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Glaucoma Risk Assessment Based on Clinical Data and Automated Nerve Fiber Layer Defects Detection

Yuji Hatanaka, *Member, IEEE*, Chisako Muramatsu, Akira Sawada
Takeshi Hara, Tetsuya Yamamoto, and Hiroshi Fujita, *Member, IEEE*

Abstract— **Glaucoma is the first leading cause of vision loss in Japan, thus developing a scheme for helping glaucoma diagnosis is important. For this problem, automated nerve fiber layer defects (NFLDs) detection method was proposed, but glaucoma risk assessment using this method was not evaluated. In this paper, computerized risk assessment for having glaucoma was attempted by use of the patients' clinical information, and the performances of the NFLDs detection and the glaucoma risk assessment were compared. The clinical data includes the systemic data, ophthalmologic data, and right and left retinal images. Glaucoma risk assessment was built by using machine learning technique, which were artificial neural network, radial basis function (RBF) network, k-nearest neighbor algorithm, and support vector machine. The inputting parameter was ten clinical ones with/without the results of NFLDs detection. As a result, proposed glaucoma risk assessment showed the higher performance than the NFLD detection. The result of the glaucoma risk assessment indicates that the computerized assessment may be useful for the determination of glaucoma risk.**

I. Introduction

A number of glaucoma patients is increasing, especially in developed countries. Glaucoma is the first leading cause of vision loss in Japan. The number of people with visual handicap is also estimated to be one million six hundred forty thousand, and 24% of these were affected with glaucoma in Japan, 2007 [1]. Fifty thousand people were blinded by glaucoma in Japan. However, many patients stay unnoticed because many of them are asymptomatic in the early stage. If they are diagnosed earlier, the permanent blindness may be avoided. Screening and periodical check-up is important for the early diagnosis of glaucoma. Thus, many researches have been trying to develop computer-aided diagnosis (CAD) systems, which analyze retinal fundus images for diagnosis of glaucoma [2-16]. Measurement of vertical cup-to-disc (C/D) ratio methods [2-4], a glaucoma risk assessment based on pixels analysis in an optic nerve head (ONH) [5], peripapillary chorioretinal atrophy (PPA) detection methods [6, 7] and nerve fiber layer defects (NFLDs) detection methods [8-16] were reported. To help glaucoma diagnosis, we developed a measurement of vertical C/D ratio method [4], a PPA detection method [7], and a NFLDs detection method [14] on retinal fundus images, respectively. Moreover, we tried to develop a depth analysis of optic nerve head (ONH) in stereo retinal fundus images pair [15], and a C/D ratio measurement by using the depth of ONH [16]. But, stereo retinal camera has not prevailed yet, thus using stereo retinal camera is difficult for current screening. A part of field was lost by a NFLD, thus NFLDs detection was very important. In our report of automated NFLD detection [4], although we reported the performance of that method, we have not described the effects of glaucoma diagnosis by using that method. The other reports also did not describe about glaucoma risk by using algorithms.

On the other hand, glaucoma is diagnosed by the ophthalmotonometry, funduscopy, and visual field examination. Ophthalmologists diagnose by using not only findings based retinal images but several kinds of clinical data including the systemic data and ophthalmologic data. Thus, diagnostic tool using clinical data, which were age, intraocular pressure (IOP), corneal curvature thickness (CCT), pattern standard deviation (PSD) of view, vertical C/D ratio, and diabetes mellitus, was proposed [17]. But, that method did not use presence of NFLD, which is important finding of glaucoma. Moreover, the findings on retina were obtained manually. As another report, a diagnostic tool focused in ONH and NFLDs was proposed [18]. 3D images were recommended in this study, but it is difficult to use 3D retinal images in the screening. Therefore, the effects based on our NFLD detection and a new computerized scheme for glaucoma risk assessment by use of clinical data and test results obtained in the glaucoma screening examination were investigated in this study.

II. Methods

A. Clinical Data

Cases used in this study was obtained from the population screening study in Tajimi, Japan which, however, excluded the 4000 cases included in the randomized study (so called "Tajimi Study" [19]). For this study, 79 cases with signs of glaucoma and without other major ocular diseases were selected and included in the high risk group. Ninety NFLDs were included in high risk group. Eighty one normal cases was selected randomly and included in the low risk group.

