Glaucoma care optimised in an ageing population

Wesselink, Christiaan

CHAPTER 3

Risk Factors for Visual Field Progression in the Groningen Longitudinal Glaucoma Study: a Comparison of Different Statistical Approaches

Journal of Glaucoma 2012;21:579-585

Christiaan Wesselink[1]
Michael W. Marcus[1]
Nomdo M. Jansonius[1,2]

1. Department of Ophthalmology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
2. Department of Epidemiology and Biostatistics, Erasmus Medical Center, Rotterdam, the Netherlands

Abstract

Purpose To identify risk factors for visual field progression in glaucoma and to compare different statistical approaches with this risk factor analysis.

Patients and Methods We included 221 eyes of 221 patients. Progression was analyzed using Nonparametric Progression Analysis applied to Humphrey Field Analyzer data. Risk factors were analyzed using the statistical approaches from the Advanced Glaucoma Intervention Study, the Early Manifest Glaucoma Trial, and the Canadian Glaucoma Study. Four intraocular pressure (IOP) variables (baseline IOP, mean IOP during follow-up, IOP fluctuation, and pretreatment IOP) and 8 other risk factors were investigated.

Results On average, 7.1 reliable fields were available after a mean follow-up of 5.3 years; 89 eyes progressed. With the Advanced Glaucoma Intervention Study approach, age [odds ratio (OR) 1.03/y; 95% confidence interval (CI), 1.00-1.06; P=0.044] predicted progression. With an additional stepwise selection procedure, mean IOP during follow-up (OR=1.16 per mmHg; 95% CI, 1.05-1.29; P=0.003), baseline Humphrey Field Analyzer mean deviation (MD; 2.72 for worse versus better than -6 dB; 95% CI, 1.50-4.95; P=0.001), and age (OR=1.03; 95% CI, 1.01-1.06; P=0.010) predicted progression. With the Early Manifest Glaucoma Trial approach, baseline IOP [hazard ratio (HR) 1.07; 95% CI, 1.02-1.11; P=0.010], baseline Frequency Doubling Perimeter MD (HR=1.75; 95% CI, 1.14-2.70; P=0.013), and age (HR=1.03; 95% CI, 1.01-1.05; P=0.006) predicted progression. Finally, with the Canadian Glaucoma Study approach, baseline IOP (HR=1.07; 95% CI, 1.02-1.11; P=0.010), baseline Frequency Doubling Perimeter MD (HR=1.75; 95% CI, 1.14-2.70; P=0.013), and age (HR=1.03; 95% CI, 1.01-1.05; P=0.006) predicted progression.

Conclusions IOP, disease stage, and age seemed to be robust independent risk factors for visual field progression in glaucoma. The IOP variable that was significant depended on the statistical approach applied.

Introduction

Over the past few decades, a number of studies have contributed to elucidating the risk factors associated with or predictive for glaucoma progression.[1-14] A good understanding of these risk factors is a prerequisite for estimating the risk of progression in individual patients. Knowledge of individual progression risks enables custom-made glaucoma care.

Elevated intraocular pressure (IOP) is an established risk factor for glaucoma progression. Several other risk factors for progression have been identified with conflicting results.[1-14] These conflicting results might be attributed to variability in (1) the study design, (2) the study population, (3) the statistical approach applied, and (4) the outcome measure (progression definition) used.

The aim of this study was to identify risk factors associated with visual field progression in glaucoma and to determine the influence of the statistical approach applied. For this purpose, we compared different statistical approaches in a single dataset, using a single outcome measure. The statistical approaches were adopted from the Advanced Glaucoma Intervention Study (AGIS),[10] the Early Manifest Glaucoma Trial (EMGT),[6] and the Canadian Glaucoma Study (CGS).[1] The selected progression definition (outcome measure) was the Nonparametric Progression Analysis (NPA).[15] The dataset was the cohort of the Groningen Longitudinal Glaucoma Study (GLGS).[15,16]

Methods

Study Population

This study was performed within the GLGS, a prospective cohort study performed in a clinical setting. The objectives, methods, rationale, and study design have been described earlier.[15,16] In short, all 875 patients with glaucoma and glaucoma suspects who visited our glaucoma outpatient service between July 1, 2000 and June 30, 2001 and who provided informed consent were included in an institutional review board-approved observational prospective follow-up using conventional perimetry, frequency doubling technique perimetry (FDT; Carl Zeiss Meditec AG,

Jena, Germany), and laser polarimetry (GDx; Laser Diagnostic Technologies, San Diego, CA).

