Methodologic Quality of Studies on Prognostic Factors for Primary Open-angle Glaucoma Progression Measured by Visual Field Deterioration

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Abstract: Glaucoma is a chronic, slowly progressing, and asymptomatic optic neuropathic disorder with a great variety of causes that involve gradual retinal ganglion cell axon loss. The disease is the second most common cause of blindness in the industrialized world. Once vision loss develops it is irreversible—although in many cases further loss can be slowed if adequate treatment is provided. If not treated, glaucoma can lead to complete vision loss in the affected eye. Primary open-angle glaucoma (POAG) is the most prevalent form of the disease in the industrialized countries, representing 94% of all glaucomas. In a Spanish study of 569 individuals, the prevalence of POAG was 2.1% (99% confidence interval 1.9%-2.3%) in the age range between 40 and 79 years. Assessing glaucomatous damage progression remains one of the most important and challenging aspects in glaucoma management. In addition, a better understanding of clinical risk factors for glaucoma worsening may help us to develop new strategies to improve glaucoma care. Over the past 2 decades, many studies have addressed the issue of risk factors associated with or predicting for glaucoma progression. Although many studies have attempted to identify the prognostic factors capable of predicting the course of POAG, the results have been varied and in some cases contradictory, and are thus of scant practical utility. This study was designed to evaluate the methodologic quality of the studies published in the literature on the prognostic factors for POAG progression measured by visual field deterioration.

Key Words: glaucoma, open angle, visual fields, disease progression, research design

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Glaucoma is an asymptomatic optic neuropathy with a great variety of causes that involve gradual retinal ganglion cell loss. It is the second leading cause of blindness in the industrialized world.[1–3] Once vision loss develops, it is irreversible, although in many cases further loss may be slowed if adequate treatment is provided. If not treated, glaucoma may lead to complete vision loss in the affected eye.[4]

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Primary open-angle glaucoma (POAG) is the most prevalent form of the disease in industrialized countries, accounting for 94% of all glaucomas.[5,6] In a Spanish study of 569 individuals, the prevalence of POAG was 2.1% [99% confidence interval (CI) 1.9%-2.3%] in the age range between 40 and 79 years.[7]

Assessment of glaucomatous damage progression remains as one of the most important and challenging issues in glaucoma management. In addition, a better understanding of clinical risk factors for glaucoma worsening may help us to develop new strategies to improve glaucoma care. However, variability in glaucomatous damage progression depending on the patient makes this a complicated objective. Visual fields (VFs) change from one examination to another, even when no actual changes are occurring. This variability may mask or mimic glaucomatous damage.[8,9] Finally, another additional problem inherent to the concept of VF progression is the lack of agreement about what should be considered as significant clinical progression.

Over the past 2 decades, many studies have addressed the issue of risk factors associated to progression.[8–12] Although many studies have attempted to identify the prognostic factors (PFs) capable of predicting the course of POAG, the results reported have been varied and sometimes conflicting, and have therefore little practical value.[13] This study was designed to evaluate the methodologic quality of studies reported in the literature on the PFs for POAG progression measured by VF deterioration.

METHODS

A descriptive study was conducted, on the basis of a systematic review of the medical literature, aimed at identifying studies on the PFs for POAG progression measured by VF deterioration. Inclusion and exclusion criteria are listed in Table 1. The strategy used for searching studies on this topic was similar to that used in a recent review by the United Kingdom *Health Technol Assess* Programme.[14] The literature search (up to July 2008) was based on both PubMed and SumSearch, using the following basic medical subject headings: "glaucoma" or "glaucoma, open-angle" and "visual fields" and "disease progression." Publications before 1995 were excluded on the basis that the VF evaluation methods used before that date are no longer considered fully valid. All articles were reviewed and selected by consensus of 4 investigators.

The methodologic quality of the selected studies was evaluated based on the following characteristics: type of study (cohort or other, prospective, or retrospective);

TABLE 1. Study Inclusion and Exclusion Criteria

Inclusion criteria
Patients with POAG (or separate analysis of patients with POAG)
Objective: assess the predictive value of a potential PF for POAG
Progression measured based on visual field
Exclusion criteria
Studies published before 1995
Noncompliance with any inclusion criterion

PF indicates prognostic factor; POAG, primary open-angle glaucoma.

duration of follow-up (< 3 y or ≥ 3 y); measurement of VF deterioration using a standardized method; sample size estimation; description of patient losses to follow-up; comparison of PFs of the cohorts; blinded assessment of disease progression; calculation of statistical differences (*P* value and 95% CI); and relative measure of effect [relative risk (RR), odds ratio, hazard ratio] (Fig. 1).

