Feasibility of Early Detection for Retinal Nerve Fiber Layer Defect with Digital Fundus Image in Glaucoma Patients

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ABSTRACT

Due to the fact that retinal nerve fiber layer defect in Glaucoma is not perceived by patients at early stage, a technique to monitor the progress of retinal nerve fiber layer defect is imperative. Currently, the tools or parameters, such as standard automated Perimetry and the cup-to-disc ratio derived from fundus images, can only screen out the glaucomatous patients whose ganglion cells in optic nerve have already lost about 50%. It would be meaningful to clinicians if the loss of optic nerve could be quantified in the early stage efficiently. For this purpose, the fundus images, which has a 45° field of view and encircle most of the optic nerve, should be leveraged and a deep learning-based algorithm should be developed to measure the RNFL defect. In this paper, the feasibility of early detection for retinal nerve fiber layer defect with fundus images in glaucoma patients is demonstrated. We built up a deep learning model to detect glaucomatous patients from healthy subjects with fundus images. The accuracy of the deep learning model for classification of Glaucoma patients was 90% and it could be seen that the model treated the features relevant to the retinal nerve fiber layer defect as the essential ones for discriminating glaucoma patients. From this experiment, it is promising to measure the severity of RNFL defects and locate them efficiently with fundus images and deep learning algorithms. Future studies would focus on development of an accurate deep learning-based algorithm, which may take visual field data as reference or labels, for retinal nerve fiber layer defect quantification.

Keywords: *Glaucoma, Fundus Image, Retinal Nerve Fiber Layer, Convolutional Neural Network.*

1. INTRODUCTION

Glaucoma, characterized by the progressive optic neuropathy, is the second leading cause of irreversible blindness [1, 2]. According to the research [3], the Glaucoma prevalence was 3.54% and its population would increase to 111.8 million in 2040. Particularly, Asia would be the top three areas affected the most then. The blindness from glaucoma, however, is preventable by early detection and treatments [4], which would further relieve the burden on national health expenditure. Yet promising, the development of techniques for early detection of Glaucoma is challenging in terms of the evaluation of the early optic nerve defect. To ameliorate and further prevent the blindness led by Glaucoma, a feasible and reliable technique for early detection of Glaucoma is still imperative.

In clinics, Perimetry, namely visual field test, and optical imaging are the major techniques to evaluate the functional and structural integrity of the optic nerve, serving as the basis for the diagnosis of Glaucoma. Standard Automated Perimetry (SAP), a type of Perimetry, is the gold standard for measuring the function of optic nerve. It is crucial for the diagnosis of Glaucoma due to its direct revelation of whether specific part of optic nerve still reacts to the incoming lights from the Perimetry or not [5]. Despite its decisive role in the diagnosis, it fails to reflect the structural changes, which precedes the functional loss, to the optic nerve, specifically the retinal nerve fiber layer (RNFL) [6]. Therefore, the optic imaging techniques, including optical coherence tomography (OCT) and fundus photography, would take an essential role in detecting the structural change, which is the sign for the early stage of Glaucoma. With the advent of OCT, the cross-sectional images of the retina can be retrieved and the thickness of the RNFL would be able to quantize accordingly [7]. While providing those benefits, OCT has a comparatively narrower field of view than fundus photography. That is, fundus photography would provide ophthalmologists with a more comprehensive view of the structural defect of RNFL. Considering the uncertainty of the region where the RNFL defect would occur, fundus photography, hence, would be the better option for early detection of Glaucoma than OCT.