Out of the original 875 patients with glaucoma and glaucoma suspects, 452 were classified as having glaucoma. Of the 452 patients with glaucoma, the disease in 372 of them was classified using standard automated perimetry [Humphrey Field Analyzer (HFA); Carl Zeiss Meditec Inc., Dublin, CA]. The Goldmann perimeter (Haag Streit AG, Bern, Switzerland) was used in 80 patients, who were excluded from this analysis. Of the 372 patients classified using the HFA (for criteria see below), 221 patients who had undergone a follow-up period as measured from the last baseline test of at least 3 years and who had at least 4 reliable visual fields were included in this study.

Perimetry

Perimetry was performed using the HFA 30-2 Swedish interactive threshold algorithm fast strategy. An abnormal test result was defined as any one of the following: (1) a glaucoma hemifield test result outside normal limits; (2) a pattern standard deviation with $P<0.05$; or (3) 3 adjacent nonedge points with $P<0.05$ in the pattern deviation probability plot, with at least 1 point reaching $P<0.01$ and with all points being on the same side of the horizontal meridian (low tension glaucoma study criterion using pattern deviation probabilities).[17] A test result was considered unreliable if false-positive classifications exceeded 10% or if both false-negative classifications and fixation losses exceeded 10% and 20%, respectively. For glaucoma at baseline, 2 consecutive reliable test results had to be abnormal in at least 1 eye. Defects had to be in the same hemifield, and at least 1 depressed test point of these defects had to have exactly the same location on both fields. Moreover, the defects had to be compatible with glaucoma and without any other explanation. The first test result was discarded because of a learning effect. Therefore, at least 3 tests had to be performed at baseline before glaucoma could be diagnosed. During the follow-up period, perimetry was performed at a frequency of 1 test per year. In case of suspected progression or unreliable test results, clinicians were allowed to increase the frequency of testing. This was a subjective decision; no formal tools or rules were used.

Progression Detection

The method used to identify progression was the NPA.[15] In this method, reliable follow-up test results are compared with 2 reliable baseline test results. NPA is based on a nonparametric ranking[18] of mean deviation (MD) values. The MD values of the follow-up fields are compared with the worse MD value of the 2 baseline fields. If the MD of a follow-up field is better than or equal to the MD of the worse baseline field, the field is considered stable. If the MD of a follow-up field is worse than the MD of the worse baseline field, the change is considered outside the normal variation (that is, suspected progression). Possible progression is diagnosed if this change is confirmed once (deterioration in 2 consecutive fields) and likely progression if confirmed more than once (deterioration in 3 or more consecutive fields). After a reading of suspected, possible, or likely progression, MD readings better than the worse baseline MD are disallowed; in this case, the patient's condition is considered stable.[15] In this way, we circumvented the fact that normally the specificity of event-based progression detection algorithms decreases with increasing numbers of follow-up fields. In NPA, the 2 baseline fields divide the MD probability space of a patient into 3 equal parts. Hence, if the eye is truly stable with no change in MD over time, the probability that the final field has an MD lower than that of both baseline fields is one third. Therefore, the specificity of suspected progression in NPA is 0.67. Similarly, the specificities of possible progression (MD of the last 2 fields lower than that of both baseline fields) and likely progression (MD of the last 3 fields lower than that of both baseline fields) are 0.83 and 0.90, respectively.[18]

Risk Factors for Progression

The possible risk factors for progression as documented in the GLGS from the very beginning were age, sex, myopia, cardiovascular disease, family history of glaucoma, pretreatment IOP, IOP at baseline, mean IOP during follow-up, IOP fluctuation (standard deviation during follow-up), and HFA, FDT, and GDx test results. All risk factors were recorded at baseline, except for the mean IOP and IOP fluctuation during follow-up. The pretreatment IOP was defined as the highest IOP ever measured before the study, before any treatment was started. Myopia was defined as a spherical equivalent of –4 D or more of myopia in at least 1 eye. Cardiovascular disease was defined in terms of whether cardiovascular medication was used or not. Family history of glaucoma was considered to be positive if the participants reported a history of glaucoma in their parents, siblings, or offspring. All

IOP measurements were performed with Goldmann applanation tonometry (Haag Streit AG, Bern, Switzerland). FDT at baseline was performed using the C-20 full-threshold mode. The HFA and FDT variable used was the MD, dichotomized as better or worse than the median value in the study population, being −6 dB for both devices. The GDx variable used was "The Number."[16] New patients were scored as "untreated on inclusion" if treatment started after inclusion. This variable corrects for a possible bias resulting from the fact that some patients had not yet been treated at the time of inclusion.

