Glaucoma, the second leading cause of blindness worldwide, is a progressive disorder characterized by changes in the optic nerve head accompanied by visual field (VF) loss. It typically affects subjects who are 40 to 80 years old and nearly 3.5% of this population. It is estimated that approximately 111.8 million people will develop glaucoma by 2040.\textsuperscript{1-3}

VF tests are used routinely in clinical practice to assess glaucoma. Standard automated perimetry (SAP) measures the sensitivity of VF in patients with glaucoma to localize functional changes in the damaged areas.\textsuperscript{4,5} Assessing a longitudinal series of VF enables clinicians to detect early progression of the disease to direct treatment resources optimally toward worsening cases.\textsuperscript{6,7} VF global measures, such as mean deviation (MD), fail to ascertain local changes.\textsuperscript{8} As such, some researchers have suggested using point-wise or region-wise models to better capture the local characteristics of VF loss.\textsuperscript{9,10}

Numerous studies have been conducted to model longitudinal VF sensitivity for each VF test location.
using linear and exponential regressions.\textsuperscript{10–16} Linear regression assumes a constant additive rate of deterioration, whereas this rate is multiplicative for exponential regression. The rate of change would be constant, fast, or slow in different parts of the same individual VF test during the time. As all VF locations do not have the same pattern, sigmoid regression may represent a better fit, particularly in cases that transit from normal to perimetric blindness.\textsuperscript{5,9,17}

Although pointwise linear regressions are more sensitive to localized changes, they may generate a high false positive rate. Besides, they have poor test-retest reproducibility because of measurement variability, particularly in locations with great damage.\textsuperscript{18–20} Dividing VF locations into regions and monitoring the progression by region-wise pattern analysis is a useful way to address this problem, which could improve prediction of deterioration.\textsuperscript{10,18,20–23} Therefore, we can analyze VF defects based on spatial dependency to evaluate the progression of the disease in each sector.

To the best of our knowledge, there is no study comparing VF behavior pointwise and region-wise using linear and nonlinear models. Therefore, this study was designed to assess VF changes over the entire perimetric range using linear, exponential, and sigmoid regression models applied to individual test locations and regions of VF.

**Methods**

In a retrospective cohort study, we investigated the behavior of VF tests (as a function of time) of 277 eyes of 139 patients with glaucoma who were recruited from the Rotterdam Eye Hospital in the Netherlands. All subjects filled in the written consent form and the study was approved by the Institutional Review Board of Rotterdam Eye Hospital. Patients aged 18 to 85 years old were examined. Patients with uveitic glaucoma, secondary glaucoma, except pigmentary, evidence of SAP VF abnormality consistent with other disease, except for locations with the initial 3 values equal as the outcome of interest and utilized in the analysis, except for locations with the initial 3 values equal to 0 dB. Moreover, patients with fewer than 15 visits were excluded from the study. The linear, exponential, and sigmoid regression models were utilized to investigate the pattern of threshold sensitivity deterioration at each VF test location during the follow-up time for each eye.

In the next step, linear, exponential, and sigmoid regressions were applied to assess the rate of deterioration at each Glaucoma Hemifield Test (GHT) sector.\textsuperscript{25} In this approach, the superior and inferior hemifields were divided into 10 glaucoma regions named Arcuate1, Arcuate2, Nasal, Central, and Paracentral. Each sector consisted of three to five VF test locations; therefore, we calculated the mean of threshold sensitivity in each region to regress it against age in predefined models mentioned above.