Glaucoma is diagnosed based on 'the second edition of Japan Glaucoma Society Guidelines for Glaucoma'. The procedure is shown in Figure 1. Therefore, the clinical data in Tajimi study included the age, height, weight, systolic and diastolic blood pressure, Self-corrected visual acuity, visual

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Y. Hatanaka is with the Department of Electronic Systems Engineering, School of Engineering, the University of Shiga Prefecture, Hassaka-cho 2500, Hikone-shi, Shiga 522-8533, Japan (phone: 81-749-28-9556; fax: 81-749-28-9576; e-mail: hatanaka.y@usp.ac.jp).

C. Muramatsu, T. Hara, and H. Fujita are with the Department of Intelligent Image Information, Graduate School of Medicine, Gifu University, Gifu 501-1194, Japan.

A. Sawada and T. Yamamoto are with the Department of Ophthalmology, Graduate School of Medicine, Gifu University, Gifu 501-1194, Japan.

field defects (VFD), spherical and cylindrical refraction, refraction axis, corneal curvature rate, CCT, IOP and retinal fundus images. The retinal fundus images were obtained using IMAGEnet digital fundus camera system (TRC-NW6S, Topcon, Tokyo, Japan) with a resolution of 768 x 576 pixels. In addition, NFLD, PPA and DH were found manually by expert ophthalmologist. Although we have been developing automated PPA detection method [7], the performance was not reached enough. Therefore, automated PPA detection will be obtained in the next study. Thus, our proposed NFLDs detection method [14] was evaluated, and then computerized glaucoma risk assessment was developed by combining clinical data with results of NFLDs detected [14] in this study.

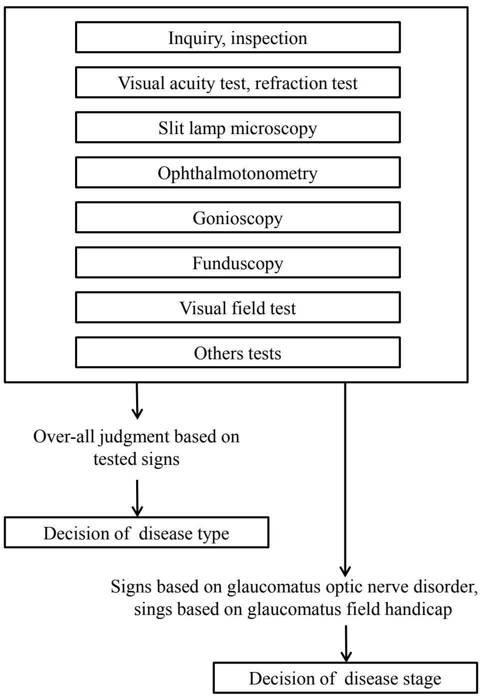

Figure 1. This flowchart shows decision procedure of glaucoma types and stages.

B. NFLDs Detection Method

The summary of the automated NFLDs detection method is described as follows. Refer to our paper [14] concerning the detailed NFLDs detection method.

In order to exclude blood vessel regions from potential false positives, the blood vessels were automatically segmented by using morphological operation and thresholding [20]. The identified regions as blood vessels were interpolated by the surrounding pixels for creating "blood-vessel-erased" images. NFLDs are most prominent in the green channel of the RGB color images, thus the color images were converted to gray scale images by use of the green channel. The NFLDs appear as dark curved bands extending radially from an ONH on the spherical surface. Therefore, the retinal images were transformed to the polar coordinate images centering on the ONH. The Gabor filtering [21] was applied in order to enhance contrasts of NFLDs, which shapes were vertical bands. The preliminary NFLD candidates were detected by a prespecified threshold value based on the average pixel value in the rectangular region. For each candidate, six image features were determined. Six features included the area, the vertical length, the average pixel values in the original and filtered images, and the contrasts in the original and filtered images. With these six features, the likelihood scores of the candidates being true NFLDs were determined by using an artificial neural network (ANN). The results of the detection methods were evaluated by use of the free-response receiver operating characteristic (FROC) analysis and the receiver operating characteristic (ROC).

