Multimodal Primary Open Angle Glaucoma Early Diagnosing Program Based on Clinical Process

Jingyi Ma (✉ 18644070873@126.com)

Second Affiliated Hospital of Harbin Medical University <https://orcid.org/0000-0002-7095-290X>

Bin Lv

Harbin Institute of Technology

Yuanyuan Li

Second Affiliated Hospital of Harbin Medical University

Pan Fan

Second Affiliated Hospital of Harbin Medical University

Xu Zhao

Harbin Institute of Technology

Huiping Yuan

Second Affiliated Hospital of Harbin Medical University

Yingtao Zhang

Harbin Institute of Technology

Research Article

Keywords: early primary open angle glaucoma, multimodal, deep learning, machine learning

Posted Date: April 15th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-384745/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: Glaucoma is one of the leading causes of blinding disease. Early detection can improve patients' quality of vision. Effectively identifying primary open angle glaucoma (POAG) using structural and functional examination is critical. Computer aided diagnosis of glaucoma requires multimodal data to find an accurate model for early glaucoma diagnosis.

Methods: This study collected 87 early POAG eyes, 85 suspected POAG eyes, and 129 healthy eyes from the ophthalmology department at Second Affiliated Hospital of Harbin Medical University. Retinal nerve fiber layer thickness (RNFLT), intraocular pressure (IOP) value, visual field examination parameters and age were obtained. A powerful deep learning network segmented the FP and extracted optic nerve head (ONH) features. Machine learning classifiers (MLCs) were adopted to get the final classification results and compared with the diagnosis results of glaucoma specialists and general non-glaucoma ophthalmologists.

Result: The program diagnosing early POAG, suspected POAG, and healthy eyes made overall Area Under the Curve of 0.97. Dice of optic disc and optic cup segmentation is 0.9631, 0.8435 respectively. Accuracy of the program (0.9004) is higher than general ophthalmologists (0.8195). Specificity of the program (0.9635) is higher than glaucoma specialists (0.9366).

Conclusions: The program delivers superior results in diagnosing early POAG. This study's hybrid deep learning-machine learning framework can assist with clinical decision for early POAG effectively.

Background

Glaucoma is one of the leading causes of blinding disease[1, 2]. Primary open-angle glaucoma (POAG) is characterized by chronic progressive optic nerve damage, which shows up as thinning of the retinal nerve fiber layer (RNFL) and progressive visual field damage[3, 4]. Due to the risk of irreversible blindness, early diagnosis of POAG is crucial for maintaining the visual function of glaucoma patients[5]. In developing countries, about 50%-90% patients with POAG are not aware of the symptoms from early stage[6]. However, an effective way is still needed to diagnose early POAG on a population level[7]. With the continuous development of computer technology and image segment technology, the research on using machine learning and deep learning to diagnose ocular diseases is growing[8, 9]. Previous studies have tried to classify manual features through machine learning classifiers (MLCs)[10–13]. Researchers used Deep learning (DL) methods to identify glaucoma or suspicious glaucoma through Fundus Photography (FP) and Optical Coherence Tomography (OCT). But by the time structural changes occur, the disease has progressed to a severe stage[14].

According to the European Glaucoma Society Terminology and Guidelines for Glaucoma[15], the early clinical diagnosis of POAG is mainly based on the characteristic changes of optic disc and visual field changes, which requires structural and functional examination. Structural examination relies mainly on FP and OCT[16], which is a noninvasive high-resolution biological imaging tomography of retina and provides quantitative analysis. By OCT scanning, retinal nerve fiber layer defect, retinal ganglion cells complex thinning and optic disc changing can be detected[17, 18]. Functional assessment relies mainly on Standard Automated Perimetry (SAP) ^[19], which also determines the progress of the disease[20]. Therefore, to improve the diagnosis accuracy, it is needed to combine structural and functional tests[21, 22].

The early diagnosis of glaucoma requires comprehensive consideration of auxiliary examination results from various aspects. Therefore, it is a challenge and opportunity for us to screen a quantity of high-quality data and develop a more systematic and explicable diagnosing model.

Considering the clinical process of glaucoma diagnosing, we try to develop a hybrid deep learning-machine learning framework to diagnose POAG from early stage and compare the diagnostic accuracy of glaucoma specialists and general ophthalmologists.

