Automated detection of retinal nerve fiber layer defects on fundus images: false positive reduction based on vessel likelihood

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ABSTRACT

Early detection of glaucoma is important to slow down or cease progression of the disease and for preventing total blindness. We have previously proposed an automated scheme for detection of retinal nerve fiber layer defect (NFLD), which is one of the early signs of glaucoma observed on retinal fundus images. In this study, a new multi-step detection scheme was included to improve detection of subtle and narrow NFLDs. In addition, new features were added to distinguish between NFLDs and blood vessels, which are frequent sites of false positives (FPs). The result was evaluated with a new test dataset consisted of 261 cases, including 130 cases with NFLDs. Using the proposed method, the initial detection rate was improved from 82% to 98%. At the sensitivity of 80%, the number of FPs per image was reduced from 4.25 to 1.36. The result indicates the potential usefulness of the proposed method for early detection of glaucoma.

Keywords: Retinal fundus images, glaucoma, retinal nerve fiber layer defects, computerized detection, false positive reduction, retinal vessels

1. INTRODUCTION

Glaucoma is the second leading cause of blindness in the world.[1] Once the nerve is damaged and the visual field is defected, it cannot be recovered. Therefore, early detection of glaucoma is important for ceasing progression and preventing total blindness. However, due to the slow progression and the lack of symptom in early stage, most patients do not consult a doctor until it gets to the advanced stages. In a population-based prevalence survey of glaucoma in Tajimi, Japan, the prevalence of the primary open-angle glaucoma in the population 40 years or older was 3.9%, and 93% of these patients were unaware of their disease.[2,3] This fact suggests the need for an effective screening paradigm.

During the general ophthalmology visits, a retinal fundus photograph is often obtained for examination of eye diseases, clinical record, and longitudinal comparison. In addition, it is sometimes employed for general health checkups. Its relative inexpensiveness and handiness make it convenient as a screening tool.

One of the earliest signs of glaucoma on retinal fundus images is retinal nerve fiber layer defect (NFLD). However, detection of NFLDs can be difficult, especially when the defected part is very subtle. Moreover, the number of ophthalmologists specialized in glaucoma diagnosis is limited, and the variability in diagnostic findings by different ophthalmologists exists. Therefore, automated detection of NFLDs could contribute in the early and efficient diagnosis of glaucoma.

We have previously developed an automated scheme for detection of NFLDs using image transformation and Gabor filters.[4] Using 162 cases, including 81 cases with NFLDs, the sensitivity of 91% with 1.0 false positives (FPs) per image was achieved based on the leave-one-out cross validation test. When the method was applied to the new dataset including 261 cases without any parameter optimization, the sensitivity was 80% with 4.25 FPs per image. This result of lower sensitivity was partially due to the subtlety of the new dataset as it included milder cases with more faint and

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narrower lesions. In this study, we investigated a multi-step detection scheme to improve sensitivity and a vessel likelihood measure to reduce FPs.

2. METHODS

2.1 Image datasets

The retinal fundus images used in this study were obtained from the database collected as a part of the Eye Health Care Project in Tajimi, Japan,[3] which includes the clinical data and eye examination results, such as visual field test, intraocular pressure, and retinal fundus images. The cases used in the randomized study, the Tajimi Glaucoma Epidemiological Study,[2] were not included in this dataset. The fundus photographs were obtained with an IMAGEnet digital fundus camera system (TRC-NW6S, Topcon; Tokyo, Japan), have a matrix size of 768 x 576 pixels, and saved in JPEG format.

In our previous study, 162 cases were selected for development and evaluation of the NFLD detection scheme.[4] Based on the image finding report, 81 cases with NFLDs in the left eyes were included and 81 age and gender-matched cases without NLFDs were randomly selected. For this study, the positive cases were retrospectively examined by two ophthalmologists independently, and 99 regions identified as NFLDs by both ophthalmologists were employed as the gold standard of NFLDs. This dataset was used as the training dataset in current study.

