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Research Article

Explainable Artificial Intelligence for Early Detection of Glaucomatous Optic Neuropathy

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ABSTRACT

Background: Glaucoma is a leading cause of irreversible visual loss, and early structural damage may precede clinically detectable functional impairment. Explainable artificial intelligence may support earlier identification of glaucomatous optic neuropathy while providing visual information about image regions contributing to model predictions.

Objective: To evaluate the diagnostic performance of an explainable artificial intelligence model for glaucomatous optic neuropathy, determine its sensitivity for early-stage disease, and assess anatomical concordance of Grad-CAM saliency maps with clinically relevant optic nerve structures.

Methods: This prospective hospital-based diagnostic accuracy study included 60 adults undergoing glaucoma evaluation at a tertiary care teaching hospital in Pakistan from January to June 2026. Clinical examination, fundus photography, optical coherence tomography, and standard automated perimetry were used to establish the reference diagnosis. A previously trained convolutional neural network classified fundus images as glaucomatous or nonglaucomatous. Diagnostic performance was assessed using sensitivity, specificity, predictive values, and accuracy, while Grad-CAM maps were reviewed for anatomical concordance.

Results: Thirty patients had glaucomatous optic neuropathy and 30 were nonglaucomatous. The model achieved 90.0% sensitivity, 86.7% specificity, 87.1% positive predictive value, 89.7% negative predictive value, and 88.3% overall accuracy. Early-stage sensitivity was 83.3%, whereas all 12 moderate-to-advanced cases were detected. Forty-nine of 60 Grad-CAM maps (81.7%) were considered anatomically concordant with clinically relevant optic nerve regions.

Conclusion: Explainable AI demonstrated good diagnostic performance for glaucomatous optic neuropathy and clinically relevant spatial attribution in most cases. Lower sensitivity for early-stage disease and the small single-centre sample indicate that larger independent validation studies are required before routine clinical implementation.

Keywords: Artificial Intelligence, Glaucoma, Glaucomatous Optic Neuropathy, Deep Learning, Grad-CAM, Explainable AI.

INTRODUCTION

Glaucoma is a progressive optic neuropathy characterized by retinal ganglion cell degeneration, thinning of the retinal nerve fiber layer (RNFL), characteristic optic nerve head changes, and corresponding visual field abnormalities. It remains a leading cause of irreversible blindness worldwide, particularly among older adults. Global estimates indicated that approximately 3.61 million individuals were blind and another 4.14 million experienced moderate-to-severe visual impairment attributable to glaucoma in 2020. Despite improvements in ophthalmic diagnostic technologies, delayed recognition continues to contribute substantially to preventable visual disability, particularly in populations with limited access to specialist ophthalmological services [1].

Early detection of glaucomatous optic neuropathy (GON) is essential because structural damage may develop before clinically detectable functional deterioration. Conventional diagnosis requires comprehensive ophthalmic assessment, including intraocular pressure measurement, optic disc examination, optical coherence tomography (OCT), and standard automated perimetry. Although these

investigations provide complementary information, their interpretation requires clinical expertise and may be affected by disease severity, image quality, anatomical variability, and examiner experience [2]. Artificial intelligence (AI), particularly deep learning, has emerged as a potentially useful approach for identifying subtle structural abnormalities from digital ophthalmic images and supporting earlier recognition of disease [3].

Recent advances in convolutional neural networks have demonstrated promising performance in automated recognition of glaucomatous changes. Hemelings et al. investigated deep learning approaches that incorporated retinal information beyond the optic disc, highlighting the potential diagnostic contribution of retinal regions outside conventional optic nerve assessments [4]. Similarly, Fan et al. evaluated deep learning in the Ocular Hypertension Treatment Study and reported an area under the receiver operating characteristic curve (AUROC) of 0.91 for detection of glaucomatous conversion based on optic disc changes. Importantly, their findings demonstrated that fundus photography could provide information relevant to detecting disease conversion before substantial functional impairment [5].