Methods

Study Population and Data Source

We conducted a series of studies using retrospective cases at Second Affiliated Hospital of Harbin Medical University. Cases were collected from the ophthalmology department from September 2014 to January 2021, including early POAG eyes, suspected POAG eyes, and healthy eyes. This research followed the Tenets of the Declaration of Helsinki.

All subjects should meet the following two inclusion criteria: the best corrected visual acuity $\geq 0.5\log\text{MAR}$, refractive error between + 3 and - 6 diopters, open angles on gonioscopy and reliable SAP exams, with false-positive errors, false-negative errors and fixation losses less than 15%. Patients with other retinal diseases, secondary glaucoma, other causes of optic neuropathy, history of intraocular surgery, or systemic diseases such as diabetes and hypertension were excluded.

The inclusion criteria of the early POAG group[23] were: intraocular pressure (IOP) fluctuation $\geq 8\text{mmHg}$ 24 hours before the use of IOP-lowering drugs, glaucomatous optic disc lesions (defined when cup-disc ratio > 0.6 , or cup-disc ratio asymmetry > 0.2 , focal defects of the neuroretinal rim, or disc hemorrhage), glaucomatous visual field damage[24] and the MD value is less than - 6dB.

The inclusion criteria of POAG suspects group[25]: increase of suspicious cup-to-disc ratio and/or measurement of intraocular pressure $> 21\text{mmHg}$ at least twice (after corneal thickness correction), OCT fiber layer scanning suggested RNFL thinning, no visual field lesions characteristic of glaucoma was observed. The exclusion criteria are the same as the earlier POAG group.

The inclusion criteria of the healthy group: intraocular pressure between 10-21mmHg (after corneal thickness correction), without family history of glaucoma, normal visual field, or normal optic disc.

All participants underwent a comprehensive ophthalmologic examination, including visual acuity, optometry, slit lamp microscope examination, gonioscopy, central corneal thickness, IOP test, SAP (SITA FAST 24 - 2, size III stimulus, Allergan Humphrey-750, Carl Zeiss Inc., Dublin, CA), and OCT (Spectralis, Heidelberg, Germany). The intraocular pressure of each patient was measured by non-contact tonometer 3 times and taking the average. IOP value of POAG patients was measured under IOP-lowering medication.

The fundus photograph was taken without mydriasis (Canon CR4-45 NM, Japan). All participants underwent SAP tests at least twice, with the first time as a trial. Reliable visual field examination results were selected. SAP parameters were obtained including visual field index (VFI), mean deviation (MD), and pattern standard deviation (PSD). All OCT images were performed by ophthalmologists with more than 5 years of experience in OCT scanning. No mydriasis was required. Scanning was operated with a diameter of 3.46mm around optic disc. The RNFL thickness (RNFLt) values of 6 quadrants (temporal, nasal, superior temporal, superior nasal, inferior temporal, and inferior nasal) were obtained. The interval of all examination for the same patient should not exceed 1 week.

The DL-ML Framework

Three glaucoma specialists (experience over 5 years) manually marked OD and OC in each photograph with patient information hidden. A senior specialist with over 10 years' experience in glaucoma checked afterward. A deep learning method was used to segment optic nerve head based on ophthalmologists' annotation (Fig. 1). And the DL computed the vertical cup to disc ratio (VCDR), the horizontal cup to disc ratio (HCDR), and calculated whether there was violation of the inferior > superior > nasal > temporal (ISNT) rule[26]. MLCs were used to get the final classification results. From examinations above, 15 features were used to test and verify MLCs including age, 6 sectoral RNFLt, VFI, MD, PSD, IOP value, HCDR, VCDR, and rim comparison results obtained by FP segmentation (Fig. 2).

The total software environment is Python version 3.6 (Anaconda, Inc). The segmentation framework was implemented in Python based on Keras[27], with the Tensorflow backend. We used the Adam[28] optimizer and set the initial learning rate as $1e-3$. Two NVIDIA GeForce RTX 2080 GPUs were used to support the computation with a mini-batch size of 4. We totally trained the segmentation network with 200 epochs in each folder. The classifiers were programmed in the Sklearn packages mainly. In the first stage, the main segmentation code was based on Wang's research[29]. In our paper, we used the segmentation

network of deeplabv3plus[30] with a backbone network of MobileNetV2[31]. In the encoder stage, we adopted channel attention[32] before the skip-add branch in every block. It could strengthen the important feature and weaken the bad feature for the segmentation task and then make the network focus on the more useful information. In the decoder stage, in order to make full use of the low-level information and high-level information and reduce the bad influence from encoder, we reduced the number of channels of low-level features and add channel attention after the combining the features and make the more important information to transmit the deeper module the get the better segmentation. Region of Interest (ROI) was defined as the region that include the optic disc. We located and cropped the images with the size of 512*512. ROI images were fed in the segmentation network and we trained the DLC and got the mask of ROI images. FP sets were tested with 8-fold cross validation (training: validation: test = 6:1:1). Finally, we marked the edge of mask on the original images to show the performance.