Statistical Analysis

Only 1 eye per patient was included. If a patient met the criteria with both eyes, a randomly chosen eye was included. Visual field progression was defined as having at least a possible progression at the end of the follow-up. Three different statistical approaches for risk factor analysis were applied, taken from 3 different glaucoma studies: AGIS,[10] EMGT,[6] and CGS.[1]

In the AGIS,[10] associations between progression and various potential risk factors were assessed using multivariate logistic regression. Those factors that were associated with progression in univariate analyses ($\chi 2$ test, unpaired t test, or Wilcoxon rank sum test, depending on the type of data) at a P value of 0.20 or less were included in the final model. Furthermore, those clinically relevant variables such as age and sex that might potentially predict or confound the detection of progression were included. No selection other than univariate preselection was applied in the AGIS. In addition to this approach, we also added interaction terms and applied a stepwise variable selection.

In the statistical approach of the EMGT,[6] Cox proportional hazard models with Breslow adjustment for ties in time to progression were used to evaluate the constancy of the hazard ratio (HR) throughout the follow-up time period. Univariate analyses of the risk factors for progression were explored using $\chi 2$ tests for categorical variables and t tests for continuous variables. Variable selection was carried out in 2 steps. First, all variables significant in the univariate analyses at a P value of 0.20 or less were included in the model. Second, a stepwise variable selection algorithm was used to assess the best statistical fit. Furthermore, separate models were used to explore and to identify those baseline and follow-up factors significantly associated with glaucoma progression.

In the statistical approach derived from the CGS,[1] risk factors for progression were first explored using Kaplan-Meier survival analyses with the log-rank test for the univariate analyses. As selection of variables in the final model was based solely on a stepwise procedure and not on the results of univariate analyses, we did not report the results of these univariate analyses. As in the CGS, IOP was the only time-dependent variable in our study and therefore was analyzed as a covariate in the multivariate analysis. Variables were entered into a Cox Proportional hazards model in a forward stepwise analysis if their P value was 0.10 or less and if the hazards were judged to be proportional when examining the negative log plots of the survivor functions. Interaction terms were explored and included in the model if the partial likelihood ratio test indicated a better model fit.

To assess the effect that the possible risk factors for glaucoma progression may have on the rate of progression (the MD slope, ie, the time derivative of MD), we performed a multiple linear regression analysis with rate of progression as the dependent variable and with the factors that were found to be significantly associated with progression in the analyses described above as independent variables.

All statistical analyses were performed using SAS 9.1.3 (SAS Institute Inc., Cary, NC), except for the statistical approach used from the AGIS where PASW Statistics 17.0.2 (SPSS, Inc., Chicago, IL) was used. Variables with a P value of 0.05 or less were considered statistically significant, unless otherwise stated.

Results

Table 3.1 shows the study population characteristics at baseline and during follow-up. The average follow-up duration (as measured from the last baseline field) was 5.3 years; on average 5.1 reliable follow-up fields were available (7.1 fields including baseline). The average MD at baseline was −9.4 dB; the average MD slope was −0.25 dB/y. According to the NPA algorithm, 89 of the 221 patients showed at least possible progression.

Table 3.1. Patient characteristics (mean with standard deviation between brackets unless stated otherwise).

	All patients	NPA progression	
		Yes	No
Number of patients	221 (100%)	89 (40%)	132 (60%)
Baseline			
Age (yr)	66.4 (12.3)	68.8 (11.5)	64.8 (12.6)
Gender (% male)	55.2	48.3	59.8
Family history (%)	16.9	20.7	14.4
Myopia (%)	18.1	16.9	18.9
Cardiovascular disease (%)	36.7	43.8	31.8
HFA MD (dB)	−9.4 (7.6)	−10.0 (6.8)	−8.9 (8.0)
FDT MD (dB)	−6.9 (5.5)	−7.8 (5.3)	−6.3 (5.7)
GDx (The Number)	52.0 (24.1)	55.9 (23.4)	49.4 (24.3)
IOP at baseline (mmHg)	16.1 (4.7)	17.0 (5.5)	15.5 (4.1)
Untreated on inclusion (%)	10.9	13.5	9.1
Pre-treatment IOP (mmHg)	30.3 (9.5)	30.2 (10.0)	30.4 (9.2)
Follow-up			
Follow-up duration (years)	5.3 (1.1)	5.3 (1.0)	5.3 (1.2)
Number of visual fields	7.1 (1.9)	7.5 (1.7)	6.9 (2.0)
HFA MD slope (dB/years)	−0.25 (0.56)	−0.69 (0.55)	0.04 (0.33)
Mean IOP (mmHg)	14.9 (2.9)	15.5 (3.0)	14.5 (2.9)
IOP fluctuation (mmHg)	2.8 (1.8)	3.2 (2.2)	2.5 (1.5)