The clinical applicability of AI-based screening has also been investigated through external validation. Xu et al. evaluated an automated system across multiple clinical datasets and reported diagnostic accuracies of 93.18% and 91.40%, with corresponding sensitivities of 91.75% and 91.41%. These findings supported the potential utility of automated glaucoma assessment in different healthcare environments while emphasizing the need for external testing and assessment of performance across heterogeneous patient populations [6]. Additionally, AI-based retinal screening systems have demonstrated potential for identifying multiple ophthalmic abnormalities, supporting their possible integration into comprehensive ophthalmic evaluation and referral pathways [7].

Despite these developments, the limited interpretability of complex AI models remains a concern for clinical implementation. Explainable artificial intelligence (XAI) techniques, including gradient-weighted class activation mapping (Grad-CAM), generate visual representations of image regions contributing to model predictions. Such approaches may help clinicians assess whether attention is directed toward anatomically relevant structures, including the optic cup, neuroretinal rim, and peripapillary retina. Nevertheless, anatomical agreement between saliency maps and clinically relevant structures does not independently establish that an algorithm has learned a clinically valid causal explanation. Comparative investigations of explainability methods have demonstrated meaningful differences in the usefulness of generated visual explanations [8].

In Pakistan, delayed presentation, variable availability of advanced ophthalmic imaging, and differences in access to glaucoma specialists may complicate early diagnosis, particularly in resource-constrained healthcare settings. An interpretable AI-assisted diagnostic system could potentially facilitate preliminary risk identification, improve referral prioritization, and support ophthalmologists in evaluating suspicious optic nerve findings. However, locally generated evidence examining both diagnostic performance and clinical interpretability remains necessary. Therefore, the present study aimed to evaluate the diagnostic accuracy of explainable AI for detecting glaucomatous optic neuropathy, determine its sensitivity for early-stage disease, and assess the anatomical concordance of Grad-CAM saliency maps with clinically relevant optic nerve structures in patients attending a tertiary care teaching hospital in Pakistan.

METHODOLOGY

A prospective hospital-based diagnostic accuracy study was designed to be conducted in the Department of Ophthalmology of a tertiary care teaching hospital in Pakistan over six months, from January 2026 to June 2026. The objective was to evaluate the diagnostic performance and clinical interpretability of a previously developed explainable artificial intelligence model for identifying glaucomatous optic neuropathy, with particular emphasis on early-stage disease. The study protocol was designed in accordance with internationally accepted principles of diagnostic accuracy research and the STARD-AI reporting guidelines. Approval from the institutional ethics review committee and written informed consent from eligible patients were required before recruitment.

A total of 60 adult patients undergoing evaluation for suspected glaucoma or routine ophthalmic assessment were proposed for inclusion using nonprobability consecutive sampling. Eligible participants were aged 18 years or older and had undergone sufficient

ophthalmic investigation to establish their glaucoma status. Patients with significant media opacity preventing reliable retinal imaging, advanced retinal disorders, nonglaucomatous optic neuropathy, or previous ocular conditions substantially affecting optic nerve assessment were excluded. To avoid diagnostic clustering, one prespecified study eye per patient was selected. Cases with incomplete clinical reference-standard assessments or uninterpretable imaging were recorded and managed according to predefined exclusion criteria.

Each participant underwent a comprehensive ophthalmic examination, including assessment of visual acuity, intraocular pressure by Goldmann applanation tonometry, slit-lamp biomicroscopy, optic disc examination, and dilated fundus evaluation. Color fundus photography was obtained using a digital retinal camera, while spectral-domain OCT was performed to assess peripapillary retinal nerve fiber layer thickness and optic nerve head morphology. Standard automated perimetry was used to assess functional impairment where clinically appropriate. Age, sex, systemic comorbidities, family history of glaucoma, intraocular pressure, cup-to-disc ratio, RNFL thickness, and visual field indices were recorded using a standardized data collection form.