In the second stage, we trained and tested the following algorithms: Support Vector Machine (SVM)[33], Random Forest (RF), Logistic Regression (LR) and Multilayer Perceptron (MLP). More concretely, MLP had one hidden layer including 512 units. All 4 machine learning methods were tested with 5-fold cross validation.

Dice, accuracy, sensitivity, specificity, F1-score, Mathews correlation coefficient (MCC), area under receiver operator characteristic curve (AUROC) were calculated as evaluation parameters for each method[34]. The formula and meaning of these performances are explained in supplementary file1.

AUROC value equals to 1 indicates a perfect model. More specifically, AUC was calculated by averaging the performance of 5-fold cross validation. The number of correct categories was summed and divided by the total number of samples in each of the three categories to find the accuracy value. To calculate the sensitivity, specificity, F1-score, and MCC value, the data were classified as follows: group 0 which sets POAG suspects as positive samples, early POAG and healthy eyes as negative samples; group 1 which sets healthy eyes as positive samples, early POAG and POAG suspects as negative samples; group 2 which sets early POAG as positive samples, POAG suspects and healthy eyes as negative samples. Three matrices were generated, and the results were calculated by averaging the performance of these three groups. Feature importance was showed by RF.

Clinician Diagnosis

Three matrices were generated, and the results were calculated by averaging the performance of these three groups. Three glaucoma specialists (group A) and three general ophthalmologists (group B) with at least 5 years of clinic experience were chosen to diagnose all cases. Complete examination results with clinical information hidden were exposed to each group. Cases were required to be diagnosed into three results: 1 (healthy eye), 2 (POAG suspects), 3 (early POAG). And the average accuracy of each group was calculated according to the diagnostic test. At the same time, we compared the performance with MLCs.

Statistical Analysis

Differences among the three groups were compared by Welch ANOVA performed by SPSS (version 22.0). The characteristics were recorded as mean $\pm$ standard deviation, and P value < 0.05 was considered statistically significant.

Results

A total of 301 eyes of 180 patients were enrolled in the study. Table 1 summarizes the demographic characteristics of patients while Table 2 shows the statistical characteristics of the subjects' data. Each group has 15 features, and each feature except age is significantly different among the three groups ($P < 0.05$). The value of RNFLT-T, VFI, and MD is not significantly different between healthy group and suspected group. Figure 3 shows further pairwise comparisons of these certain features.

Dice values of optic disc and optic cup recognition are 0.9631 and 0.8745 respectively. Figure 4 shows the ROC curve of four MLCs, and Table 2 shows the other evaluation parameters. SVM gets top AUC value (0.970), the best accuracy, F1score and MCC result. The diagnostic accuracy of glaucoma specialists is 0.9192, and that of general ophthalmologists was 0.8195. The

diagnostic accuracy value of SVM, LR, RF, MLP (0.9004, 0.8903, 0.8704, 0.8306) was lower than that of glaucoma specialists, but still higher than that of general ophthalmologists. Specificity of SVM (0.9635) and RF (0.9541) is higher than glaucoma specialists (0.9366). The performance of ophthalmologists diagnosing is summarized in Table 2.

Figure 5 shows the feature importance. The top six features: RNFLt-TI (0.155), RNFLt-TS (0.143), RNFLt-NS (0.099), VCDR (0.099), HCDR (0.076), PSD (0.067) made most contribution to the algorithm.