**Regression Methods for Modeling the Pattern of Changes in VF Tests**

First, the pointwise approach was applied, and the values of VF tests were modeled by linear, exponential, and sigmoid regression methods on threshold sensitivities (dB) at each location except for the two physiologic blind spots. The linear model is mathematically defined by \( y = \alpha + \beta x + \epsilon; \) it treats as a logarithmic transformation of a simple linear regression model (\( \ln y = \alpha + \beta x + \ln \epsilon; \)). Exponential regression is used to model variables in which the increase starts slowly and then speeds up rapidly without bound, or where deterioration begins rapidly and then slows down to get closer and closer to zero (the latter is considered here). The model includes \( e^\beta \) that represents the rate of change, particularly in locations with great damage.\textsuperscript{18–20} The values of 52 VF test locations were considered as the outcome of interest and utilized in the analysis, except for locations with the initial 3 values equal to 0 dB. Moreover, patients with fewer than 15 visits were excluded from the study. The linear, exponential, and sigmoid regression models were utilized to investigate the pattern of threshold sensitivity deterioration at each VF test location during the follow-up time for each eye.

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of change in sensitivity per year with increasing in age and the error term is denoted by \( \varepsilon \). For estimating the parameters of this nonlinear model, the Newton-Raphson method was used.

The third model that was used in this study was an S-shape regression model, namely sigmoid as a nonlinear regression model defined by \( y = \frac{\gamma}{1 + e^{-\alpha x}} + \varepsilon \); in which, with the initial value of sensitivity \( \gamma \), the decrease starts slowly until the \( \alpha \) threshold is reached (the point where the curve begins a steep deterioration). Then, deterioration gets steeper with the slope of \( \beta \) over time. The larger values of \( \alpha \) and \( \beta \) correspond to later start and steepness of decline overtime, respectively. The error term is showed by \( \varepsilon \) representing the part of \( y \) that is not explained with \( x \). Parameter estimation was carried out using the Newton-Raphson method.

In the next step, linear, exponential, and sigmoid regressions were applied to assess the rate of deterioration at VF test locations and GHT regions. The goodness of fit in these three methods was assessed by the root mean squared error (RMSE) values computed for each model. It was calculated by computing the sum of squares of residual (the difference between the predicted and actual sensitivities at each time point) and dividing by its degree of freedom \((n-p)\) then taking the square root of the outcome:

\[
RMSE = \sqrt{\frac{1}{n-p} \sum_{i=1}^{n} (y_i - \hat{y}_i)^2},
\]

where \( p \) is the number of terms in the model. The best fit for both locations and sectors was determined according to the lowest RMSE amount. The Pairwise \( t \)-test with Bonferroni correction was also used to compare RMSE of three models based on pointwise and region-wise approaches.

In addition, it was investigated which model had a better fit in conditions where the mean of the 2 initial sensitivities were higher than 22, 26, and 30 dB and the mean of the 2 final sensitivities were lower than 10 dB to provide an assessment of the behavior of deterioration across the entire perimetric range.\(^{17} \) All the statistical analyses were done using Stata software version 14.2 and the level of significance was 0.05.

### Results

Eyess with fewer than 15 visits and locations with the 3 initial values equal to 0 dB were excluded (18 eyes were removed). A total of 259 eyes from 132 patients with glaucoma were selected for the downstream analyses (some patients contributed one eye only). A total of 131 eyes (50.6\%) were in the early stage, 56 (21.6\%) were in the moderate stage, and 72 (27.8\%) were in the advanced stage of glaucoma.

At the first visit, the mean (SD) of age and IOP (SD) was 59.9 (9.8) years and 15.0 (4.9) mm Hg, respectively. In this study, the minimum and maximum number of visits were 15 and 23, and the mean (SD) of the follow-up was 9.3 (0.7) years. Table 1 represents the demographic characteristics of the patients. Figure 1 demonstrates the distribution of the initial and final threshold sensitivities for all VF test locations.