HFA = Humphrey Field Analyzer; MD = mean deviation; FDT = Frequency Doubling Technique perimeter; GDx = nerve fiber analyzer; IOP = intraocular pressure; NPA = Nonparametric Progression Analysis.

Table 3.2 depicts the results of univariate risk factor analyses of all variables explored in the GLGS according to AGIS and EMGT statistical approach. As variable selection in the CGS was solely based on a stepwise procedure, we did not present results for univariate analyses for the CGS statistical approach. Nine variables (age, sex, history of cardiovascular disease, HFA MD, FDT MD, GDx test result, baseline IOP, mean IOP during follow-up, and IOP fluctuation) satisfied the criteria of the AGIS and EMGT statistical approaches. These variables were included in the logistic regression model and in the Cox proportional hazard model for the AGIS and EMGT approaches, respectively.

Table 3.2. Univariate risk factor analyses for NPA progression according to the AGIS and EMGT statistical approaches.

Variables	AGIS approach p-value	EMGT approach p-value
Baseline		
Age (yr)	0.008†	0.017^
Gender (% male)	0.091‡	0.091‡
Family history (%)	0.224‡	0.224‡
Myopia (%)	0.693‡	0.693‡
Cardiovascular disease (%)	0.069‡	0.069‡
HFA MD (% < −6 dB)	0.013‡	0.013‡
FDT MD (% < −6 dB)	0.017‡	0.017‡
GDx (The Number)	0.052†	0.048^
IOP (mmHg)	0.148†	0.021^
Untreated on inclusion (%)	0.303‡	0.303‡
Pre-treatment IOP (mmHg)	0.762†	0.906^
Follow-up		
Follow-up Duration (yr)	0.960†	NA
Mean IOP (mmHg)	0.017^	0.017^
IOP fluctuation (mmHg)	0.045†	0.005^

† Wilcoxon rank sum test; ‡ Chi-square test.; ^ Unpaired t test.

HFA = Humphrey Field Analyzer; MD = mean deviation; FDT = Frequency Doubling Technique perimeter; GDx = nerve fiber analyzer; IOP = intraocular pressure; NPA = Nonparametric Progression Analysis.

Table 3.3 presents the results of the multivariate analyses with dependent variable NPA progression, using the AGIS, EMGT, and CGS statistical approaches. With the AGIS approach, age was the only independent predictor of NPA progression with an odds ratio (OR) of 1.03 per year of increase in age. An interaction term between mean IOP and IOP fluctuation added to the model was not significant. Applying a stepwise variable selection resulted in a model that had the HFA MD (OR 2.72 for worse versus better than -6 dB), mean IOP during follow-up (OR 1.16 per mmHg increase), and age (OR 1.03) as independent risk factors for progression. With the EMGT and CGS approaches, 3 variables were found to be independent predictors of NPA progression. The FDT MD, baseline IOP, and age increased the risk of NPA progression by 75% for worse versus better than −6 dB, 7% per mmHg increase in baseline IOP, and 3% per year of increase in age, respectively in both approaches. None of the interaction terms used in the CGS approach were significant.

Table 3.3. *Odds ratios and hazard ratios for the logistic regression model (AGIS) and Cox proportional hazards models (EMGT, CGS), for dependent variable progression according to the NPA.*

