, has been well documented in the literature.[27,47–50] The use of systemic antihypertensive agents as a risk factor for further VA deterioration and lower diastolic BP as a factor that tends to be associated with for further HFA 10-2 deterioration in advanced glaucoma seem compatible with each other, indicating that compromised local circulation is an important prognostic factor of the central visual function of advanced glaucoma. As mentioned above, systemic antihypertensive agents have been reported to be a risk factor for the progression of NTG in LoGTS, but our study included many patients with glaucoma who did not demonstrate NTG. The current result of multivariate analysis including types of glaucoma as explanatory variables implied that the use of systemic antihypertensive agents was an independent risk factor regardless of the type of glaucoma. To confirm the effect of antihypertensive agents on glaucoma progression in eyes without NTG, we evaluated risk factors for analyses separately for eyes with NTG and for other eyes with glaucoma but not NTG using the COX proportional hazards model. In eyes with glaucoma but not NTG, antihypertensive agents were found to be a significant risk factor for HFA 24-2 deterioration and VA deterioration ($P = 0.001$ and $P = 0.042$, respectively; Supplemental Tables 4–9). It may be interesting to note that antihypertensive therapy was suggested as a significant prognostic factor for eyes with glaucoma but not NTG with advanced damage and controlled IOP, of which pathogenesis may be considered to be relatively more pressure dependent. Because of the small number of eyes with NTG, the study may have been insufficiently powered to detect an association in that group. Notably, a negative correlation between β-PPA size and IOP was found in healthy Japanese individuals, suggesting that β-PPA may be related to IOP-independent factors of glaucoma.[51]

Study Limitations

This study has some limitations. We studied risk factors for further deterioration of visual function of an eye with advanced glaucoma. Therefore, the identified risk factors were not necessarily those for deterioration of vision-related quality of life (VR-QOL) because VR-QOL generally was assessed based on integrated binocular vision. This study included eyes with advanced VF damage (mean HFA 24-2 MD, approximately −26 dB) and VA of 20/40 or worse to ensure fixation during VF tests, thereby ensuring the reliability of the test results. Thus, it should be noted that the current results would not be applicable to eyes with advanced glaucoma whose VA was impaired to worse than 20/40 because of glaucomatous damage. The treatment methods of the patients were left to the discretion of each facility, and no uniform treatment protocol was observed. Because all of the eyes involved in the study showed advanced glaucomatous damage, each glaucoma subspecialist in charge attempted to provide the maximum IOP reduction practically possible, but it is possible that differences in the treatment methods caused differences in the clinical course; however, no significant difference was found in the IOPs of enrolled eyes during the study period among the 7 facilities. Participants who underwent glaucoma surgeries during the study period were treated as censored cases in the present study. Because the eyes undergoing glaucoma surgery might have a higher probability of further deterioration of central visual function, the present results might have underestimated the risk for VF and VA impairment in patients with advanced glaucoma. Among 13 eyes that had undergone trabeculectomy alone, 2 showed

Table 3. Risk Factors for Further Deterioration of Humphrey Field Analyzer 24-2 Test Results

Variables	Multivariate Risk Ratio	95% Confidence Interval	P Value*
HFA 24-2 MD (per 1.0 dB higher)	1.43	1.22–1.68	<0.001
Use of systemic antihypertensive agents at baseline	3.18	1.38–7.38	0.009

HFA = Humphrey Field Analyzer; MD = mean deviation.
*Adjusted for the total number of variables included using Bonferroni's method.

Table 4. Risk Factors for Further Deterioration of Visual Acuity

Variables	Multivariate Risk Ratio	95% Confidence Interval	*P* Value*
Age at baseline (per 1 yr older)	1.05	1.00–1.11	0.143
BCVA at baseline (per 0.1 logMAR lower)	1.66	1.14–2.44	0.042
SD of IOP during follow-up (per 1 mmHg higher)	1.83	1.03–2.99	0.194
β-PPA-to-disc area ratio at baseline (0.1)	1.61	1.28–2.00	<0.001
Use of systemic antihypertensive agents at baseline	4.36	1.58–12.02	0.025

BCVA = best-corrected visual acuity; IOP = intraocular pressure; logMAR = logarithm of the minimum angle resolution; PPA = peripapillary atrophy area; SD = standard deviation.
Explanatory variables with a $P < 0.05$ are listed.
*Adjusted for the total number of variables included using Bonferroni's method.

further deterioration of BCVA after surgery, but the rate (2/13 [15%]) was not far from 19%, which was estimated as the probability of further VA deterioration of the current cohort at 5 years. Finally, the present study focused on the central visual functions in advanced glaucoma and did not evaluate the progression of the disease from a structural perspective. Spectral-domain OCT devices were not used widely when the current study started. OCT was not performed routinely in the patient group in the present study. Spectral-domain OCT measurements in the macular region recently were reported to be useful in assessing structural changes, even in eyes with advanced-stage glaucoma.[52,53] Analyzing the clinical courses of advanced glaucoma using spectral-domain OCT is the topic of our next study on advanced glaucoma.

In summary, we reported the results of a 5-year, prospective. longitudinal, observational study of eyes with advanced glaucoma (mean HFA 24-2 MD, approximately −26 dB). The probabilities of HFA 10-2 and 24-2 VF and BCVA deterioration were 0.269, 0.173, and 0.194 at 5 years, respectively, with a mean treated IOP of 13.0 mmHg. In the eyes of the participants in the current study, worse baseline VA and use of systemic antihypertensive agents were thought to be risk factors for further deterioration of both central VA and VF, and greater β-PPA area-to-disc ratio was an additional indicator for further VA deterioration. The current study suggests that greater β-PPA area-to-disc ratio and lower VA could be used as simple prognostic factors for the central VA of eyes with advanced glaucoma and that a medical history of hypertension should also be considered in the management of advanced glaucoma.

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Abbreviations and Acronyms:
AGIS = Advanced Glaucoma Intervention Study; **BCVA** = best-corrected visual acuity; **BP** = blood pressure; **HFA** = Humphrey Field Analyzer; **IOP** = intraocular pressure; **logMAR** = logarithm of the minimum angle of resolution; **LoGTS** = Low-Pressure Glaucoma Treatment Study; **MD** = mean deviation; **NTG** = normal-tension glaucoma; **PPA** = peripapillary atrophy; **TD** = total deviation value; **VA** = visual acuity; **VF** = visual field.

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