Table 1
Demographic characteristics of patients

	Early POAG	POAG suspects	Healthy eye
Subjects	45	66	69
Eyes	87	85	129
Gender (% female)	42.53	42.35	58.14

Table 2
Statistical Characteristics of the Subjects' Data

	Early POAG (n = 87)	POAG suspects (n = 85)	Healthy eye (n = 129)	P Value*
Age, Mean (SD), y	39.25 ± 14.98	39.48 ± 16.36	39.88 ± 13.83	0.949
IOP, Mean (SD), mmHg	18.33 ± 4.67	18.28 ± 3.62	17.06 ± 2.98	0.010
MD, Mean (SD), dB	-4.04 ± 1.33	-2.90 ± 1.94	-2.51 ± 1.72	0.001
PSD, Mean (SD), dB	3.73 ± 1.77	2.11 ± 1.24	1.76 ± 0.66	0.001
VFI, Mean (SD), %	0.94 ± 0.04	0.97 ± 0.03	0.98 ± 0.02	0.001
cpRNFL thickness, Mean (SD), µm				
Temporal	59.49 ± 16.17	78.49 ± 18.80	82.98 ± 16.06	0.001
Nasal	47.81 ± 8.74	57.12 ± 16.80	70.96 ± 14.83	0.001
Temporal Superior	86.53 ± 29.6	110.93 ± 23.80	144.32 ± 18.86	0.001
Nasal Superior	66.75 ± 30.22	91.51 ± 25.57	119.03 ± 23.08	0.001
Temporal Inferior	88.98 ± 26.52	126.92 ± 21.78	154.29 ± 19.78	0.001
Nasal Inferior	75.63 ± 23.21	94.51 ± 24.75	117.52 ± 4.41	0.001
CDR computed by DLCs, Mean (SD)				
HCDR	0.75 ± 0.06	0.65 ± 0.10	0.58 ± 0.12	0.001
VCDR	0.75 ± 0.07	0.63 ± 0.09	0.54 ± 0.12	0.001
Rim width comparison (%)				
I < S	67.82	44.71	49.10	0.001
S < T	26.44	29.41	25.58	0.490
IOP, intraocular pressure; MD, mean deviation; PSD, pattern standard deviation; VFI, visual field index; cpRNFL, circumpapillary retinal nerve fiber layer; ONH, optic nerve head; HCDR, horizontal cup to disc ratio; VCDR, vertical cup to disc ratio. *Welch ANOVA, p < 0.05 means statistically different.				

Table 3
Performance of Different Machine Learning Classifiers

	Accuracy	Sensitivity	Specificity	F1-score	Sensitivity at 80%specificity	Sensitivity at 90%specificity	AUC	MCC
SVM	0.9004	0.8709	0.9635	0.8926	0.9529	0.8235	0.970	0.8440
RF	0.8903	0.8693	0.9541	0.8855	0.8941	0.8000	0.964	0.8303
MLP	0.8704	0.8760	0.9280	0.8651	0.8353	0.8353	0.962	0.8003
LR	0.8306	0.8029	0.9258	0.8203	0.8235	0.7176	0.952	0.7355
general ophthalmologists	0.8195	0.9118	0.8373	NA	NA	NA	NA	NA
glaucoma specialists	0.9192	0.9486	0.9366	NA	NA	NA	NA	NA
SVM, Support Vector Machine; RF, Random Forest; MLP, Multilayer Perceptron; LR, Logistic Regression; AUC, area under the receiver operating characteristic curve; MCC, Mathews correlation coefficient; NA, not applicable.								

Discussion

Glaucoma has become the leading cause of blinding disease. Early diagnosis of POAG is crucial for maintaining visual function. In a research of rural areas of East China[35], more than 90% of POAG cases are undetected in early stage, and nearly 30% of subjects with glaucoma are blind in at least one eye. Therefore, we try to develop a model to help primary hospitals diagnose POAG from early stage thoroughly. In our study, we introduce a diagnosis model based on clinical process to distinguish early POAG, POAG suspects and healthy eyes, and compare the diagnosis results of clinicians.

Previous attempts have been made to combine structure and function to detect POAG. In the studies of Raza et al.[36] and Leonardo et al.[37], researchers combined OCT and SAP results, and the results obtained were better than that obtained by analyzing OCT results alone, indicating that structure and function combining models show better diagnostic results. Kim et al. [38] applied random forest to detect glaucoma. They collected patient's age, IOP, Central corneal thickness (CCT), average RNFLT, Glaucoma Hemifield Test (GHT), MD, and PSD value and trained the MLCs and got AUC of 0.979. However, the inclusion of advanced POAG patients in this study may significantly improve the accuracy of the results. A thorough examination is important to recognize POAG from early stage. Therefore, in our study, we used image and data features to make a DL-ML framework to diagnose early POAG for the first time and obtained satisfactory diagnostic results.