In this study, another dataset was collected on the basis of the image finding report for right eyes. It consists of 130 cases with NFLDs and 131 age and gender-matched cases without NFLDs; one NFLD case was excluded because of the image replication. This dataset was used as the test dataset. No image of the patients in the previous dataset was included. One ophthalmologist reviewed the images and identified the NFLD regions without any other clinical information in the same way as the training dataset. Two hundred three NFLDs were employed as the target NFLDs in this study.

2.2 Overview of the previous method

The detailed process of our previous detection method was described elsewhere.[4] Briefly, an original color fundus image was converted to a monochrome image by selecting the green channel as NFLDs are depicted with the highest contrast in green plane. In order to exclude blood vessel regions from potential candidates, a “vessel-erased” image[5] was created. The major blood vessels were detected using black top-hat transformation, and the pixels corresponding to the detected vessel regions were replaced by the surrounding non-vessel pixels. Subsequently, the images were transformed in the similar way as the polar transformation but using ellipse functions so that the directions of the retinal nerves are roughly vertically aligned as shown in Fig. 1. After images were preprocessed, the initial candidates of NFLDs were detected by applying Gabor filters of three sizes. Six image features were determined for each candidate region, and the candidates were classified into NFLDs or FPs using linear discriminant analysis (LDA).

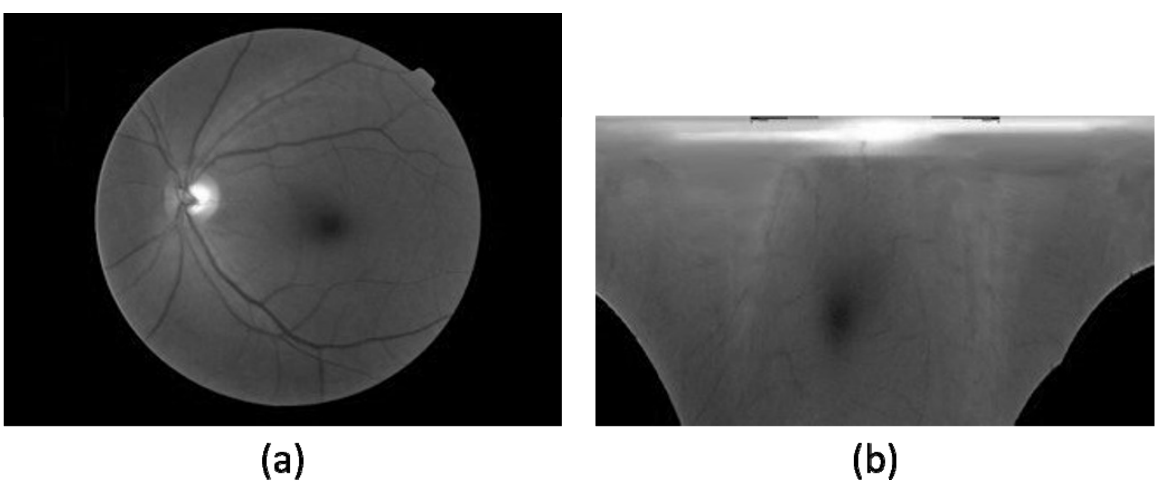

Figure 1. Modified polar transformation using ellipse functions. (a) Original image and (b) transformed image

2.3 Overview of the proposed method

The proposed detection procedure is shown in Fig. 2. In this study, a multi-step candidate detection technique was investigated to improve sensitivity and specificity. By adding the new filter sizes, the number of candidate regions detected by Gabor filters were increased. At the same time, some candidates were excluded by combining the results of two other detection techniques using adaptive thresholding and clustering. One of the main sources of FPs is retinal blood vessels. In order to reduce such FPs, a measure of vessel likelihood was determined for each candidate region. The measure is based on the characteristic difference of tube-like vessels and sheet-like NLFDs. Finally, five new image features were added for classifying NFLDs and FPs using LDA.