	Odds ratio	95% confidence interval	*P* value
AGIS approach			
Age (years)	1.03	1.00 - 1.06	0.044
Gender (male)	0.63	0.35 - 1.14	0.127
Cardiovascular disease	1.47	0.80 - 2.71	0.220
HFA MD (< −6 dB)	1.77	0.81 - 3.86	0.154
FDT MD (< −6 dB)	1.54	0.73 - 3.27	0.261
GDx (The Number)	1.01	0.99 - 1.02	0.483
Baseline IOP (mmHg)	1.03	0.94 - 1.12	0.569
Follow-up duration (years)	1.01	0.78 - 1.32	0.918
Mean IOP during follow-up (mmHg)	1.09	0.95 - 1.26	0.220
IOP fluctuation (mmHg)	1.17	0.98 - 1.39	0.091
AGIS approach with interaction term			
Age (years)	1.03	1.00 - 1.06	0.038
Gender (male)	0.63	0.34 - 1.14	0.123
Cardiovascular disease	1.50	0.81 - 2.78	0.197
HFA MD (< −6 dB)	1.78	0.81 - 3.88	0.149
FDT MD (< −6 dB)	1.53	0.72 - 3.24	0.269
GDx (The Number)	1.01	0.99 - 1.02	0.509
Baseline IOP (mmHg)	1.02	0.94 - 1.12	0.603
Follow-up duration (years)	1.02	0.79 - 1.32	0.878
Mean IOP during follow-up (mmHg)	1.04	0.85 - 1.27	0.696
IOP fluctuation (mmHg)	0.85	0.34 - 2.07	0.712
Mean IOP * IOP fluctuation	1.02	0.97 - 1.07	0.476
AGIS approach with stepwise selection			
Age (years)	1.03	1.01 - 1.06	0.010
HFA MD (< −6 dB)	2.72	1.50 - 4.95	0.001
Mean IOP during follow-up (mmHg)	1.16	1.05 - 1.29	0.003
	Hazard ratio	**95% confidence interval**	***P* value**
EMGT approach			
Age (years)	1.03	1.01 - 1.05	0.006
FDT MD (< −6 dB)	1.75	1.14 - 2.70	0.013
Baseline IOP (mmHg)	1.07	1.02 - 1.11	0.010
CGS approach			
Age (years)	1.03	1.01 - 1.05	0.006
FDT MD (< −6 dB)	1.75	1.14 - 2.70	0.013
Baseline IOP (mmHg)	1.07	1.02 - 1.11	0.010

HFA = Humphrey Field Analyzer; MD = mean deviation; FDT = Frequency Doubling Technique perimeter; GDx = nerve fiber analyzer; IOP = intraocular pressure; NPA = Nonparametric Progression Analysis.

Table 3.4 shows the results of a multiple linear regression analysis with the rate of progression as the dependent variable, and with mean IOP during follow-up, HFA MD, and age as independent variables. The rate of progression worsened (that is, became more negative) by 0.04 dB/y per mmHg of increase in mean IOP during follow-up and was 0.18 dB/y more negative in patients with a baseline HFA MD of -6 dB or worse compared with those with a better baseline MD. With baseline IOP in the model instead of mean IOP during follow-up, the rate of progression worsened by 0.02 dB/y per mmHg of increase in baseline IOP (95% confidence interval, −0.03 to −0.01 dB/y per mmHg; P=0.030).

Table 3.4. *Results of multiple linear regression analyses with rate of progression (mean deviation slope) as dependent variable.*

	Regression coefficient	95% confidence interval	*P* value
(Intercept)	0.771	0.226 to 1.315	0.006
HFA MD (% < −6 dB)	−0.179	−0.324 to −0.034	0.016
Mean IOP follow-up (mmHg)	−0.043	−0.067 to −0.019	<0.001
Age (years)	−0.004	−0.010 to 0.001	0.136

HFA = Humphrey Field Analyzer; MD = mean deviation; IOP = intraocular pressure.

Discussion

IOP, baseline damage (as assessed with HFA or FDT), and age were found to be robust independent risk factors for glaucoma progression. The IOP variable that was significant depended on the statistical approach applied.

IOP

Four IOP variables were included in our analyses. In all the analyses (except for the AGIS approach without stepwise selection), at least one of these variables was found to be a risk factor for glaucoma. This is not an unexpected finding, as IOP is a well-known risk factor for progression,[1,5,6,9,12,13] although there are reports that have failed to show such a relationship in normal tension glaucoma.[2,3] In our population, every mmHg increase in baseline or mean IOP increased the progression risk by 7% or 16%, respectively. This finding corroborates the increase of 12% per mmHg increase in average IOP during follow-up as reported in the EMGT[6] and the larger increase of 19% per mmHg increase in mean follow-up IOP

as reported in the CGS.[1] Our findings further buttress the importance of controlling the IOP of patients with glaucoma.