C. Classifier for Glaucoma Risk Assessment Based on Machine learning

The glaucoma risk assessment methods were developed by sixteen kinds of machine learning technique, which were based on five kinds of ANN, five kinds of radial basis function (RBF) network, k-nearest neighbor algorithm (kNN), and four kinds of support vector machine (SVM). In this step, we developed the scheme by using 'Visual Mining Studio Ver.7' from Mathematical System Inc.. Sigmoid function is most famous in objective function and activation function for ANN. Therefore, we used sigmoid function in the NFLDs detection step. But, five combinations of objective function and activation function were tested in this step. Because a matrix built by the input features and cases was too large, thus we thought such functions affected the performance of the glaucoma risk assessment. We tested five kinds of ANN based on five combinations of objective function and activation function, which were linear-sum of square, sigmoid binomial, softmax-binomial, softmax-multinomial, and sigmoid-sum of square. We also tested the same five combinations as ANN for RBF network. Manhattan function and Euclid function were then tested as distance funcion for kNN. Moreover, linear, gaussian, polynomial, and sigmoid functions were tested as kernel functions of SVM. Their classifiers were tested by using leave-one-out cross-validation, respectively. The input parameters describes in Section III.

III. RESULTS AND DISCUSSION

A. NFLD Detection

Figure 2 shows the FROC curve by NFLDs detection. For example, 90% of NFLDs were detected when number of false positives per image was 0.94. When 90% of NFLDs were detected, the sensitivity and specificity of case base was 90%, 54%, respectively. Moreover, this method was analyzed by using the ROC, and area under the curve (AUC) was 0.799. The ROC curve of NFLDs detection was shown in Figure 3. However, this study has some limitation. For inputting the optimal results of NFLDs detection into a glaucoma risk assessment, this result was evaluated by use of the resubstitution test method. Although only simple image features were used to reduce biases, it is preferable to use different database for training and testing the algorithms. Our method should be evaluated on independent database in the future.

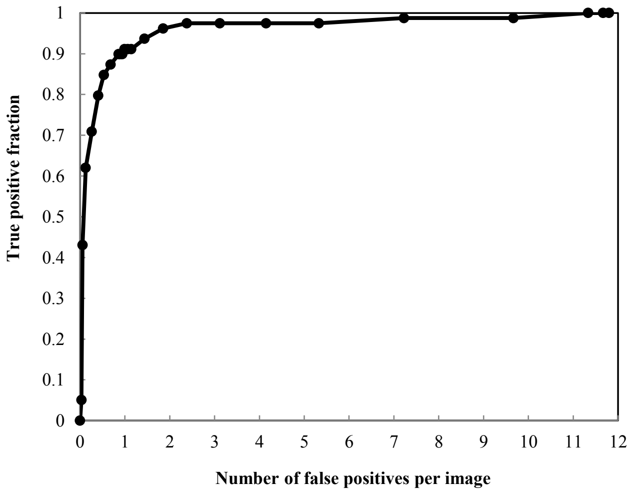

Figure 2. FROC curve for detection of NFLDs by the proposed method.

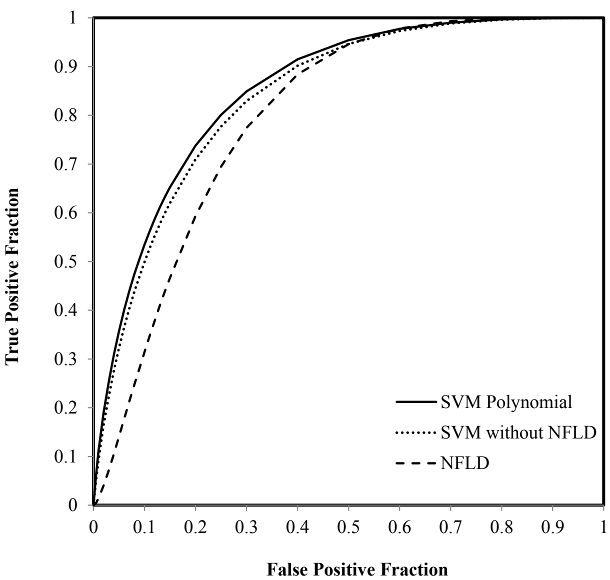

Figure 3. Comparison of ROC curves by SVM, SVM without NFLDs detection and NFLDs detection.