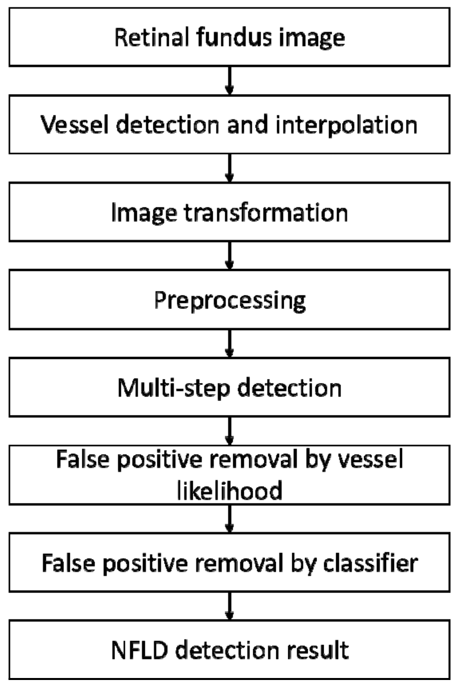

Figure 2. Flowchart of the proposed NFLD detection method

2.4 Preprocessing

The image brightness in fundus images are often uneven because of the photographic condition. In order to facilitate the detection, background brightness was corrected.[4] Using red channel images, the background trend was estimated by pixel averaging, and the fraction of the inverted background value was added to the green channel image. In this study, for detecting narrow lesions, an unsharp mask filter was applied. Subsequently, small noises enhanced as a by-product were reduced using a median filter.

2.5 Multi-step detection

In our previous method, Gabor filters with three sizes were applied to enhance NFLD regions. The filter sizes were 41 x 61, 41 x 61, and 81 x 61 pixels with the corresponding standard deviations of the Gaussian functions in x and y directions of 6 and 15, 12 and 20, and 24 and 36 pixels, respectively. However, the one with the smallest size was not suitable for enhancing the localized, narrow NFLDs included in the new dataset. In addition, the one with the largest size was not effective in detecting NFLDs. For detecting narrower NFLD regions, four filters with different parameters were used in this study. The sizes of the filters were 11 x 31, 13 x 31, 21 x 31, and 41 x 61 pixels, and the standard deviations of the Gaussian functions were 3 and 10, 3 and 10, 6 and 10, and 12 and 20 pixels, respectively. These four filters were applied to a preprocessed image and by selecting the maximum output of the four filters in each pixel, the NFLD-enhanced image was created. Subsequently, smoothing operation was performed to the image for creating the NFLD-attenuated image. By thresholding the subtraction image of the two, the first NFLD candidates were detected. Figure 3 shows the first step detection procedure.