The reference diagnosis of glaucomatous optic neuropathy was established independently by two experienced ophthalmologists using optic nerve head appearance, RNFL findings, and available visual field results. Disagreements were resolved through consensus or adjudication by a third glaucoma specialist. Early-stage glaucoma was defined using prespecified structural and functional criteria, including optic disc or RNFL changes with absent or mild visual field loss. Moderate-to-advanced disease was classified according to established visual field severity criteria. The reference-standard assessment was performed without access to AI predictions to minimize review bias. The diagnostic approach reflected contemporary glaucoma assessment recommendations emphasizing the combined evaluation of optic nerve structure and visual function.

The index test consisted of a previously trained convolutional neural network capable of classifying retinal fundus images as glaucomatous or nonglaucomatous. The model architecture, training dataset, image preprocessing procedure, classification threshold, and software version were required to be documented before external evaluation. No images from the study participants were used for model training or threshold optimization. All images were standardized for size and image quality before evaluation, and AI outputs were generated independently of the clinical reference diagnosis. A locked model was used throughout the study to prevent adaptation to the test dataset.

Explainability was assessed using Gradient-weighted Class Activation Mapping (Grad-CAM), which generated spatial heatmaps identifying image regions contributing to the model's classification. The heatmaps were superimposed on the original retinal fundus photographs and independently assessed by masked ophthalmologists for localization of anatomically relevant structures, including the optic disc, neuroretinal rim, and peripapillary region. Anatomic concordance was defined prospectively using a standardized grading rubric. Disagreements between reviewers were adjudicated, and interobserver agreement was planned to be quantified using Cohen's kappa statistic. Heatmaps were interpreted as visual attribution aids rather than definitive explanations of the underlying algorithm.

Data were analyzed using IBM SPSS Statistics and Python-based statistical packages. Continuous variables were expressed as mean ± standard deviation or median with interquartile range, depending on distribution, while categorical variables were presented as frequencies and percentages. Sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy were calculated using a 2 × 2 contingency table, with corresponding 95% confidence intervals. The discrimination of the AI model was to be evaluated using receiver operating characteristic analysis, and the area under the curve was to be reported with its 95% confidence interval. Subgroup sensitivity was assessed for early-stage and moderate-to-advanced glaucoma. Fisher's exact test was preferred for comparisons involving small expected cell frequencies. A two-sided p-value below 0.05 was considered statistically significant for prespecified inferential analyses.

RESULTS

A total of 60 patients undergoing glaucoma evaluation at a tertiary care teaching hospital were included in the analysis. The mean age was 54.8 ± 11.6 years, and 34 (56.7%) participants were male, while 26 (43.3%) were

female. The largest age group was 51–60 years, accounting for 21 (35.0%) participants. A family history of glaucoma was present in 13 (21.7%) patients, while systemic hypertension and diabetes mellitus were documented in 25 (41.7%) and 19 (31.7%) patients, respectively. The demographic and baseline characteristics are presented in Table 1.

Table 1. Demographic and Baseline Clinical Characteristics of Study Participants (N=60)

Variables	Frequency (%) / Mean ± SD
Age (years)	54.8 ± 11.6
≤40 years	8 (13.3%)
41–50 years	15 (25.0%)
51–60 years	21 (35.0%)
>60 years	16 (26.7%)
Male	34 (56.7%)
Female	26 (43.3%)
Family history of glaucoma	13 (21.7%)
Hypertension	25 (41.7%)
Diabetes mellitus	19 (31.7%)
Current smoking	12 (20.0%)
Intraocular pressure (mmHg)	19.8 ± 5.6

Clinical assessment, OCT imaging, and standard automated perimetry were used to characterize optic nerve status. Based on the reference-standard classification, 30 (50.0%) patients had glaucomatous optic neuropathy, including 18 (30.0%) with early-stage and 12 (20.0%) with moderate-to-advanced disease. The remaining 30 (50.0%) participants were classified as nonglaucomatous. Structural abnormalities, including increased vertical cup-to-disc ratio, reduced retinal nerve fiber layer thickness, and neuroretinal rim thinning, were included among the evaluated clinical features (Table 2).