Figure 6 shows several examples of good and poor performance of segmentation. It suggests that small cup or notch may result in poor segmentation results. Despite the performance of DLCs segmentation was credible which gave relatively accurate measurement of ONH features.

Our study has other strengths. First, due to the black box effects, previous studies are hard to explain to clinicians. In our study, feature importance can be provided by RF, which make the model more understandable to ophthalmologists. Feature importance showed by RF has high consistence with clinic diagnosing. Patients with greater VCDR have greater risk of early stage POAG[39]. According to the reported studies[40, 41], superior and inferior part of the RNFL defect often occurs in the early POAG because of the anatomy of the retinal nerve fiber. It is proved that the importance of RNFL local thickness features shows same value of POAG clinical manifestation[42]. Moreover, Previous studies have found that during the occurrence and development of early POAG, the change of MD value of visual field is relatively stable, while RNFL appears relatively rapid thinning[43]. PSD is more valuable for the diagnosis of early POAG as an indicator for the evaluation of local visual field defects[44]. Therefore, RNFL thickness related features and PSD values are higher than those of MD in the early clinical diagnosis of POAG.

Second, studies have shown that high myopia is one of the high-risk factors for POAG[45]. In our study, we excluded patients with high myopia and avoided RNFL thinning due to refractive factors, thus obtaining more reliable results.

The diagnostic specificity of SVM and RF is higher than glaucoma specialists. According to Quigley's opinion[46], it is more important to use a high specificity test to screen for glaucoma in developing countries. In addition, the diagnostic accuracy of general ophthalmologists (0.8195) was lower than MLCs. Interestingly, studies comparing diagnosing ability between AI and ophthalmologists often shows better performance of AI, which are similar to our results[37, 47]. Therefore, we can predict that in the future application of machine diagnosis, it can help general ophthalmologists and primary hospitals to make more accurate prediction and avoid missed diagnosis or misdiagnosis to some extent.

One of the limitations is that this study recruited Chinese patients only, and the number of training set is relatively small. Further study with larger sample size is required. In addition, POAG mainly damages Retinal ganglion cells (RGCs), and RGC is most abundant in macular area. Another limitation of our study is that we used RNFLt of OCT only to diagnose early POAG. Previous studies have shown that visual field changes occur earliest within the 5-degree range of fixed point of view in glaucoma patients, suggesting that macular area is the affected site of early glaucoma[48]. SD-OCT combined with RGC algorithm can accurately measure the thickness change of ganglion cell layer in macular area. Since the measured location is macular area, the influence of optic disc structure abnormality on the thickness measurement of RNFL can be avoided, and the loss of RGCs can be more objectively displayed. The latest OCT program can independently detect the thickness of Ganglion Cell Layer (GCL) of retina[49]. Better results may be obtained by using the GCL thickness training model.

Conclusions

In summary, we presented a system combining DL method and MLCs based on clinical process. It performed excellently in differentiating early stage POAG, POAG suspects and healthy eyes. All four MLCs outperform general ophthalmologists in diagnosing POAG. In early POAG, POAG suspects and healthy people, VCDR, RNFLt-TI, RNFLt-TS, HCDR, PSD value play more important roles in the AI model. Although it remains several limitations, it can be helpful in the clinical practice. A thorough diagnosis model of early POAG can be established and help ophthalmologists in the primary eye care setting.

Abbreviations

CDR: cup to disc ratio

DL: Deep learning

FP: Fundus Photography

IOP: intraocular pressure

LR: Logistic Regression

MD: mean deviation

MLCs: machine learning classifiers

MLP: Multilayer Perceptron

ONH: optic nerve head

OCT: Optical Coherence Tomography

POAG: primary open angle glaucoma

PSD: pattern standard deviation

RF: Random Forest

RNFLt: Retinal nerve fiber layer thickness

SAP: standard Automated Perimetry

SVM: Support Vector Machine

VFI: visual field index

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the Second Affiliated Hospital of Harbin Medical University.

Consent for publication

Written informed consent for publication was obtained from all participants.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

We declared that materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

Funding

Not applicable.

Author's Contributions

Jingyi Ma, Yuanyuan Li, and Pan Fan collected subjects and made FP marking. Bin Lv, Xu Zhao made the segmentation and final classification of the algorithm. Jingyi Ma, Bin Lv, Huiping Yuan, Yingtao Zhang finished the writing, reviewing and editing. All authors have read and agreed to the published version of the manuscript.