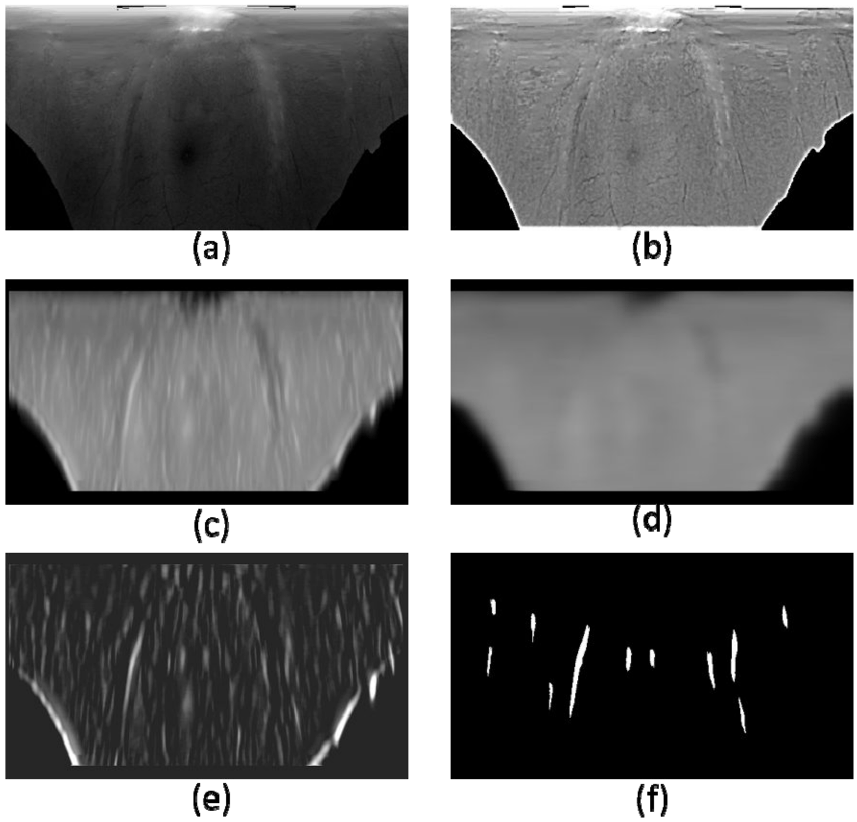

Figure 3. First step NFLD detection procedure. (a) Transformed G plane image, (b) preprocessed image, (c) NFLD enhanced image using Gabor filters, (d) NFLD attenuated image using a smoothing filter, (e) subtraction image of (c) and (d), and (f) NFLD candidate regions by thresholding.

Although the variation in background brightness was reduced by preprocessing, a universal threshold would not serve for detection of NLFDs at different locations. The thickness of normal retinal nerve layer varies around the optic disc, and accordingly the intensity of the retina gradually changes around the disc. In order to detect local intensity changes corresponding to NFLDs, the second detection technique was based on the adaptive thresholding.

The third detection method was based on the clustering. After excluding the optic disc region, the k-mean clustering method was applied to the image. The number of clusters was set to 12, which was determined empirically. For each cluster, the average pixel value and area were determined. The candidate pixels were detected by the selective thresholding in each cluster.

The results of three methods were combined by retaining the candidate regions detected by the first method if they intersected with the pixels detected by the second and third detection methods.

2.6 Vessel likelihood measure

Although the major vessel regions were suppressed in the vessel erased images, some regions corresponding to vessels are still detected as FPs. In this study, we focused on the difference in shape between the NFLDs and vessels. Both are generally depicted as dark strips on fundus images; however, while retinal vessels are a tube-like structure, nerve layer covers the fundus like a sheet. Therefore, it is expected that vessels have black intensity peaks near the center line whereas pixel values inside NFLDs are more uniform. We located the point of the maximum depth (minimum pixel value) in each cross section of the candidate regions. If the points were stretched as a line, the candidate region was considered as highly likely a vessel. On the other hand, the points were more randomly spread for NFLD regions. The candidates with the high likelihood measures were removed as FPs.

2.7 Feature extraction

In our previous study, six image features characterizing the shape and contrast were determined for reduction of FPs. In this study, five features were added to decrease the number of FPs. One is to characterize the shapes of NFLDs and vessels in the original image. In the transformed images, they are generally depicted as a vertical strip. However, in the original images, NFLDs can be observed in a fan-like shape whereas diameters of vessels stay almost constant or decrease as they get away from the optic disc. Therefore, the difference in widths of a candidate region in optic disc side and temporal side (distal to optic disc) was determined. Another feature was the positional feature based on the probabilistic atlas created with the training cases which represents the frequent site of NFLDs. Other three are based on the pixel values and contrast of the candidate regions. As the vessel likelihood measure, these features were intended to distinguish between NFLD regions with relatively constant pixel values and FP regions with larger variations in pixel values.

2.8 Classification and evaluation

A total of 11 features were input to LDA for classification of NFLDs and FPs. The LDA was trained with the training dataset and then applied to the test dataset. The detection performance was evaluated by using free-response receiver operating characteristic (FROC) analysis. The result was compared with that by the previous method and the statistical test was performed using jackknife alternative FROC (JAFROC) software [6].