B. Classifier for Glaucoma Risk Assessment

We calculated the P values of all parameters by use of the Student's t test for continuous variables and chi-squared test for nominal variables. The P values were summarized in TABLE I. The results shown in Table 1 were based on the data for the left eyes; however, the results were almost comparable based on data for the right eyes. In this study, we removed systemic parameters, which were sex, age, height and weight. Although the higher age is, the higher glaucoma risk is, we then removed age parameter in this study because the number of cases was not many. Moreover, DH was not used for this study, because there is not a case with DH in this study. A patient with visual field defect (VFD) is might be having glaucoma, but P value of VFD was low because there were a bit cases with VFD. Thus, VFD was removed in this study. Although the P value of cylindrical refraction was fifth in these parameters, there are many cases with missing data of them, thus it was removed. Therefore, we used eleven parameters, which were systolic and diastolic pressure, self-corrected visual acuity, spherical refraction, refraction axis, corneal curvature and thickness, intra ocular pressure, glade of angle, presence of PPA, and presence of NFLDs detected for this study.

Sixteen classifiers were tested by inputting eleven parameters, and TABLE II shows the AUCs based on ROC analysis. The AUC of polynomial SVM was highest in 16 classifiers. This AUC was better than that of NFLDs detection, because NFLDs detection algorithm produced many false positives. But, the AUC of polynomial SVM without NFLDs detection dropped to 0.842, thus NFLDs detection was needed. Figure 3 shows ROC curves by polynomial SVM, NFLDs detection and polynomial SVM without NFLDs detection. The curve of NFLDs detection was inferior to them of SVM and SVM without NFLDs. From the above results, NFLDs detection method has to improve the performance, but the current NFLDs detection method would assist in the

TABLE I. COMPARISON OF THE CLINICAL DATA FOR THE HIGH RISK AND LOW RISK GROUPS

Parameters	High risk	Low risk	P value	Rank
Male / Female	33 / 46	33 / 48	-	-
Age (mean±SD)	60±9.4	60±9.1	0.433	11
Systolic pressure	144	136	0.0617	6
Diastolic pressure	86	80	0.0375	4
Self-corrected visual acuity	0.61	0.68	0.0891	8
Visual field defect (VFD)	9 / 79	6 / 81	0.444	12
Spherical refraction	0.552	0.566	0.472	13
Cylindrical refraction	-0.741	-0.881	0.0452	5
Refraction axis	76.4	95.3	0.00349	3
Corneal curvature	7.58	7.64	0.0666	7
Corneal thickness	0.516	0.522	0.109	9
Intra ocular pressure	14.4	14.3	0.500	14
Glade of angle	3.34	3.30	0.275	10
Presence of PPA	41 / 79	12 / 81	$3.50*10^{-7}$	2
Automated NFLD detected	75 / 79	39 / 81	$9.63*10^{-9}$	1

High and low risk of male / female show numbers of cases, respectively. They of age show mean±SD (standard deviation), respectively. They of VFD, PPA, and NFLD show number of cases, respectively. The other parameters show means, respectively.

TABLE II. COMPARISON OF CLASSIFIERS BASED ON AUC

Classifiers	Functions	AUC
ANN	Linear-Sum of Square	0.834
	Sigmoid Binomial	0.806
	Softmax-Binomial	0.825
	Softmax-Multinomial	0.825
	Sigmoid-Sum of Square	0.795
RBF Network	Linear-Sum of Square	0.830
	Sigmoid Binomial	0.812
	Sigmoid Binomial	0.809
	Softmax-Binomial	0.804
	Softmax-Multinominal	0.804
kNN	Manhattan	0.786
	Euclid	0.765
SVM	Linear	0.8535
	Gaussiun	0.788
	Polynomial	0.8542
	Sigmoid	0.592

performance of glaucoma risk assessment using clinical data. When the accuracy was optimal, the sensitivity, specificity and accuracy of polynomial SVM were 80%, 75% and 78%, respectively.

The initial investigation of the glaucoma risk analysis indicated that the computerized risk assessment by use of the clinical data and some test results obtained in the screening exams can be useful for early diagnosis of glaucoma, especially when conducting physicians are non-specialists.

The further improvement in the risk determination can be expected by including the results from the other image analysis, such as the determination of the cup-to-disc ratio [2] and rim-to-disc ratio, and PPA detection [3]. When these image analyses are incorporated, the method will be evaluated again.

IV. Conclusion

Testing our proposed automated NFLDs detection method, the AUC by ROC analysis was 0.799. We then developed a glaucoma risk assessment algorithm by using the clinical data and automated NFLD detection method on retinal fundus images. The performance of polynomial SVM was best in sixteen classifiers tested. The performance of SVM was better than that of NFLDs detection. As a result, the sensitivity, specificity, and accuracy were 80%, 75%, 78%, respectively.

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