

Joint Modeling of Longitudinal Visual Field Changes and Time to Detect Progression in Glaucoma Patients: A Secondary Data Analysis

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What's Known

- Assessing longitudinal visual field changes enables clinicians to detect disease progression in glaucoma patients.
- Typically, linear mixed-effects models or Cox regression are used to analyze glaucoma data and identify factors associated with visual field deterioration, or the time to progression detection.

What's New

- The effect of various risk factors on progression detection was evaluated using a joint model. The findings of the present study indicated an inverse association between the risk of progression and mean deviation values.
- Older age, higher mean intraocular pressure (IOP), and early-stage disease were identified as factors associated with an increased risk of progression.

Abstract

Background: Glaucoma causes irreversible damage to the optic nerve and can lead to blindness if it is not treated appropriately. Evaluation of longitudinal changes in the visual field (VF) and detecting progression in a timely manner are critical for effective disease management. This study aimed to identify factors associated with VF impairment and disease progression using a Bayesian joint model.

Methods: A total of 129 glaucoma patients (228 eyes) were recruited from an ongoing cohort study initiated in 1998 at the Rotterdam Eye Hospital in the Netherlands. Standard Automated Perimetry (SAP) was performed for each patient at regular 6-month follow-up intervals. Covariates included sex, age at baseline, mean intraocular pressure (IOP), and disease severity. A Bayesian joint model was employed, integrating a linear mixed effects model (LMM) for longitudinal mean deviation (MD) values and a Cox proportional hazards model for progression time. The statistical analyses were conducted using R software and the 'JMbays2' package.

Results: Progression was observed in 33.8% of eyes. A significant association was found between MD changes and progression risk ($\alpha = -0.39$, $P < 0.001$). Older age ($P = 0.01$), early-stage disease ($P < 0.001$), and higher mean IOP ($P < 0.001$) were associated with an increased risk of progression.

Conclusion: Considering longitudinal MD changes, age at baseline, mean IOP, and disease severity were significantly associated with the time to progression detection. Sex was not found to be a significant factor in glaucoma progression.

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Keywords • Glaucoma • Joint model • Longitudinal studies • Disease progression • Survival analysis

Introduction

Glaucoma is a chronic condition that causes irreversible damage to the optic nerve and can lead to blindness if not treated appropriately.^{1,2} It typically affects individuals aged 40-80 years, and it is predicted that by 2040, approximately 112 million people worldwide will be affected by the disease.³ Glaucoma imposes a significant financial burden on patients and society, including both direct and indirect costs, with disease severity.^{4,5} Additionally, the gradual loss of vision associated with glaucoma adversely affects patients' daily activities. Therefore, understanding the spectrum

As glaucoma severity increases, deterioration tends to follow a more central pattern.³⁹ Consequently, assessing progression in advanced stages of the disease is challenging due to increased variability in VF measurements.⁴⁰ Previous studies reported that initial MD was a significant factor in the rate of VF deterioration and future progression of the disease.^{11, 13, 26} According to the findings of the present study, disease severity at baseline was associated with MD changes. In early-stage patients, VF loss demonstrated progressive deterioration from disease onset. Interestingly, our survival sub-model revealed that advanced disease stages appeared protective against further VF progression, with both severe and moderate stages exhibiting lower progression risk than early-stage glaucoma. This paradoxical effect might be explained by greater variability in VF deterioration measurements and substantially reduced residual visual function in patients with end-stage disease. Additionally, functional loss and progression detection are more readily observable in patients with early-stage damage due to the longer duration from the onset of defects until the end-stage disease.⁴⁰

One of the limitations of this study was the limited number of risk factors available in our dataset. Here, progression detection was based on the changes in MD values over time. Future studies could benefit from applying alternative criteria for detecting progression, such as changes in VF test locations or using optic nerve imaging. Furthermore, clinical data might contain more than one event, such as different surgical interventions. The use of joint modeling of longitudinal data and competing risks could provide additional insights by considering other types of endpoints in glaucoma patients.

Conclusion

Among the available patients' information, age at baseline, mean IOP, and disease severity were statistically significant in both sub-models. Furthermore, after adjusting for the present risk factors, the estimated associated parameter demonstrated a strong association between the hazard of progression and MD changes. Taken together, the joint model offered the advantage of simultaneously estimating progression risk and MD changes, which provided a better inference regarding the impact of risk factors on the response variable.

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Authors' Contribution

S.S: Conceptualization, data curation, formal analysis, methodology, writing original draft and reviewing and editing; E.H: Methodology, reviewing and editing; M.M, H.G.L, K.A.V, S.Y: Reviewing and editing and S.P: Conceptualization, methodology, supervision, reviewing and editing. All Authors participated in the design of the study, have read and approved the final manuscript, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest: None declared.

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