Acknowledgements

We are deeply grateful to Jing Bosun, Fang Cheng, Bin Bin Yang, Lin Gao, and Yaxuan Xue for their support in diagnosing part of this study. We thank all researchers and reviewers who have contributed to this study.

Authors' information

Affiliations

Jingyi Ma, Yuanyuan Li, Pan Fan, and Huiping Yuan:

The Department of Ophthalmology, the Second Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang Province, 150086, China

Bin Lv, Xu Zhao, Yingtao Zhang:

School of Computer Science and Technology, Harbin Institute of Technology, Harbin, Heilongjiang Province, 150001, China

References

1. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90:262–7.
2. Tham Y-C, Li X, Wong T-Y, Quigley HA, Aung T, Cheng C-y. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014;121:2081–90.
3. Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet*. 2004;363:1711–20.
4. Shaikh Y, Yu F, Coleman A. Burden of undetected and untreated glaucoma in the United States. *Am J Ophthalmol*. 2014;158:1121–9.e1121.
5. Moyer VA. Screening for glaucoma: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2013;159:484–9.
6. Leite MT, Sakata L, Medeiros F. Managing glaucoma in developing countries. *Arq Bras Oftalmol*. 2011;74:83–4.
7. Newman-Casey PA, Verkade AJ, Oren G, Robin AL. Gaps in glaucoma care: a systematic review of monoscopic disc photos to screen for glaucoma. *Expert Rev Ophthalmol*. 2014;9:467–74.
8. Buch VH, Ahmed I, Maruthappu M. Artificial intelligence in medicine: current trends and future possibilities. *Br J Gen Pract*. 2018;68:143–4.
9. Schmidt-Erfurth UM, Sadeghipour A, Gerendas B, Waldstein SM, Bogunović H. Artificial intelligence in retina. *Prog Retin Eye Res*. 2018;67:1–29.
10. Miri MS, Abramoff M, Kwon YH, Sonka M, Garvin MK. A machine-learning graph-based approach for 3D segmentation of Bruch's membrane opening from glaucomatous SD-OCT volumes. *Med Image Anal*. 2017;39:206–17.
11. Ting DSW, Cheung CY, Lim G, Tan G, Nguyen DQ, Gan A, Hamzah H, Garcia-Franco R, Yeo IYS, Lee S-Y, et al. Development and Validation of a Deep Learning System for Diabetic Retinopathy and Related Eye Diseases Using Retinal Images From Multiethnic Populations With Diabetes. *JAMA*. 2017;318:2211–23.
12. Devalla SK, Sreedhar RPK, Perera BK, Mari SA, Chin JM, Tun KS, Strouthidis TA, Thiery NG, Girard AH. MJA: DRUNET: a dilated-residual U-Net deep learning network to segment optic nerve head tissues in optical coherence tomography images. *Biomed Opt Express*. 2018;9:3244–65.
13. Asaoka R, Murata H, Hirasawa K, Fujino Y, Matsuura M, Miki A, Kanamoto T, Keda Y, Mori K, Iwase A, et al. Using Deep Learning and Transfer Learning to Accurately Diagnose Early-Onset Glaucoma From Macular Optical Coherence Tomography Images. *Am J Ophthalmol*. 2019;198:136–45.
14. Ting D, Peng L, Varadarajan A, Keane P, Burlina P, Chiang M, Schmetterer L, Pasquale L, Bressler N, Webster D, et al. Deep learning in ophthalmology: The technical and clinical considerations. *Prog Retin Eye Res*. 2019;72:100759.
15. European Glaucoma Society Terminology and Guidelines for Glaucoma. 4th Edition - Chap. 2: Classification and terminology Supported by the EGS Foundation: Part 1: Foreword; Introduction; Glossary; Chap. 2 Classification and Terminology. *Br J Ophthalmol*. 2017; 101:73–127.
16. Hood D, Slobodnick A, Raza AS, Moraes CGD, Teng CC, Ritch R. Early glaucoma involves both deep local, and shallow widespread, retinal nerve fiber damage of the macular region. *Invest Ophthalmol Vis Sci*. 2014;55:632–49.
17. Jung J, Seo JH, Kang MS, Shin J. Comparison of glaucoma diagnostic ability of ganglion cell-inner plexiform layer according to the range around the fovea. *BMC Ophthalmol*. 2019;19:270.
18. Daneshvar R, Yarmohammadi A, Alizadeh R, Henry S, Law SK, Caprioli J, Nouri-Mahdavi K. Prediction of Glaucoma Progression with Structural Parameters: Comparison of Optical Coherence Tomography and Clinical Disc Parameters. *Am J Ophthalmol*. 2019;208:19–29.
19. Z W, LJ S, FB D, A D, FA M. Frequency of Testing to Detect Visual Field Progression Derived Using a Longitudinal Cohort of Glaucoma Patients. *Ophthalmology*. 2017;124:786–92.
20. Hodapp E, Parrish RK, Anderson DR. Clinical decisions in glaucoma. St Louis: Mosby-Year Book; 1993.

