LINEAR REGRESSION ANALYSIS IN GLAUCOMA VISUAL FIELD FOLLOW-UP

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Introduction

Linear regression analysis has been used to judge the progression of glaucomatous visual fields for more than a decade. Global indices as well as threshold values from individual test point locations have been subjected to such analyses. Linear regression analysis has obvious advantages, e.g., the patient’s own variability is taken into account when judging whether progression has occurred. However, this statistical approach also has clear disadvantages, e.g., several observations are needed. Increasing media opacities are also likely to disturb the results.

Aim

The aim of the current pilot project was to study some aspects of linear regression analysis for glaucomatous visual field follow-up. Several different ways of using such analyses were compared as to their ability to identify true progression while retaining specificity, i.e., to avoid falsely flagging non-progressive visual field series as worsening. We also wanted to differentiate between visual field loss caused by glaucoma and that caused by cataract. Comparisons included the performance of different global indices, the effect of the number of available field tests, proper cut-offs for numbers of significant test point locations in analyses of point-specific data, and the influence of progressive media opacities.

Methods

A retrospective pilot study was performed. Patient records were searched to find eyes with manifest or suspect glaucoma with at least five Humphrey Full Threshold 30-2 tests performed over a time period of five years or longer. We eliminated patient records...
records in which diseases other than glaucoma and cataract, *e.g.*, stroke or age-related macular degeneration, could have influenced test results. Remaining eyes with long field series were divided into groups showing long-term stability or deterioration. There were also some series with small improvements. The classification was subjective and based mainly on inspections of gray-scale representations and total deviation probability maps. All fields in the available series were taken into account to generate a judgment of the development of the field over the whole time series.

Deteriorating eyes were then subdivided into three groups: 1. eyes with pure progression of glaucoma; 2. eyes with progression of cataract but without progression of glaucoma; and 3. eyes with mixed or allegedly mixed progression caused by both progression of glaucoma and increasing media opacities.

Eyes in group 1 always had stable visual acuities of 0.9 or better during the observation period and there was no note in the records of any disturbing cataract.

Eyes in group 2 had progressively increasing media opacities and deteriorating visual acuity and had all undergone cataract surgery during the follow-up period. Postoperative visual fields had to be very similar to fields early in the visual field series, in order to ascertain that glaucoma-induced progression of field defects had not occurred concurrently with the worsening caused by increasing cataract.

Group 3 was a large group. Glaucoma worsening and increasing cataract very frequently occurred at the same time. Patterns were often typical with increasing arcuate, nasal, paracentral and altitudinal field loss caused by glaucoma, and increasing diffuse, general depression of sensitivity caused by increasing lens opacities.

Our aim was to differentiate between progression of glaucoma, progression of cataract, and no progression. Therefore, we excluded from further analysis eyes with mixed progression or eyes that could not be classified with certainty. We analyzed three groups of eyes (ten eyes each), as follows: 1. stable eyes; 2. eyes with progression of glaucoma; 3. eyes with progression of cataract. The characteristics of these patients are shown in Table 1.

Global and pointwise linear regression analyses were performed. The global estimates were mean deviation (MD), and number of points flagged as significantly progressing in conventional total deviation glaucoma change probability maps (GCPMs), and also in the newer pattern deviation GCPMs.

Analyses based on data from all individual test point locations (except two points in the blind spot area) included threshold values, and total and pattern deviations from the age-corrected normal threshold value.

Numbers of test points were counted in each eye where linear regression analysis indicated significant deterioration at the $p<0.05$ level. We also calculated the number of eyes that showed at least one such progressive point. In a comparison of two methods for analyzing the results of visual field follow-up, Viswanathan *et al.* classified glaucoma eyes with at least one such progressive point as progressive.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Group of eyes</th>
<th>No. of eyes</th>
<th>Patient age mean/range</th>
<th>No. of tests mean/range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable</td>
<td>10</td>
<td>63/53-72</td>
<td>12.4/8-16</td>
</tr>
<tr>
<td>Progression of glaucoma</td>
<td>10</td>
<td>62/49-72</td>
<td>13.1/9-16</td>
</tr>
<tr>
<td>Progression of cataract</td>
<td>10</td>
<td>70/62-80</td>
<td>10.2/6-15</td>
</tr>
</tbody>
</table>
The regression analyses were performed using all available fields, five fields and three fields only. Analyses based on numbers of significantly progressing points in GCPMs were never based on fewer than five tests, since the two first tests form a baseline for further analysis.