Fundus photography would act as a feasible and effective way to detect the early defect of the RNFL. Common digital fundus image (DFI), derived from fundus photography, has a field of view (FOV) about 45° and covers the most essential anatomical structures, including optic disc (OD) and macula [8]. With these two in the FOV, it could be inferred that most of RNFL appears in fundus image as well. Traditionally, for diagnosis of Glaucoma in clinics, an indicator, called cup-to-disc ratio (C/D Ratio), is subjectively derived by ophthalmologists from a fundus image. A normal cup-to-disc is about 0.3 and it would suggest a greater possibility of Glaucoma as its value increase. Although it served as a widely used measurement, it had a greater inter-rater and intra-rater variability [9, 10]. Moreover, it failed to reflect the early development of Glaucoma in fundus image, whose RNFL gradually loses. Besides C/D Ratio, Inferior Superior Nasal Temporal (ISNT) rule, inferior-superior-nasal-temporal rule in specific, also helps ophthalmologists measure the change of the region between the optic disc and optic cup (OC) [11]. However, it suffered from the same problem encountered in application of C/D Ratio, unable to detect the early development of Glaucoma. To address this problem, a indicator measuring RNFL in fundus image should be established. A few studies attempted to measure the fundus texture in image, but they did not correspond to the loss of RNFL [12]. Furthermore, since it not easy to detect all the loss of RNFL in fundus image by human eye due to various image quality, other ground truth for loss of RNFL, such as visual field data, and a more robust algorithm should be leveraged to quantify RNFL.

Deep Neural Network (DNN), a contemporary modeling technique in computer vision, could help quantize the integrity of the retinal nerve fiber layer through supervised learning. By directly learning how to bridge the gap between input images and corresponding labels, convolutional neural network (CNN) has achieved state-of-art results in image classification [13]. As mentioned before, a quantifiable method for RNFL is in need. With the advantage of CNN, it would be possible to discover RNFL in fundus image given the appropriate ground truth is provided. Visual field data, indicating the location of RNFL defect, would take an essential role as the ground truth for RNFL defect in fundus image. Nevertheless, there is few researches on mapping these two categories of data and building a model to learn the RNFL loss in fundus image supervised by visual field data.

This paper was organized as follows. The related researches were discussed in section 2. Section 3 describes the proposed neural network architecture and how to detect Glaucoma with RNFL in DFIs. About the experimental results were revealed in Section 4. Conclusions about this paper were given in the last Section.

2. LITERATURE REVIEW

In clinics, the relationship between optic disc and cup in DFIs is one of the assessment that could screen out Glaucomatous patients, there were five indexes to describe that relationship, C/D Ratio, ISNT rule, Disc damage likelihood Scale (DDLS) and Glaucoma risk index (GRI). Haleem, Muhammad Salman, et al[14] carried out critical estimations of existing automatic extraction approaches based on the features comprising of C/D Ratio, RNFL, and PPA (Parapapillary Atrophy) among others.

C/D Ratio is the most common approach used by ophthalmologists to screen out Glaucomatous patients with fundus images. However, it is too difficult to annotate the OD and OC. Thomas proposed an algorithm based on mathematical morphology for detecting the OD and OC [15]. OD is the brightest region in DFIs. They used thresholding with morphological techniques to detect the OD. First, they found the position approximately. Secondly, extract the contours via the watershed transformation. However, it was not able to handle all the DFIs especially in low contrast.

Issa et al.[16] presented an adaptive thresholding technique for segmentation of OD and OC based on the features extraction from DFIs. Optic nerve head region is in both red and green channel. Hence, the image was split into red and green channel. Threshold was determined from the preprocessed image after the smoothed histogram. OD/OC was segmented from the red channel and green channel respectively. The proposed algorithm achieved the accuracy of 92.06% and each image took around 3.313 seconds, but this was not workable for all DFIs. Authors mentioned if the images were in the presence of PPA, the segmentation performance would decrease because only brighter pixels would be threshold.

Recent years, DNN became more and more popular, especially CNN. Zilly et al. [17], they use an ensemble learning based architecture to learn the convolutional filters and proposed a novel entropy sampling method to reduce its computational effort. They only used around 50 images to train the CNN model. Experimental result revealed that under the same number of samples, entropy sampling achieved superior result to uniform sampling.

In general, the more images for training, the better performance of CNN models. However, Raghavendra only used 1,462 DFI and the eighteen-layer CNN to their proposed CAD, achieved accuracy of 98.13%, sensitivity of 98% and specificity of 98.3%[18]. Experimental results demonstrate the robustness of the system, which can be used as a supplementary tool for the clinicians to validate their decisions.