Using the AGIS statistical approach, none of the IOP variables were significant risk factors for progression, with IOP fluctuation closest to significance (P=0.091). After the additional stepwise variable selection, however, mean IOP during follow-up was a highly significant predictor of progression (P=0.003). If the analyses were repeated after excluding mean IOP during follow-up and after including either baseline IOP or IOP fluctuation, the included IOP variable reached significance. It is interesting to note that, the same phenomenon appeared both in the original AGIS analyses[10] and in a recent study in which IOP fluctuation was defined by the IOP range during follow-up.[8] These results would suggest that IOP fluctuation and either baseline IOP or average IOP during follow-up are not unrelated. In our study, IOP fluctuation was positively correlated with both the baseline IOP (r=0.40; P<0.001) and the mean IOP during follow-up (r=0.37; P<0.001). On account of the linear dependency among these variables, simultaneous inclusion in a model may lead to unstable coefficients of effect estimates. To rule out the possibility of collinearity, we carried out multicollinearity diagnostic statistics produced by linear regression analysis using Procedure Regression (PROC REG) with options variance inflation factor and tolerance in SAS.[19] None of the variance inflation factors was larger than 2.5 suggesting that there was no formal need to drop any IOP variable from the AGIS multivariate model as shown in Table 3.3. In addition, interaction terms were explored, but were found to be insignificant.

Baseline Disease Stage

Three methods of testing baseline disease stage were analyzed for their ability to predict glaucoma progression (HFA, FDT, and GDx test results). We found HFA or FDT test results to be a significant risk factor for progression, but none of the final models showed FDT and HFA test results as both being significant risk factors in the same model. This is a plausible finding as FDT and HFA both measure functional visual field loss and, as to be expected, their scores were highly correlated (r=0.60; P<0.001). As multicollinearity diagnostic statistics learned that none of the variance inflation factors was larger than 2.5 (see above), both variables could be analyzed in the same model.

An increased risk along with an increasing glaucoma stage was also reported in other studies.[5,7-9] The EMGT reported an HR of 1.55,[5] although in a later report the increase was not significant (HR 1.38, P=0.051).[6] In the CGS, using univariate analysis it seemed that a better baseline visual field was related to progression, but, in a multivariate regression analysis, this factor did not show significance.[1] The AGIS visual field score in the AGIS analyses showed no relationship with glaucoma progression.[10] It should be noted that the exclusion criteria in the AGIS, EMGT, and CGS were based, among other things, on visual field score, resulting in a narrowing of the baseline disease-stage range. In our study, with a mean (SD; 95% central range) baseline MD of −9.4 dB (7.6 dB; 95% confidence interval, −0.3 to −28.2 dB), such an exclusion criterion was not applied.

Variable "The Number" from the baseline GDx was not found to be a significant risk factor for progression. This variable remained insignificant, even if HFA and FDT were excluded from the analyses. Some previous studies have shown that a smaller neuroretinal rim or an enlarged cup-to-disk ratio predicts progression,[4,7,12,14,20] although not all studies have reported this association.[11]

Finally, the assessment of disease stage as a risk factor requires a careful consideration of the sensitivity and specificity of the outcome measure as a function of disease stage, especially because the MD variability increases with disease stage. The specificity of the outcome measure used in this study, NPA, is independent of the variability, whereas the sensitivity decreases with variability.[18] Despite this decreasing sensitivity with increasing variability (ie, with disease stage), we found disease stage to be an independent risk factor, suggesting that it is a robust finding. Hence, (perimetric) disease stage should be seen as a factor that requires careful consideration when making therapeutic decisions.

Other Factors

Although many variables such as age, sex, myopia, family history of glaucoma, and the history of cardiovascular disease were explored, age was, in addition to IOP and disease stage, the only factor in our population that predicted progression in more than 1 analysis. For every yearly increment in age, the risk of progression increased by 3%. Several other investigators have reported a similar relationship between age and the progression of glaucoma,[1,5-8,10-12] whereas other studies were unable to confirm this association.[2,3,9,13,14] Family history and myopia seem to be

associated with glaucoma[21-25] but not with its progression.[1,3,5,11] Sex was a significant factor for progression in a minority of studies and this varied in terms of whether men[11] or women[1,3] had a greater risk. A history of cardiovascular disease[1,5,10] would not seem to be an independent predictor of glaucoma progression.