21. Mwanza J-C, Warren JL, Budenz DL. Utility of combining spectral domain optical coherence tomography structural parameters for the diagnosis of early Glaucoma: a mini-review. *Eye Vis.* 2018;5:9.
22. Blumberg DM, Dale E, Pensec N, Cioffi GA, Radcliffe N, Pham M, Al-Aswad L, Reynolds M, Ciarleglio A. Discrimination of Glaucoma Patients From Healthy Individuals Using Combined Parameters From Spectral-domain Optical Coherence Tomography in an African American Population. *J Glaucoma.* 2016;25:e196–203.
23. Thompson AC, Jammal AA, Berchuck SI, Mariottoni EB, Medeiros FA. Assessment of a Segmentation-Free Deep Learning Algorithm for Diagnosing Glaucoma From Optical Coherence Tomography Scans. *JAMA Ophthalmology.* 2020;138:333–9.
24. Heatley GA: Automated Static Perimetry, Second Edition. *Arch Ophthalmol.* 1999; 117:1671.
25. Jamous KF, Kalloniatis M, Hennessy MP, Agar A, MBIostat AH, Zangerl B. Clinical model assisting with the collaborative care of glaucoma patients and suspects. *Clin Experiment Ophthalmol.* 2015;43:308–19.
26. Phene S, Dunn RC, Hammel N, Liu Y, Krause J, Kitade N, Schaekermann M, Sayres R, Wu DJ, Bora A, et al: Deep Learning and Glaucoma Specialists: The Relative Importance of Optic Disc Features to Predict Glaucoma Referral in Fundus Photos. *Ophthalmology.* 2019; 126.
27. Chollet F: *Keras: The Python Deep Learning library.* Astrophysics Source Code Library; 2018.
28. Kingma D, Ba J. Adam: A Method for Stochastic Optimization. *Comput Sci.* 2014.
29. Wang S, Yu L, Yang X, Fu C-W. Patch-Based Output Space Adversarial Learning for Joint Optic Disc and Cup Segmentation. *IEEE Trans Med Imaging.* 2019;99:1–1.
30. Chen L-C, Zhu Y, Papandreou G, Schroff F, Adam H: Encoder-Decoder with Atrous Separable Convolution for Semantic Image Segmentation. *European Conference on Computer Vision.* 2018:833–851.
31. Sandler M, Howard A, Zhu M, Zhmoginov A, Chen L-C. *MobileNetV2: Inverted Residuals and Linear Bottlenecks.* 2018.
32. Hu J, Shen L, Sun G, Albanie S: Squeeze-and-Excitation Networks. *IEEE Transactions on Pattern Analysis and Machine Intelligence.* 2017; PP.
33. Suykens JAK. Support Vector Machines: A Nonlinear Modelling and Control Perspective. *Eur J Control.* 2001;7:311–27.
34. Yousefi S, Goldbaum M, Balasubramanian M, Jung T-P, Zangwill LM, Liebmann JM, Girkin CA, Bowd C. Glaucoma progression detection using structural retinal nerve fiber layer measurements and functional visual field points. *IEEE Trans Biomed Eng.* 2014;61:1143–54.
35. Song W, Shan L, Cheng F, Fan P, Zhang L, Qu W, Zhang Q, Yuan H. Prevalence of glaucoma in a rural northern china adult population: a population-based survey in kailu county, inner mongolia. *Ophthalmology.* 2011;118:1982–8.
36. Raza AS, Zhang X, Moraes CGD, Reisman CA, Liebmann JM, Ritch R, Hood D. Improving glaucoma detection using spatially correspondent clusters of damage and by combining standard automated perimetry and optical coherence tomography. *Invest Ophthalmol Vis Sci.* 2014;55:612–24.
37. Shigueoka L, Vasconcellos JPCd, Schimiti RB, Reis ASC, Oliveira GOd, Gomi E, Vianna JR, Lisboa RDdR, Medeiros FA, Costa VP. Automated algorithms combining structure and function outperform general ophthalmologists in diagnosing glaucoma. *PLoS One.* 2018;13:e0207784.
38. Kim SJ, Cho KJ, Oh S. Development of machine learning models for diagnosis of glaucoma. *PLoS One.* 2017;12:e0177726.
39. C S, CG DM, Prata IF, Ritch TS, JM R. L: Risk calculation variability over time in ocular hypertensive subjects. *J Glaucoma.* 2014;23:1–4.
40. Pomorska M, Krzyżanowska-Berkowska P, Misiuk-Hojło M, Zając-Pytrus H, Grzybowski A. Application of optical coherence tomography in glaucoma suspect eyes. *Clin Exp Optom.* 2012;95:78–88.
41. Caprioli J. Discrimination between normal and glaucomatous eyes. *Invest Ophthalmol Vis Sci.* 1992;33:153–9.
42. Bowd C, Zangwill LM, Berry CC, Blumenthal EZ, Vasile C, Sanchez-Galeana C, Bosworth CF, Sample PA, Weinreb RN. Detecting early glaucoma by assessment of retinal nerve fiber layer thickness and visual function. *Invest Ophthalmol Vis Sci.* 2001; 42.