Before the visual field defect begins, the ganglion cells have already loss about 50%. Hence, the estimation of the changes in RNFL can be referred to a method for the

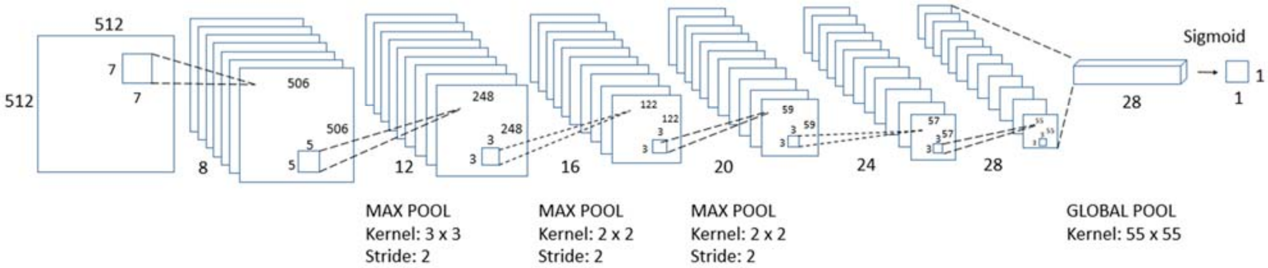

Fig. 1 Proposed systematic neural network architecture

early diagnosis and treatment of glaucoma [19]. They are very expensive by using OCT and GDx offering RNFL assessment. Furthermore, they require very careful interpretation by experts. Last but not least, these imaging techniques are not feasible solution for mass screening and routine checkup of glaucoma in peripheral settings. RNFL and retina cup enlargement are the early signs that can be found on the DFI as well. As the result, fundus images provide a practical solution for accurate and efficient glaucoma risk assessment [20].

In 2017, Watanabe et al. proposed a multi-steps solution to detect RNFL, included Gabor filter, clustering, and adaptive thresholding [21]. The number of false positives was too large because of too many rules. They used the deep convolutional neural network with deconvolutional layer to train the model to detect RNFL regions. It revealed that CNN was able to learn the features and achieved almost the same effectiveness for RNFL detection as by the means of SVM.

This paper aims to demonstrate the feasibility of the quantification of RNFL defect in fundus images with deep learning techniques. For the details about the proposed method would be discussed in the next chapter.

3. METHODOLOGY

3.1 Training Dataset

High-Resolution Fundus (HRF) Image Database [22] was chosen as the training dataset. There were 15 images of healthy patients, 15 images of patients with diabetic retinopathy (DR) and 15 images of glaucomatous patients. In this study, only the images of healthy and glaucomatous patients were included for further modeling and analysis.

3.2 Model Architecture

To discover features relevant to the diagnosis of Glaucoma, convolutional neural network (CNN) is used. The structure of CNN is shown in Fig. 1, mainly consisting of 6 convolution blocks. Each convolution block is a convolution kernel followed by an activation layer. ReLU is the activation function in this case. Moreover, max pooling layers are inserted following the first 3 convolution blocks to reduce the dimensionality and extract high-level features. To generate the logits from this CNN, global average pooling layer is used to condense the output from last convolution block and then a 1x1 convolution kernel is applied. Then, the logits would be transformed into class probability by sigmoid function.

As the main purpose is to investigate the feasibility of the quantification of RNFL, a visualization technique for CNN is applied to show whether a well-trained CNN would take RNFL defect as an indicator for Glaucoma. The implementation of this visualization technique follows the class activation map proposed by Zhou et al [23]. This visualization is achieved by calculating the weighted sum of the feature maps rendered by the last convolution block. The weights of each feature map are the importance of each global averaged feature to the class. In this case, these suggest the importance for diagnosis of Glaucoma.