Statistical Methodology

The various statistical approaches used constitute a major setback when comparing different risk factor analysis studies. To explore the influence of the statistical technique used on the results of risk factor analysis, we compared the statistical approaches used by the AGIS, the EMGT, and the CGS in a single dataset and with a single outcome measure. In the CGS, a preselection was not performed and the CGS approach was more conservative in its use of a P value of 0.10 as the selection criterion for the stepwise selection procedure, whereas EMGT and AGIS used a P value of 0.20 in the univariate preselection. The CGS and EMGT used Cox regression in contrast to the logistic regression used by AGIS. The mathematical algorithms used by these 2 models also differ. It is interesting to note that, the answer to the ongoing discussion[26] of whether it is IOP fluctuation or another IOP variable that is the primary harmful factor in glaucoma progression depends, at least in our dataset, solely on the statistical approach used and on which IOP variables were also analyzed in the same model. This underlines the importance of (1) a sound statistical design before the onset of the analyses to prevent "searching" for significance, (2) reticence in generalizing risk factors found, and (3) caution in the implementation of risk factors found in other reports. The significance of risk factors should always be seen in the light of previous (and later) reports. The risk factors found in our study are in agreement with the results of many other studies and this would tend to support the idea that they are indeed significant risk factors for glaucoma progression.

We compared the statistical approaches of AGIS, EMGT, and CGS, but not their outcome measures. The outcome measures used in these 3 studies were the AGIS scoring system in AGIS,[27] the Glaucoma Progression Analysis (GPA) in the EMGT,[28] and the Glaucoma Chance Probability in the CGS.[29] The use of a single outcome measure enabled a more direct comparison of the statistical approaches. Moreover, the AGIS scoring system is not readily available and the Glaucoma Chance Probability cannot be run on Swedish interactive threshold algorithm test

results. We compared NPA and GPA in an earlier study.[15] NPA had a fairly good agreement with GPA in early glaucoma, whereas NPA was more sensitive than GPA in patients with advanced glaucoma. The latter finding can be explained by the fact that GPA uses pattern deviation analysis. This makes the use of NPA more appropriate in our dataset with many patients with advanced disease. We repeated the risk factor analyses with outcome measure GPA. Similar associations were found but, as to be expected, the associations were less profound and did not reach significance in some analyses.

Because of the finite number of visual field tests in our observational study, some cases with progression may have been misclassified as stable because confirmation was not yet performed at the end of the study. Similarly, some stable cases may have been erroneously classified as cases with progression because falsification after possible or likely progression was not yet performed. The misclassified cases could have resulted in conservative risk estimates. An inherent property of all event-based progression detection algorithms is that the specificity decreases with an increasing number of tests. We circumvented this limitation by disallowing MD readings better than the worse baseline MD after a reading of suspected, possible, or likely progression (see Methods section, progression detection subsection). The number of visual fields differed slightly between cases and controls (Table 3.1) and this might have influenced our results. We explored this issue by repeating all analyses with the number of visual fields added as a covariate. No significant changes were found. As mentioned in the Methods section, the GLGS is an observational study. Hence, as in all observational studies, some confounding by indication cannot be excluded.

In conclusion, IOP, disease stage, and age seem to be significant independent risk factors for visual field progression in glaucoma. The results from risk-factor analyses may depend on the statistical approach applied.

References

1. Chauhan BC, Mikelberg FS, Balaszi AG, et al. Canadian Glaucoma Study: 2. risk factors for the progression of open-angle glaucoma. Arch Ophthalmol 2008;126:1030-1036.

2. Daugeliene L, Yamamoto T, Kitazawa Y. Risk factors for visual field damage progression in normal-tension glaucoma eyes. Graefes Arch Clin Exp Ophthalmol 1999;237:105-108.

3. Drance S, Anderson DR, Schulzer M. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. Am J Ophthalmol 2001;131:699-708.

4. Jonas JB, Martus P, Horn FK, Jünemann A, Korth M, Budde WM. Predictive factors of the optic nerve head for development or progression of glaucomatous visual field loss. Invest Ophthalmol Vis Sci 2004;45:2613-2618.

5. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol 2003;121:48-56.

6. Leske MC, Heijl A, Hyman L, et al. Predictors of long-term progression in the early manifest glaucoma trial. Ophthalmology 2007;114:1965-1972.

7. Martus P, Stroux A, Budde WM, Mardin CY, Korth M, Jonas JB. Predictive factors for progressive optic nerve damage in various types of chronic open-angle glaucoma. Am J Ophthalmol 2005;139:999-1009.