3. RESULTS

The proposed method was tested on 261 cases including 130 cases with 203 NFLDs. Figure 4 shows the FROC curves obtained by the previous and proposed methods. If a candidate region is overlapped with the gold standard NFLD region, it was considered as a true positive region. Using the previous method, the initial detection sensitivity was 82%. It was improved to 98% by the proposed method with the multi-step detection scheme. At these sensitivities, the number of FPs was 6.0 for both methods. In the proposed method, some of the FPs were removed by the vessel likelihood measure. By varying the threshold on the LDA scores, the numbers of FPs per image were 4.25 and 1.36 by the previous method and proposed method, respectively, at the sensitivity of 80%. Based on the JAFROC analysis, the difference in detection performance was statistically significant ($p<0.001$).

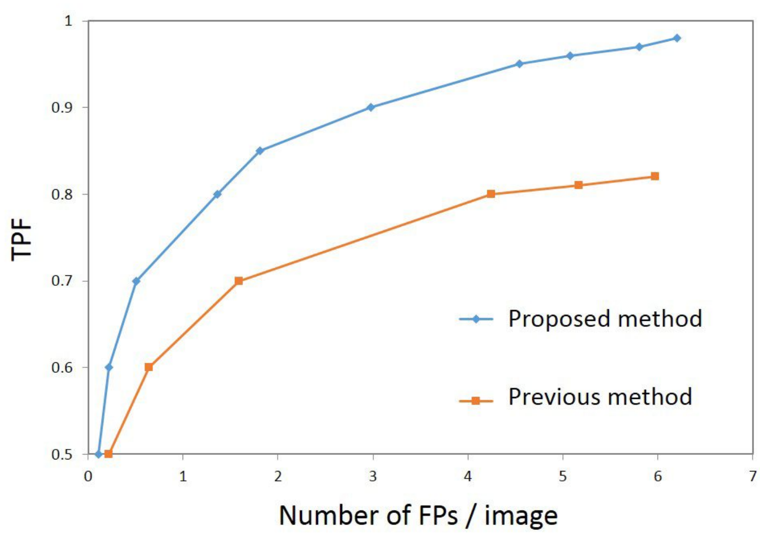

Figure 4. FROC curves for NFLD detection by the previous and proposed methods.

4. DISCUSSION AND CONCLUSION

In this study, we attempted to improve the computerized scheme for detection of NFLDs on retinal fundus images. When our previous method was applied to the new test dataset, the sensitivity was lower and the number of FPs was larger than those for the previous dataset. One of the reasons for lower sensitivity was that the new cases included narrower NFLDs, which were not effectively enhanced by the Gabor filters used in the previous study. In this study, we added the filters with smaller parameters. Although the sensitivity increased, the number of FPs further increased. To compensate for that, two other methods for detecting locally low intensity regions were included and the results were combined. The initial detection sensitivity was improved from 82 to 98%. This improvement, however, may appear larger than the actual effect. The some of the narrow NFLDs were located side by side, and they were detected as one by the previous method. Moreover, for cases with multiple lesions, detection of one lesion may be sufficient in screening. The effect of the computerized detection in clinical practice must be further investigated.

A large fraction of FPs was due to blood vessels. For reducing such FPs, we determined the vessel likelihood measure and new image features. They were intended to characterize the structural difference between NFLDs and vessels. Some FPs at vessel sites were effectively removed by these measures. Compared with the previous method, the number of FPs at the sensitivity of 80% was reduced by 68%. Although LDA was trained with the training dataset and the methods were evaluated on the new dataset, the proposed techniques were included to improve the result on test dataset and therefore, training and testing were not independent. The effectiveness of the proposed method must be validated with a new database.

Overall, the result suggests a potential usefulness of the proposed method for detection of NFLDs on retinal fundus images. Computerized detection may help ophthalmologists in accurate and efficient diagnosis of fundus images which could contribute in early detection of glaucoma.

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