We fitted linear, exponential, and sigmoid regression models to each VF test location (52 locations), which resulted in 12,243 pointwise regressions for each model. We then computed the mean (SD) values of RMSE for each model (Table 2). For each eye and each VF test location, the model that generated the least RMSE was recorded as the best fitting model. Linear regression could detect a constant rate of progression for approximately 26\% of the VF test locations, whereas exponential and sigmoid nonlinear regression models suggested better fits in approximately 39\% and 34\% of the VF test locations, respectively. Overall, exponential regression provided the best fit in 39\% of the VF test locations, however, sigmoid regression generated the least mean RMSE across all VF test locations. Sigmoid regression consistently provided the least RMSE in VF test locations with initial sensitivity better than 22 dB (about 71\%), 26 dB (about 86\%), and 30 dB (about 93\%). Statistical comparison between models was significant \((P < 0.001)\), however, this result might occur due to the large sample size.

Figure 2 demonstrates the percentage of the best fit (least RMSE) for each model visualized by each VF test location. Figure 3 presents VF worsening of several VF test locations with sensitivity greater than 22 dB.
and the corresponding fitted models based on linear, exponential, and sigmoid regressions for samples eyes in our study.

A total of 2156 models were fitted to GHT regions based on each regression model. Similar to the pointwise approach, the exponential model generated the best fit (least RMSE) in about 38% of all models, and linear and sigmoid regression models were the best fit in approximately 28% and 34% of the cases, respectively (Table 3). Region-wise regression models consistently generated a lower RMSE compared to the pointwise regression models. The RMSE comparison among the three models revealed that there was no significant difference between the linear and exponential regressions ($P = 0.291$), but there were meaningful differences between sigmoid regressions and the other two models ($P < 0.001$), however, the effect of sample size on significance should be considered.

Nonlinear region-wise regressions (exponential and sigmoid combined) yielded a considerable proportion of the best fits with approximately 70% of the best fits in both inferior and superior hemifields (Fig. 4). Furthermore, like the pointwise approach, the results revealed that sigmoid regression was highly preferable in regions with the initial VF sensitivity in normal ranges.

### Table 2. RMSE Results Based on Pointwise Linear, Exponential, and Sigmoid Regression Models Applied on Sensitivity Values in 52 Visual Field Test Locations

| Characteristic                              | Overall ($N = 12,243$) | $>22$ ($n = 236$) | $>26$ ($n = 97$) | $>30$ ($n = 15$) |
|---------------------------------------------|-------------------------|-------------------|-------------------|-------------------|
| **Linear RMSE in dB, mean (SD)**           | 3.31 (2.7)              | 6.09 (2.7)        | 6.72 (3.8)        | 5.67 (1.0)        |
| **Exponential RMSE in dB, mean (SD)**      | 3.09 (1.9)              | 6.09 (1.4)        | 6.48 (1.4)        | 6.68 (1.2)        |
| **Sigmoid RMSE in dB, mean (SD)**          | 2.95 (1.8)              | 4.30 (1.8)        | 3.76 (1.6)        | 3.49 (1.3)        |
| **Linear best fit, No. (%)**               | 3226 (26.3)             | 40 (17.0)         | 7 (7.2)           | 1 (6.7)           |
| **Exponential best fit, N (%)**            | 4806 (39.3)             | 27 (11.4)         | 6 (6.2)           | 0 (0.0)           |
| **Sigmoid best fit, N (%)**                | 4211 (34.4)             | 169 (71.6)        | 84 (86.6)         | 14 (93.3)         |

RMSE, root mean square error; SD, standard deviation.
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Figure 2. The percentages that pointwise linear, exponential, and sigmoid regression models generated the best fit (least RMSE) based on each VF test location. RMSE, root mean square error.