3.3 Evaluation Metrics

To determine the performance of the trained model in this paper, four parameters were used: accuracy (ACC), specificity (SP), sensitivity (SE) and precision (PRC). The mathematical equation for each metric is described in the following:

$$\textbf{Sensitivity (SE)} = TP / ((TP+FN)) \quad (1)$$

$$\textbf{Specificity (SP) = TN / (TN+FP))} \quad \textbf{(2)}$$

$$\textbf{Accuracy (ACC) = (TP+TN) / (TP+FN+TN+FP))} \quad \textbf{(3)}$$

$$\textbf{Precision (PRC) =TP / (TP+FP)} \quad \textbf{(4)}$$

3.4 Training and Testing Details

For all 30 images included, 20 images were used for training, 10 images drawn from healthy patients and the others from glaucomatous patients. The rest of images were used for testing and investigating the possible features for diagnosis of Glaucoma.

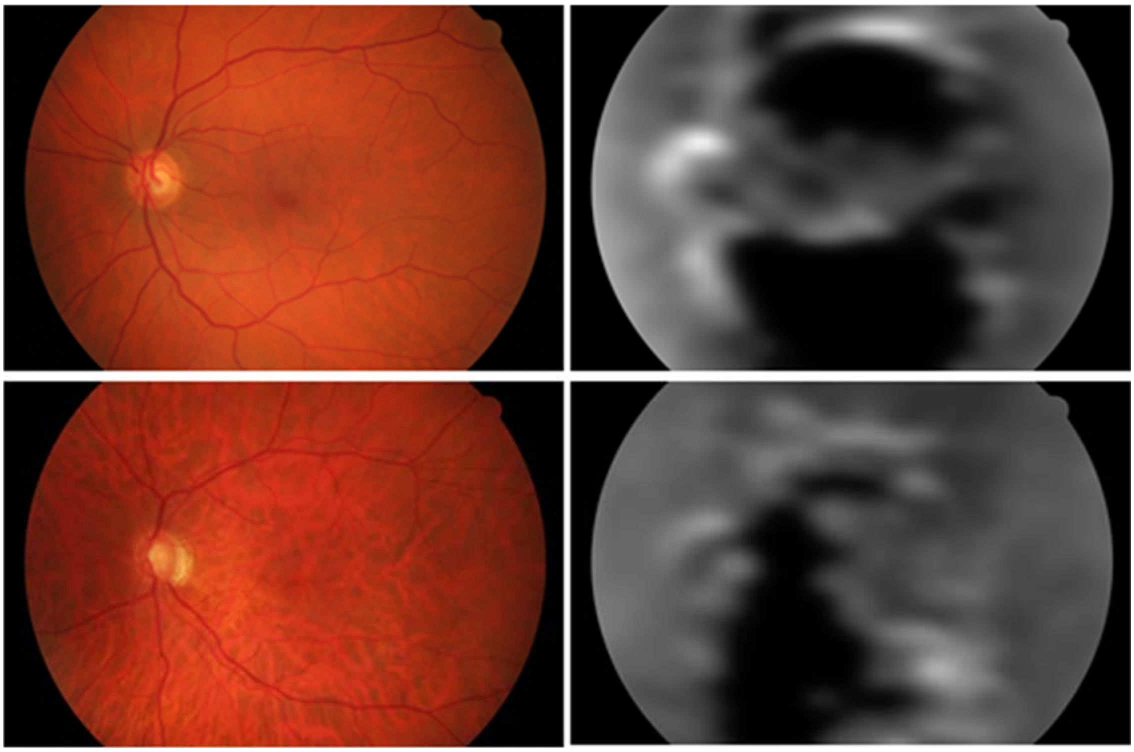

Fig. 2 Pairs of the fundus image and its corresponding class activation map

During training, the parameters were tuned to prevent the model from overfitting. For that purpose, learning rate, dropout rate and L2-regularization weight were set to 0.001, 0.3 and 0.00005 respectively. Moreover, Adam optimizer was used for updating all the weights in the model.

As to testing, ACC, SE, SP and PRC were calculated from the predictions of the rest 10 images. The results is shown in the next section.

4. EXPERIMENTAL RESULT

Table 1: Model Performance.