Cohort studies describe the natural history or clinical course of the disease step by step, and calculate the RR attributable to a specific PF. These are the ideal studies for determining PFs.[15] Ideally, cohort studies should be prospective, because retrospective studies (historical cohorts) involve a risk of information and selection bias.[16–20]

To date, only a few studies have been conducted to determine how long and how frequent the follow-up of glaucoma progression should be.[21] On the basis of the criteria of consulted clinicians, authors concluded that a 3-year follow-up may be adequate to detect progression of the disease in most patients. In this sense, according to a recent study by Chauhan et al,[21] 3 years of follow-up allow for progression to be established with an 80% statistical power percentage, assuming 3 annual examinations, with an annual progression rate of -1.0 dB. This condition was therefore selected as the threshold used to assess the quality of the studies evaluated.

As a result of differences in the currently accepted criteria for measuring progression of VF deterioration (including among others those from Advanced Glaucoma Intervention Study, Collaborative Initial Glaucoma Treatment Study, Glaucoma Change Probability, and Point-wise Linear Regression Analysis),[22] studies using standardized computed perimetric methods were only considered (Humphrey, Octopus, etc).[23]

1. Cohort study?
2. Case-control study?
3. Prospective study?
4. Retrospective study?
5. Patient follow-up for at least three years?
6. Measurement of visual field deterioration using a standard method?
7. Predetermination of sample size?
8. Reporting of patient losses to follow-up?
9. Were the known prognostic factors considered in the compared cohorts?
10. Was the evaluation of progression made on a masked basis?
11. Was the p-value or 95%CI reported?
12. Was the effect measure specified (relative risk, hazard ratio, odds ratio)?

FIGURE 1. Methodologic quality features of studies on prognostic factors for primary open-angle glaucoma progression. CI indicates confidence interval.

The minimum sample size of each cohort required for detecting a specific prognostic difference between the compared cohorts, one with the factor and the other without it, must be calculated before starting the study. Otherwise, the sample size may be too small to detect differences between the groups, leading to false-negative results.[16,24,25] Sample size calculation before study conduct was therefore regarded as a methodologic quality criterion.

Losses to follow-up are one of the most important sources of bias in cohort studies. If 30% or more participants are lost during follow-up, the validity of the study should be questioned.[17]

Other methodologic quality criteria considered included comparability of baseline PFs of the cohorts; blinded assessment (to avoid biased assessment of results)[25]; and presentation of the results not only on the basis of the detected statistical differences between cohorts (*P* value and 95% CI), but also on the basis of the association measures (RR, odds ratio, and hazard ratio), that is, calculating the risk of progression in the cohort with the purported PF versus the cohort without the PF.

Studies with a retrospective design (with potential bias) and/or with a patient follow-up shorter than 3 years and/or with measurement of VF deterioration by a nonstandardized method were considered as low quality studies.

RESULTS

The initial search yielded a total of 265 references. From these, 95 studies were identified, 47 of which were selected after a detailed review.[10,11,25–70] The study selection process and the reasons for excluding 48 of the initially identified studies are detailed in Figure 2. In the case of the Collaborative Normal-Tension Glaucoma Study,[10] Early Manifest Glaucoma Trial,[11] and Advanced Glaucoma Intervention Study, for which different results have been published over the years, publications referring to different PFs, different types of patients, or different sample sizes were included, and when multiple publications resulting from the same study were found, the most recent one was selected.

All selected studies were cohort studies, and 61.7% were prospective studies (Table 2). Duration of follow-up

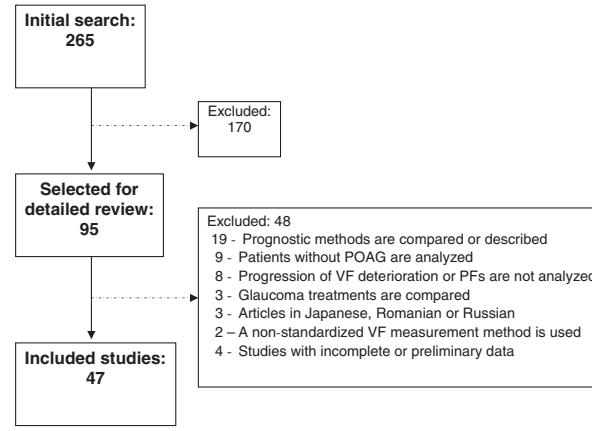

FIGURE 2. Study selection process. PF indicates prognostic factor; POAG, primary open-angle glaucoma; VF, visual field.

