Correspondence

Comment on: An Artificial Intelligence-Based Prognostic Model for Prediction of Functional Glaucoma Progression From Clinical and Structural Data

TO THE EDITOR,

Mohammadzadeh et al.[1] present a valuable deep learning (DL)–based prognostic model integrating clinical and multimodal structural data to predict glaucoma progression in 1599 eyes. The reported performance of the best model (area under the curve [AUC] 0.839, accuracy 76.0%) and its superiority over logistic regression underscore its potential. However, several methodological considerations merit further discussion. Despite its nonlinear modeling capacity, the framework does not explicitly account for structural dependencies, feature redundancy, or interpretability of learned representations across biologically interrelated ophthalmic measurements. Notably, although performance remained acceptable in external validation (AUC 0.754), the decline further highlights challenges in generalizability, indicating that high prediction accuracy does not inherently guarantee feature importance reliability.[2] Accordingly, these considerations warrant further clarification regarding the framework's structural and interpretive foundations.

In this regard, a central issue lies in the treatment of multimodal inputs without explicitly modeling their underlying correlation structure or hierarchical dependencies within the feature fusion framework. Structural measurements from different imaging modalities frequently represent overlapping manifestations of a shared neurodegenerative process and are therefore characterized by substantial redundancy. Without explicit feature structuring, models may conflate correlated signals or distribute weights unaligned with underlying biological processes. This concern is further supported by the discrepancy between recall (90%) and precision (46%) in progression prediction, suggesting limited specificity and positive predictive value, which underscores the need for clearer feature interpretation. Consequently, interpretability of the learned features remains uncertain.

An additional consideration relates to the definition of the outcome variable. In this study, glaucoma progression is defined according to repeated linear regression of visual field mean deviation slopes across fixed time windows. Although providing a standardized criterion, this embeds an implicit linearity assumption into labeling, constraining the capture of complex continuous biological processes.[3] As a result, a nonlinear DL model is trained to predict an outcome derived from linear constraints, which may attenuate the advantages of nonlinear representation learning and obscure more complex disease trajectories. This issue is also evident in the fast-progression subgroup, where high discrimination (AUC 0.869) coexists with low precision (29%), which may reflect the combined influence of outcome definition and class imbalance.

To address these limitations, complementary preprocessing and model-independent analytical strategies may be beneficial. Unsupervised feature-structuring approaches, such as Feature Agglomeration[4] and the concepts of Highly Variable Gene Selection adapted for multi-modal variance mapping,[5] could be considered prior to model training to reduce dimensionality and facilitate identification of coherent structural clusters across modalities. These approaches may help align input features with biologically meaningful organization while mitigating redundancy. In parallel, nonparametric measures—including Spearman's rho and Kendall's tau—could provide a model-agnostic framework to evaluate whether observed relationships reflect stable rank-based associations independent of model specification.[6] These strategies may improve interpretability and reproducibility across clinical datasets.

Overall, incorporating these strategies alongside DL modeling would not diminish predictive performance but enhance interpretability, robustness, and translational relevance. A framework integrating representation learning with explicit structural characterization and model-independent validation may provide a more comprehensive and biologically grounded approach to predicting glaucoma progression.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Kiyo Yoshida: Conceptualization, Writing – original draft. **Souichi Oka:** Investigation. **Yoshiyasu Takefuji:** Project administration, Supervision, Writing – review & editing.

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