ACC	SP	SE	PRC
90%	80%	100%	83.33%

SE: Sensitivity, SP: Specificity, ACC: Accuracy, PRC: Precision

The result of model performance is shown in Table [Table 1]. The overall testing accuracy (ACC) is 90%, and specificity (SP) and sensitivity (SE) are 80% and 100% respectively. In testing, 5 images from glaucomatous patients were correctly classified, but there was 1 image from healthy subject misclassified as glaucoma, resulting in the lower SP.

Although this trained model may not fully learn what the general features of glaucoma are in fundus images due to lack of large dataset, it is still promising to investigate how this model acquired the general features among the training and testing images. Two pairs of the fundus image and its corresponding class activation map were shown in Fig. 2. From these two activation maps, it could be seen that the activation regions, which were painted as bright regions, not only surrounded the optic disc but also appeared in peripheral regions, especially the ones along the blood vessels. As the optic nerves extend along blood vessels from the optic disc, this may indicate that the trained model learned to use RNFL defect as one of the decisive features for the diagnosis of Glaucoma. Since the RNFL defect may be defected in fundus images with CNN, the development of algorithms to quantify the severity of RNFL defect with fundus images is possible.

5. CONCLUSION

With deep learning techniques, it is possible to automatically quantify the RNFL defect in fundus images. For the future purpose to determine the severity and locations of RNFL defect in fundus images accurately, the visual field data, treated as labels, would be introduced in the modeling process. As a deep learning model could acquire the knowledge for locating the RNFL defect efficiently, it would be of much help for ophthalmologists in clinics.

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REFERENCES

[1] S. Kingman, “Glaucoma is second leading cause of blindness globally.,” *Bull. World Health Organ.*, vol. 82, no. 11, pp. 887–888, Nov. 2004.

[2] H. A. Quigley and A. T. Broman, “The number of people with glaucoma worldwide in 2010 and 2020.,” *Br. J. Ophthalmol.*, vol. 90, no. 3, pp. 262–267, Mar. 2006.

[3] Y.-C. Tham, X. Li, T. Y. Wong, H. A. Quigley, T. Aung, and C.-Y. Cheng, “Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis.,” *Ophthalmology*, vol. 121, no. 11, pp. 2081–2090, Nov. 2014.

[4] A. Peeters, J. S. A. G. Schouten, C. A. B. Webers, M. H. Prins, F. Hendrikse, and J. L. Severens, “Cost-effectiveness of early detection and treatment of ocular hypertension and primary open-angle glaucoma by the ophthalmologist.,” *Eye (Lond)*, vol. 22, no. 3, pp. 354–362, Mar. 2008.

[5] L. M. Alencar and F. A. Medeiros, “The role of standard automated Perimetry and newer functional methods for glaucoma diagnosis and follow-up.,” *Indian J. Ophthalmol.*, vol. 59 Suppl, pp. S53-8, Jan. 2011.

[6] T. Alasil, K. Wang, F. Yu, M. G. Field, H. Lee, N. Baniasadi, J. F. de Boer, A. L. Coleman, and T. C. Chen, “Correlation of retinal nerve fiber layer thickness and visual fields in glaucoma: a broken stick model.,” *Am. J. Ophthalmol.*, vol. 157, no. 5, pp. 953–959, May 2014.

[7] I. I. Bussel, G. Wollstein, and J. S. Schuman, “OCT for glaucoma diagnosis, screening and detection of glaucoma progression.,” *Br. J. Ophthalmol.*, vol. 98 Suppl 2, pp. ii15-9, Jul. 2014.

[8] M. D. Abràmoff, M. K. Garvin, and M. Sonka, “Retinal imaging and image analysis.,” *IEEE Rev. Biomed. Eng.*, vol. 3, pp. 169–208, 2010.

[9] R. Varma, W. C. Steinmann, and I. U. Scott, “Expert agreement in evaluating the optic disc for glaucoma.,” *Ophthalmology*, vol. 99, no. 2, pp. 215–221, Feb. 1992.