43. Medeiros F, Zangwill LM, Bowd C, Mansouri K, Weinreb RN. The Structure and Function Relationship in Glaucoma: Implications for Detection of Progression and Measurement of Rates of Change. *Invest Ophthalmol Vis Sci*. 2012;53:6939–46.
44. Park SC, Moraes CGD, Teng CCW, Tello C, Liebmann JM, Ritch R. Initial parafoveal versus peripheral scotomas in glaucoma: risk factors and visual field characteristics. *Ophthalmology*. 2011;118:1782–9.
45. Marcus MW, Vries MMd, Montolio FGJ, Jansonius N. Myopia as a Risk Factor for Open-Angle Glaucoma: A Systematic Review and Meta-Analysis. *Ophthalmology*. 2011;118:1989–94..e1982.
46. Quigley HA. Current and Future Approaches to Glaucoma Screening. *J Glaucoma*. 1998;7:210–20.
47. Yang J, Zhang C, Wang E, Chen Y, Yu W. Utility of a public-available artificial intelligence in diagnosis of polypoidal choroidal vasculopathy. *Graefes Arch Clin Exp Ophthalmol*. 2020;258:17–21.
48. Heijl A, Lund L. The frequency distribution of earliest glaucomatous visual field defects documented by automatic perimetry. *Acta Ophthalmol (Copenh)*. 1984;62:658–64.
49. Garcia-Medina JJ, Del-Rio-Vellosillo M, Palazon-Cabanes A, Pinazo-Duran MD, Zanon-Moreno V, Villegas-Perez MP. Glaucomatous Maculopathy: Thickness Differences on Inner and Outer Macular Layers between Ocular Hypertension and Early Primary Open-Angle Glaucoma Using 8×8 Posterior Pole Algorithm of SD-OCT. *J Clin Med*. 2020;9:1503.

Figures

Figure 1

Deep learning system for segmentation of fundus photographs. ASPP, atrous spatial pyramid pooling; Conv, convolution.

Figure 2

An overall framework of the diagnosing system. SVM, Support Vector Machine; RF, Random Forest; LR, Logistic Regression; MLP, Multilayer Perceptron.

Figure 3

Multiple comparisons. Abbreviations: RNFLT-T, temporal retinal nerve fiber layer thickness; MD, mean deviation; VFI, visual field index. *** Significant at 1% level.

Figure 4

ROC curves for different MLCs.

Feature Importance

Figure 5

Feature importance showed by Random Forest. Abbreviations: IOP, intraocular pressure; MD, mean deviation; PSD, pattern standard deviation; VFI, visual field index; cpRNFLT, circumpapillary retinal nerve fiber layer; HCDR, horizontal cup to disc ratio; VCDR, vertical cup to disc ratio; S, superior; T, temporal.

Figure 6

Examples of Segmentation. A: Good Performance, B: Poor performance. Each row presents one example. The green and blue contours indicate the boundary of OC and OD, respectively. DLCs, deep learning classifiers.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplementary1.docx](#)