Table 3. RMSE Results Based on Regionwise Linear, Exponential, and Sigmoid Regression Models Applied on Sensitivity Values in 10 GHT Regions

| Characteristic | Overall (N = 2156) | Initial VF, dB |
|----------------|-------------------|----------------|
|                |                   | >22 (n = 37)   | >26 (n = 17) | >30 (n = 3) |
| Linear RMSE in dB, mean (SD) | 2.00 (1.1) | 3.83 (1.2) | 4.27 (1.2) | 3.12 (0.9) |
| Exponential RMSE in dB, mean (SD) | 2.00 (1.1) | 3.99 (1.4) | 4.74 (1.3) | 4.55 (1.8) |
| Sigmoid RMSE in dB, mean (SD) | 1.90 (1.1) | 2.68 (0.9) | 2.65 (0.8) | 2.16 (0.2) |
| Linear best fit, N (%) | 602 (27.9) | 6 (16.2) | 1 (5.9) | 1 (33.3) |
| Exponential best fit, N (%) | 821 (38.1) | 8 (21.6) | 1 (5.9) | 0 (0.0) |
| Sigmoid best fit, N (%) | 733 (34.0) | 23 (62.2) | 15 (88.2) | 2 (66.7) |

RMSE, root mean square error; SD, standard deviation.

Figure 5 demonstrates VF worsening of GHT regions with mean sensitivity better than 22 dB and the corresponding fitted models based on linear, exponential, and sigmoid regressions for sample eyes in our study.

Discussion

Glaucoma is a slowly progressing disease. If not treated appropriately, glaucoma may inherently impact the quality of life of patients and affect their daily activities. Moreover, a high probability of anxiety and depression was reported among patients with glaucoma. Therefore, identifying VF worsening through investigation of longitudinal VF tests is critical to prevent or slow irreversible vision loss.

In the current study, pointwise and region-wise linear, exponential, and sigmoid regressions were applied to model the VF worsening over time (via regressing VF values against the age of the patients). Although the sigmoid model had the lowest mean RMSE generally, findings suggest that the exponential regression had the best fit for patients undergoing routine glaucoma treatment for both pointwise and region-wise approaches in each location and GHT region (see Tables 2, 3). Furthermore, RMSE was apparently lower for region-wise regression compared to pointwise regression models. This fact can be explained by lower measurement variability due to taking the average of VF sensitivity in each GHT region.

Linear and exponential regressions have a constant rate of change over time, and they are popular models due to their simplicity of use and interpretations. In our data set, VF worsening in the perimetric range was nonlinear in nearly 70% of test locations, and pointwise exponential regression was the best model in the fit. This result is consistent with previous studies which acknowledged that nonlinear models led to a substantial improvement over linear models and could track VF change during the follow-up time more...
Figure 3. Visual field worsening of VF test locations from sample eyes were modeled based on pointwise linear, exponential, and sigmoid regression approaches.
precisely.6,11,16,27,28 Pathak et al. designed a study to compare the linear and nonlinear mixed effect models in tracking the rate of change in pointwise VF sensitivity over time. They concluded that the nonlinear method was preferable and provided a better fit than ordinary least squares linear model.16 Similar to their findings, we also observed that nonlinear models provide a better fit. In addition, they denoted the advantage of the exponential model in a longitudinal series of MD over time as well.28 Caprioli et al. examined the rate of VF progression for each VF test location through three models of linear, exponential, and quadratic that resulted in a far better fit for the exponential model.27 Our findings are in agreement with Caprioli et al. in the superiority of the exponential regression for modeling VF worsening over time.

The other finding of the present study was the superiority of the sigmoid model in patients in which their mean of the first 2 initial sensitivities was greater than 22 dB. Chen et al. suggested the appropriateness of the logistic model in modeling longitudinal VF loss.5 Our results are also in agreement with those reported by Otarola et al. in which the sigmoid regression outperformed in patients with the initial sensitivities in the normal range. However, their result was overall in favor of sigmoid regression.17 Considering the features of the sigmoid model, its natural asymptotes reflect periods of being normal, visual loss, and the end point of perimetric blindness. There is a sensible symmetry around the inflection point in the sigmoid model mathematically that may not be met in actual conditions. It clinically means that the rate of progression for VF loss in early stages would be identical with end stages, whereas higher variability measurement exists in lower sensitivities. In addition, this model has one more parameter than the other two considered models.5,17