Table 2. Ophthalmic Characteristics and Reference-Standard Glaucoma Classification (N=60)

Variables	Frequency (%) / Mean ± SD
Vertical cup-to-disc ratio	0.64 ± 0.17
Average RNFL thickness (µm)	82.4 ± 15.8
Intraocular pressure (mmHg)	19.8 ± 5.6
Visual field mean deviation (dB)	−4.8 ± 4.2
Glaucomatous optic neuropathy	30 (50.0%)
Early-stage glaucoma	18 (30.0%)
Moderate-to-advanced glaucoma	12 (20.0%)
Nonglaucomatous participants	30 (50.0%)

The AI classifier correctly identified 27 of 30 patients with glaucomatous optic neuropathy and classified 26 of 30 nonglaucomatous participants correctly. There were three false-negative and four false-positive classifications. The resulting sensitivity was 90.0% (95% CI: 74.4–96.5%), specificity was 86.7% (95% CI: 70.3–94.7%), and overall diagnostic accuracy was 88.3% (95% CI: 77.8–94.2%). The positive and negative predictive values were 87.1% and 89.7%, respectively (Table 3).

Table 3. Diagnostic Performance of Explainable AI for Detecting Glaucomatous Optic Neuropathy (N=60)

Diagnostic parameter	Value
True positive	27
False positive	4
True negative	26
False negative	3
Sensitivity	90.0% (74.4–96.5%)
Specificity	86.7% (70.3–94.7%)
Positive predictive value	87.1% (71.1–94.9%)
Negative predictive value	89.7% (73.6–96.4%)

Diagnostic accuracy	88.3% (77.8–94.2%)

The ability of the proposed AI model to identify early glaucomatous changes was also assessed within the staging framework. Of the 18 patients classified as having early-stage disease, 15 were correctly identified, giving an early-stage detection sensitivity of 83.3%. All 12 patients with moderate-to-advanced glaucomatous optic neuropathy were correctly identified. Diagnostic sensitivity was numerically lower for early-stage than for more advanced disease, although the small subgroup sizes would limit the precision of this comparison (Table 4).

Table 4. Stage-Specific Sensitivity of AI-Based Glaucoma Detection

Disease classification	Total (n)	Correctly identified n (%)	Sensitivity (95% CI)
Early-stage glaucoma	18	15 (83.3%)	83.3% (60.8–94.2%)
Moderate-to-advanced glaucoma	12	12 (100.0%)	100.0% (75.8–100.0%)
All glaucoma cases	30	27 (90.0%)	90.0% (74.4–96.5%)

The interpretability component was designed to determine whether AI-generated saliency maps highlighted clinically relevant optic nerve structures. Grad-CAM was selected to visualize regions contributing to the model's predictions, particularly the optic cup, neuroretinal rim, and peripapillary retinal region. For purposes, 49 (81.7%) of 60 saliency maps were considered anatomically concordant with clinically relevant regions by masked clinical reviewers. Such concordance would indicate spatial agreement with expected anatomical features, rather than establish that the model's decision-making process was causally explained (Table 5).

Table 5. Clinical Evaluation of AI Explainability Using Grad-CAM (N=60)

Explainability measure	n (%)
Anatomically concordant saliency maps	49 (81.7%)
Nonconcordant or indeterminate saliency maps	11 (18.3%)
Concordant maps in glaucoma-positive patients (n=30)	25 (83.3%)
Concordant maps in nonglaucomatous patients (n=30)	24 (80.0%)

DISCUSSION

The present study evaluated the diagnostic performance and anatomical interpretability of an explainable AI model for identifying glaucomatous optic neuropathy among 60 patients undergoing glaucoma assessment. The model demonstrated 90.0% sensitivity, 86.7% specificity, and 88.3% overall accuracy. These findings suggest that AI-assisted assessment may support the identification of glaucomatous optic nerve abnormalities, although the relatively small sample limits the precision and generalizability of the estimates.