TABLE 2. Methodologic Characteristics of the Selected Studies on Prognostic Factors for Primary Open-angle Glaucoma Progression (N = 47)

Item	N	%	References
1. Cohort studies*	47	100	10,11,25–70
2. Prospective studies	29	61.7	10,26–29,33,35,37,40–42,44–47,49–52,54–57,60, 62,63,65,70
3. Patient follow-up for at least 3 y	46	97.9	10,11,25–70
4. Measurement of visual field deterioration with a standard method†	46	97.9	10,11,25–53,55–70
5. Sample size estimation	1	2.1	70
6. Reporting of patient losses to follow-up	1	2.1	70
7. Description of the known prognostic factors in the compared cohorts	28	59.6	10,26–29,33–36,40–47,50,54–56,59,61,64,67,69,70
8. Blinded assessment of progression	1	2.1	70
9. *P* value or 95% confidence interval reported (statistical significance)	47	100	10,11,25–70
10. Reported relative measure of effect (relative risk, hazard ratio, and odds ratio)	12	25.5	26,30,34,40,42,52,53,57,58,63,65,70

*Randomized clinical trials are included.
†Humphrey Field Analyzer, Octopus, Peritest, etc.

was at least 3 years in 97.9% of cases. Standard VF measurement methods (Humphrey Field Analyzer, Octopus, Peritest, etc) had been used in 97.9% of the studies. The required statistical sample size estimation was performed in only one of the studies, and a single study reported losses to follow-up (Table 2). The known PFs of the cohorts were duly compared in 59.6% of the studies. All studies reported the statistical significance values, but only 25.5% calculated the relative measures of effect (Table 2).

A poor methodologic quality was found in 40.4% of the studies, all of which were retrospective studies and/or studies with follow-up periods shorter than 3 years and/or used nonstandardized measurements of VF deterioration (Table 3).

DISCUSSION

Assessment of glaucomatous damage progression continues to be one of the most significant issues in glaucoma management.

According to this study, 40.4% of studies reviewed showed a poor methodologic quality. All of these were studies of a retrospective nature and/or with a follow-up time shorter than 3 years and/or with nonstandardized measurement of VF deterioration. The most important reason why studies did not meet the high quality criteria was their retrospective design (38.3% of studies reviewed).[10,30–32,34,36,38,39,43,48,53,58,59,61,64,66–69] In retrospective studies (historical cohorts), the information contained in the registries may be missing (incomplete) or of poor quality (information bias).[16] In contrast, in retrospective studies, progression and exposure to PFs occurs before the actual start of the research. As a result, if knowledge of progression affects the selection or classification of individuals exposed or not exposed to the PFs, there may be a selection bias representing a systematic error that causes differences in the prognoses of the compared subject cohorts.[17–20] A retrospective design may be valid provided the problems described above are avoided, which is difficult because of the problems inherent to the design itself. In any case, there is no doubt that a prospective design is more advisable.

TABLE 3. Methodologic Quality of Studies on Prognostic Factors for Primary Open-angle Glaucoma Progression

Quality	N	%
High	28	59.6
Low*	19	40.4

*Retrospective studies and/or studies with patient follow-up shorter than 3 y and/or with visual field deterioration measured using a nonstandardized method.

The ideal design of a study on the PFs for POAG progression measured by VF deterioration should be as follows: a prospective cohort study lasting at least 3 years in which standard methods for VF measurement were used, the sample size required for showing the relationship between the PF studied and VF progression was previously estimated, and patients lost during the study were followed up.

This review did not address the representativeness of the populations analyzed in the different studies, because adequate assessment of this aspect based on the published data is difficult. This is an important issue, however, because the general population may differ from the reported cohorts.[17] In contrast, an increased population representation may also adversely affect the internal validity of a study due to patient heterogeneity.

Although most studies examined hypothetical PFs by subgroup, according to the presence or absence of the known PFs, some studies only reported the full results for the overall patients, making it difficult to extract data for specific subgroups of known PFs.

Several considerations are in order regarding the quality criterion of minimum study duration of 3 years. The ability of a specific method for detecting VF progression depends both on baseline glaucomatous damage as well as on intratest and intertest variability, that is, on the number of tests performed to determine baseline damage. In addition, VF progression depends both on the criteria used to define progression and on the number of VFs required to confirm such progression. A given follow-up time is therefore required to be able to show glaucomatous progression in VF. The time required to show such

progression depends on several factors, including the method used to assess progression, the frequency of tests performed, the magnitude of progression, and follow-up time. Thus, the Chauhan et al[21] study showed that, assuming a low variability, 2.5 years would be required, performing 2 campimetric tests per year, to be able to detect a rapid progression of 2 dB per year. By contrast, if variability was moderate or high, 3 and 4.5 years would be required, respectively, for detecting a rapid progression of 2 dB per year.

The main conclusion of this review is that improvements are needed in the methodologic quality of studies on POAG progression. Elucidation of the PFs for POAG progression would only require a few prospective, multicenter, and multinational cohort studies involving homogeneous patient populations to ensure that the required sample sizes are studied, and a minimum follow-up period of 3 years. For this, creation of national and multinational cooperative research groups would be convenient. These groups could be formed with the participation of medical associations in the fields of ophthalmology and glaucoma.

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