8. Musch DC, Gillespie BW, Lichter PR, Niziol LM, Janz NK; CIGTS Study Investigators. Visual field progression in the Collaborative Initial Glaucoma Treatment Study the impact of treatment and other baseline factors. Ophthalmology 2009;116:200-207.

9. Nakagami T, Yamazaki Y, Hayamizu F. Prognostic factors for progression of visual field damage in patients with normal-tension glaucoma. Jpn J Ophthalmol 2006;50:38-43.

10. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. Ophthalmology 2004;111:1627-1635.

11. Spry PG, Sparrow JM, Diamond JP, Harris HS. Risk factors for progressive visual field loss in primary open angle glaucoma. Eye 2005;19:643-651.

12. Stewart WC, Kolker AE, Sharpe ED, et al. Factors associated with long-term progression or stability in primary open-angle glaucoma. Am J Ophthalmol 2000;130:274-279.

13. Suzuki Y, Shirato S, Adachi M, Hamada C. Risk factors for the progression of treated primary open-angle glaucoma: a multivariate life-table analysis. Graefes Arch Clin Exp Ophthalmol 1999;237:463-467.

14. Tezel G, Siegmund KD, Trinkaus K, Wax MB, Kass MA, Kolker AE. Clinical factors associated with progression of glaucomatous optic disc damage in treated patients. Arch Ophthalmol 2001;119:813-818.

15. Wesselink C, Heeg GP, Jansonius NM. Glaucoma monitoring in a clinical setting: glaucoma progression analysis vs nonparametric progression analysis in the Groningen Longitudinal Glaucoma Study. Arch Ophthalmol 2009;127:270-274.

16. Heeg GP, Blanksma LJ, Hardus PL, Jansonius NM. The Groningen Longitudinal Glaucoma Study. I. Baseline sensitivity and specificity of the frequency doubling perimeter and the GDx nerve fibre analyser. Acta Ophthalmol Scand 2005;83:46-52.

17. Katz J, Sommer A, Gaasterland DE, Anderson DR. Comparison of analytic algorithms for detecting glaucomatous visual field loss. Arch Ophthalmol 1991;109:1684-1689.

18. Jansonius NM. Bayes' theorem applied to perimetric progression detection in glaucoma: from specificity to positive predictive value. Graefes Arch Clin Exp Ophthalmol 2005;243:433-437.

19. Allison PD. Binary Logistic Analysis: Details and Options. In: Logistic regression using SAS: Theory and application. Cary, NC: SAS Institute Inc.; 2005:31-80.

20. Medeiros FA, Alencar LM, Zangwill LM, Bowd C, Sample PA, Weinreb RN. Prediction of functional loss in glaucoma from progressive optic disc damage. Arch Ophthalmol 2009;127:1250-1256.

21. Mitchell P, Hourihan F, Sandbach J, Wang JJ. The relationship between glaucoma and myopia: the Blue Mountains Eye Study. Ophthalmology 1999;106:2010-2015.

22. Wu SY, Nemesure B, Leske MC. Refractive errors in a black adult population: the Barbados Eye Study. Invest Ophthalmol Vis Sci 1999;40:2179-2184.

23. Grodum K, Heijl A, Bengtsson B. Refractive error and glaucoma. Acta Ophthalmol Scand 2001;79:560-566.

24. Wong TY, Klein BE, Klein R, Knudtson M, Lee KE. Refractive errors, intraocular pressure, and glaucoma in a white population. Ophthalmology 2003;110:211-217.

25. Czudowska, MA, Ramdas WD, Wolfs RCW, et al. Incidence of glaucomatous visual field loss: a ten-year follow-up from the Rotterdam Study. Ophthalmology 2010;117:1705-1712.

26. Sultan MB, Mansberger SL, Lee PP. Understanding the importance of IOP variables in glaucoma: a systematic review. Surv Ophthalmol 2009;54:643-662.

27. AGIS investigators. Advanced Glaucoma Intervention Study. 2. Visual field test scoring and reliability. Ophthalmology 1994;101:1445-1455.

28. Heijl A, Leske MC, Bengtsson B, Bengtsson B, Hussein M; Early Manifest Glaucoma Trial Group. Measuring visual field progression in the Early Manifest Glaucoma Trial. Acta Ophthalmol Scand 2003;81:286-293.

29. Heijl A, Lindgren G, Lindgren A, et al. Extended emperical statistical package for evaluation of single and multiple fields in glaucoma: Statpac 2. In: Mills RP, Heijl A, eds. Perimetry update 1990/1. New York (NY): Kugler; 1990:305-315.