The diagnostic accuracy observed in our study was comparable to the findings of Bhuiyan et al., who reported 89.67% accuracy, 83.33% sensitivity, and 93.89% specificity using an automated glaucoma-suspect screening system. However, their external validation accuracy decreased to 83.54%, suggesting that diagnostic performance may vary between datasets [9]. Ajitha et al. also demonstrated the feasibility of automated glaucoma recognition from fundus photographs using deep learning, supporting the potential role of image-based classification in ophthalmic screening [10].

Lin et al. developed GlaucomaNet and reported AUROC values of 0.904 and 0.997 across two datasets, highlighting the diagnostic potential of neural networks incorporating clinically relevant image features [11]. Fan et al. subsequently evaluated transformer-based glaucoma detection using 66,715 fundus photographs from 1,636 participants and five additional external datasets containing 16,137 photographs. Their findings emphasized the relevance of model architecture and generalizability when interpreting AI performance [12]. Direct numerical comparisons with the present study remain limited because these investigations reported AUROC rather than sensitivity at an identical operating threshold.

An important observation was the lower sensitivity for early-stage glaucoma (83.3%) compared with moderate-to-advanced disease (100.0%). Hasan et al. evaluated 602 eyes using OCT-based explainable machine learning and reported AUROC values of 0.96, 0.98, and 1.00 for early, moderate, and advanced glaucoma, respectively. Their results similarly suggest that more advanced structural abnormalities may be easier to distinguish [13]. However, the complete detection of advanced cases in our study involved only 12 patients and should not be interpreted as evidence of perfect diagnostic sensitivity.

Structural measurements also provided relevant clinical context. The mean RNFL thickness was 82.4 ± 15.8 µm, while the mean vertical cup-to-disc ratio was 0.64 ± 0.17. Mariottoni et al. reported an AUROC of 0.938, sensitivity of 87.3%, and specificity of 86.4% for deep learning-assisted detection of glaucomatous structural progression from OCT measurements [14]. Mandal et al. further investigated differentiation of glaucoma progression from age-related OCT changes, reinforcing the clinical relevance of structural assessment [15]. Nevertheless, progression detection and cross-sectional glaucoma classification represent different diagnostic tasks.

Regarding explainability, 49 of 60 Grad-CAM maps (81.7%) were judged anatomically concordant, including 83.3% among glaucoma-positive patients and 80.0% among nonglaucomatous participants. Sriwatana et al. demonstrated that improved image preprocessing enhanced the interpretability and predictive performance of models estimating visual field loss, with a reported RMSE of 4.44 dB [16]. Gao et al. investigated automated vertical cup-to-disc ratio determination, supporting the anatomical relevance of optic disc and cup features [17]. Hemelings et al. additionally developed a generalizable deep learning model for glaucoma screening based on retinal image characteristics [18]. These studies support the clinical relevance of evaluating interpretable features, although saliency-map concordance alone cannot establish causal validity.

The findings must also be considered in relation to imaging technologies and population characteristics. Belghith et al. reported an adjusted AUROC of 0.92 for a three-dimensional OCT-based glaucoma classifier [19]. Katuru et al. found that OCT-based deep learning outperformed disc photograph-based models, with AUROC values of 0.90 and 0.86, respectively ($p<0.005$) [20]. These observations demonstrate that input modality may influence diagnostic performance. Rao et al., in a prospective evaluation involving 243 participants, reported 93.7% sensitivity and 85.6% specificity using an offline smartphone-based AI screening system, providing evidence relevant to resource-constrained settings [21].

The principal limitations of the present study were its small, single-centre sample, wide confidence intervals, and artificially balanced glaucoma prevalence of 50.0%. Consequently, predictive values may differ in routine screening populations. Furthermore, the provided results did not establish external validation, reader agreement, or whether the same patients were entirely excluded from model development. Larger multicentre studies with independent validation and standardized explainability assessment are required before clinical implementation in Pakistan.

CONCLUSION

Explainable artificial intelligence showed good diagnostic accuracy for glaucomatous optic neuropathy and identified anatomically relevant optic nerve regions in most Grad-CAM maps. Its lower sensitivity for early-stage disease, together with the small single-centre sample, supports further multicentre external validation before routine clinical use.

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