The stable group was analyzed in order to provide estimates of the specificity of the various analytical approaches. In order to exclude any untoward effects of any non-recognized visual field deterioration, the test order was randomized in this group.

Results

Global analyses

Figure 1 shows the number of eyes in the three groups of eyes that showed significant deterioration, based on the three different global estimates when using all tests. Thus, the great majority of progressing eyes were identified as such using all three global indices, when all tests were included. Analyses based on the number of significantly progressing points in change probability maps showed slightly lower sensitivities but had no false positive results. MD and total deviation GCPMs did not differentiate between progression caused by glaucoma or cataract, but pattern deviation GCPMs did. The results obtained after five tests were not of much use; only two eyes showed progression. Analyzing MD after three tests was not meaningful; in two of the three groups of eyes, one eye showed significant deterioration and another significant improvement.

Analyses based on individual test point locations

Including all tests, the two progressive groups showed large numbers of progressive test point locations when analyses were based on threshold or total deviation values (Fig. 2). As intended, in the cataract group, the number of such progressive points was small when analyses were based on pattern deviation values. The stable group showed a small number of progressive points. Analyses using only five tests showed small numbers of significantly progressing points with all methods of analysis in all groups (not illustrated).

Using only one significantly progressing point as a criterion for judging an eye to be deteriorating proved meaningless (Fig. 3); as expected, most eyes, also in the stable group,
were then judged to be progressing. Thus, this method lacked specificity.

The results obtained when using five or more significantly progressing test point locations as a cut-off value for classifying an eye as being deteriorating are shown in Figure 4. The sensitivity is excellent, and specificity is high. Progression of cataract could again largely be excluded if the analysis was based on pattern deviations.

Fig. 2. Results based on analyses of individual test point locations. Regression of threshold and total deviation values yield large numbers of significant points in progressive glaucoma and cataract while specificity is high. Again, results based on pattern deviations are not triggered by progressive cataract.

Fig. 3. Number of significant eyes if a field is judged to be deteriorating, based on significant progression in only one test point. As expected, most eyes are judged to be progressing, even stable eyes.

Fig. 4. Number of significantly progressing eyes using five significant test points as cut-off value. The results are close to ideal.
Discussion

Thus, the results showed that linear regression analysis was usually able to identify visual field progression, if the number of tests per eye was high. Five or three tests were not nearly sufficient, however. The practical clinical conclusion is that linear regression, as opposed to GCPM, is not a useful tool when only a few field tests are available.

Linear regression analysis of threshold values, MD values, or total deviation values could not differentiate between worsening caused by glaucoma or by cataract. The pattern deviation concept, however, proved very useful in this respect. The number of false positives was low in the cataract groups, both when analyses were based on the number of significant pattern GCPM points, and when regression analyses were performed on pattern deviation values at individual test point locations.

The number of significantly progressing points needed to label an eye as progressing is important. Since 74 test point locations were analyzed, a few test point locations can be expected to be significant at the \( p<0.05 \) level, just by chance alone. But the number of significantly progressing points would be expected to be quite small in stable fields. As expected, the results of the current study proved that labelling a field as progressing with only significantly progressing test points will lead to false positive results most of the time. The criteria recommended by Viswanathan et al.\(^6\) are, therefore, inappropriate. Five test points gave good results in the present small material.

In summary, the results indicate that the suitability of linear regression analysis depends on how and when it is used. Regression analyses were not effective when only a few tests were available. Problems with mass significance had to be taken into account when results from many test point locations were used. Analyses based on MD, raw threshold values or total deviations from age-corrected normal threshold values, could not separate progression of glaucoma from progression caused by cataract. On the other hand, pattern-based analyses did achieve such a separation.

Judging progression in repeated visual field tests from glaucoma eyes is clinically important. The management of a glaucoma patient is often based directly on the time course of measured visual field loss. Therefore, while the trends in the present pilot study seem quite clear, the clinical relevance is great enough to extend the study to a larger number of glaucomatous eyes. The results from such a study could form a basis for valuable recommendations on the best usage of regression analyses for visual field follow-up in glaucoma.

Acknowledgments

This study was supported by an unrestricted grant from the Alcon Research Institute, and by funds administered by Malmö University Hospital.

References