[10] H. D. Jampel, D. Friedman, H. Quigley, S. Vitale, R. Miller, F. Knezevich, and Y. Ding, “Agreement among glaucoma specialists in assessing progressive disc changes from photographs in open-angle glaucoma patients.,” *Am. J. Ophthalmol.*, vol. 147, no. 1, p. 39–44.e1, Jan. 2009.

[11] N. Harizman, C. Oliveira, A. Chiang, C. Tello, M. Marmor, R. Ritch, and J. M. Liebmann, “The ISNT rule and differentiation of normal from glaucomatous eyes.,” *Arch. Ophthalmol.*, vol. 124, no. 11, pp. 1579–1583, Nov. 2006.

[12] M. Claro, L. Santos, W. Silva, F. Araújo, N. Moura, and A. Macedo, “Automatic Glaucoma Detection Based on Optic Disc Segmentation and Texture Feature Extraction,” *CLEI Electronic Journal*, Aug. 2016.

[13] E. Rahimy, “Deep learning applications in ophthalmology.,” *Curr. Opin. Ophthalmol.*, vol. 29, no. 3, pp. 254–260, May 2018.

[14] S. Dutta, B. C. Manideep, S. M. Basha, R. D. Caytiles, and N. C. S. N. Iyengar, “Classification of diabetic retinopathy images by using deep learning models,” *IJGDC*, vol. 11, no. 1, pp. 99–106, Jan. 2018.

[15] T. Walter and J.-C. Klein, “Segmentation of color fundus images of the human retina: detection of the optic disc and the vascular tree using morphological techniques,” in *Medical Data Analysis*, vol. 2199, J. Crespo, V. Maojo, and F. Martin, Eds. Berlin, Heidelberg: Springer Berlin Heidelberg, 2001, pp. 282–287.

[16] A. Issac, M. Parthasarthi, and M. K. Dutta, “An adaptive threshold based algorithm for optic disc and cup segmentation in fundus images,” in *2015 2nd International Conference on Signal Processing and Integrated Networks (SPIN)*, 2015, pp. 143–147.

[17] J. Zilly, J. M. Buhmann, and D. Mahapatra, “Glaucoma detection using entropy sampling and ensemble learning for automatic optic cup and disc segmentation.,” *Comput. Med. Imaging Graph.*, vol. 55, pp. 28–41, Jan. 2017.

[18] U. Raghavendra, H. Fujita, S. V. Bhandary, A. Gudigar, J. H. Tan, and U. R. Acharya, “Deep convolution neural network for accurate diagnosis of glaucoma using digital fundus images,” *Inf Sci (Ny)*, vol. 441, pp. 41–49, May 2018.

[19] S. Y. Lee, K. K. Kim, J. M. Seo, D. M. Kim, H. Chung, K. S. Park, and H. C. Kim, “Automated quantification of retinal nerve fiber layer atrophy in fundus photograph.,” *Conf. Proc. IEEE Eng. Med. Biol. Soc.*, vol. 2, pp. 1241–1243, 2004.

[20] R. Panda, N. B. Puhan, A. Rao, D. Padhy, and G. Panda, “Automated retinal nerve fiber layer defect detection using fundus imaging in glaucoma.,” *Comput. Med. Imaging Graph.*, vol. 66, pp. 56–65, Jun. 2018.

[21] R. Watanabe, C. Muramatsu, K. Ishida, A. Sawada, Y. Hatanaka, T. Yamamoto, and H. Fujita, “Automated detection of nerve fiber layer defects on retinal fundus images using fully convolutional network for early diagnosis of glaucoma,” in *Medical Imaging 2017: Computer-Aided Diagnosis*, 2017, vol. 10134, p. 1013438.

[22] A. Budai, R. Bock, A. Maier, J. Hornegger, and G. Michelson, “Robust vessel segmentation in fundus images.,” *Int. J. Biomed. Imaging*, vol. 2013, p. 154860, Dec. 2013.

[23] B. Zhou, A. Khosla, A. Lapedriza, A. Oliva, and A. Torralba, “Learning deep features for discriminative localization,” in *2016 IEEE Conference on Computer Vision and Pattern Recognition (CVPR)*, 2016, pp. 2921–2929.