It should be noted that the pointwise approach is more sensitive to the local progression of VF. In previous studies, a great test-retest variability of VF sensitivities has been revealed in damaged test locations.12,29 Due to the spatial dependency between some VF test locations, different techniques of clustering, typically consistent with retinal nerve fiber layer bundle patterns, have been proposed to evaluate the functional changes.10,20,30,31 We conducted this study based on predefined regions by GHT.25 Accordingly, the mean values of RMSE were smaller for region-wise models compared with pointwise ones (see Tables 2, 3). Previous studies, such as the one carried out by Hirasawa et al., demonstrated a lower absolute prediction error of mean TD values in region-wise analysis compared with pointwise analysis.20 The other studies also confirmed the appropriateness of region-wise analysis in terms of reduction in prediction error.19,22

In our study, the region-wise regression analysis revealed that deterioration occurred in a nonlinear manner during the follow-up period in almost all sectors. Accordingly, exponential regression modeled the VF changes better in the nasal, paracentral, and central regions. Many studies have been carried out tracking the rate and speed of deterioration in each VF region, but they did not compare different regression models.16,18,29,30

A significant body of research has been conducted on pointwise and region-wise analysis or other advanced statistical approaches for different purposes including prediction.10,16,32–34 In this study, we used a different approach demonstrating a high percentage of nonlinear decay in VFs of glaucomatous eyes with a
Figure 5. VF worsening of GHT regions from sample eyes were modeled based on region-wise linear, exponential, and sigmoid regression approaches.
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great caution for clinicians in the case of facing normal sensitivities that may progress later in a sigmoid shape. Although, biologic underpinnings of glaucoma disease may not be represented by models accurately, it may provide valuable insights for clinicians regarding VF changes through a simplified form of progression. This would be attained by identifying the model that fits the data more truly. Our study showed the superiority of the exponential regression over the other two models and in conditions with more aggressive form of decay, sigmoid regression had a better performance. Although the pointwise approach enabled us to evaluate local changes, such models suffer from a high degree of variability. Hereon, region-wise analysis may partially address the VF variability.

A major limitation of our study is the unknown number of incisional surgeries, such as trabeculectomy, the implantation of a large drainage tube, or laser trabeculoplasty. Although we believe only a handful of patients went through surgical intervention, the models may be influenced by these interventions. Thus, the results should be interpreted with caution as these interventions may change the trend of VF loss into a nonlinear pattern during the follow-up time.

Conclusion

We compared pointwise and region-wise VF worsening over time based on linear, exponential, and sigmoid regression models and observed that sigmoid provided overall lower RMSE in both pointwise and region-wise analyses. However, the exponential model provided the largest number of best fits (least RMSE) in both pointwise and region-wise analyses. Our analyses also suggested the sigmoid regression consistently provided the best fit in subjects with (pointwise and region-wise) VF sensitivity values corresponding to the first visits in the normal range but (pointwise and region-wise) VF sensitivity values corresponding to the last visits in the total loss range. This fact may suggest that rate of VF worsening is not constant and may change across the course of the disease.

Acknowledgments

The present paper was partially supported from the dissertation of Samaneh Sabouri and was supported by Grant no. 20843 (23360-01-01-99) and ethics code: IR.SUMS.REC.1400.082 from Shiraz University of Medical Sciences, Shiraz, Iran. The authors would like to thank The Rotterdam Ophthalmic Institute for providing us this dataset under the license agreement and we are also thankful of Shiraz University of Medical Sciences, Shiraz, Iran and Center for Development of Clinical Research of Nemazee Hospital and Nasrin Shokrpour for editorial assistance.

Disclosure: S. Sabouri, None; S. Pourahmad, None; K.A. Vermeer, Acoustic Insight and Novo Research Consultancy, Voorburg; H.G. Lemij, None; S. Yousefi, None

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