Image enhancement of color fundus photographs for age-related macular degeneration: the Shanghai Changfeng Study

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Abstract

● **AIM:** To develop and evaluate a new fundus image optimization software based on red, green, blue channels (RGB) for the evaluation of age-related macular degeneration (AMD) in the Chinese population.

● **METHODS:** Fundus images that were diagnosed as AMD from the Shanghai Changfeng Study database were analyzed to develop a standardized optimization procedure. Image brightness, contrast, and color balance were measured. Differences between central lesion area and normal retinal area under different image brightness, contrast, and color balance were observed. The optimal optimization parameters were determined based on the visual system to avoid image distortion. A paired-sample diagnostic test was used to evaluate the enhancement software. Fundus optical coherence tomography (OCT) was used as the gold standard. Diagnostic performances were compared between original images and optimized images using McNemar's test.

● **RESULTS:** A fundus image optimization procedure was developed using 86 fundus images of 74 subjects diagnosed with AMD. By observing gray-scale images, choroid can be best displayed in red channel and retina in green channel was found. There was limited information in blue channel. Totally 104 participants were included in the paired sample diagnostic test to assess the performance of the optimization software. After the image enhancement, sensitivity increased from 74% to 88% (*P*=0.008), specificity decreased slightly from 88% to 84% (*P*=0.500), and Youden index increased by 0.11.

● **CONCLUSION:** The standardized image optimization software increases diagnostic sensitivity and may help ophthalmologists in AMD diagnosis and screening.

● **KEYWORDS:** age-related macular degeneration; image enhancement; image optimization; retina

INTRODUCTION

Age-related macular degeneration (AMD) is a serious eye disease characterized by progressive deterioration of macular areas[1]. In 2020, AMD ranks the fourth leading global causes of blindness in those over 50 years old[2]. Large-scale screening of AMD relies on fundus photography[3-4]. However, any disease that affects the cornea, lens, and vitreous body can lead to media opacity, resulting in the degradation of fundus image quality, usually present as low contrast, uneven exposure, and blurred images[5]. In a Diabetic Retinopathy Screening Programme carried out in 2003, 11.9% of fundus photographs were considered to be ungradable images despite a staged mydriasis protocol[6-9]. Poor quality of fundus images

may interfere with clinical diagnosis and clinical decision and is becoming one of the concerns related to fundus photography. With the advent of various computer technologies, medical image processing has been applied to multiple disciplines: ophthalmology, dermatology, pathology, and imaging[10-12]. Various methods of retinal image enhancement have emerged[10-12]. Today, increasing numbers of ophthalmologists and image processing engineers are seeking opportunities to cooperate in fundus photographs optimization. The Age-Related Eye Disease Study 2 (AREDS2) research team explored a standardized fundus image optimization process for AMD diagnosis[13]. The histogram-based process aimed to adjust image brightness, contrast, and color balance for ungradable images, and help standardize the documentation of AMD in multicenter studies[13]. In 2017, Tsikata *et al*[14] developed an automatic image processing software utilizing the optimization parameters in the AREDS2 study. However, the fundus image optimization parameters apply only to Caucasian subjects[13-14]. Due to racial differences in fundus pigmentation, the optimization parameters in the AREDS2 study may not apply to the Chinese population. Standard image optimization methods for the Chinese population need to be further explored. In 2018, Jin *et al*[15] developed an image enhancement method for retinal diseases, with the area under the curve (AUC) for AMD diagnosis increased from 0.918 to 0.975. However, the enhancement and the image processing method is not targeted at AMD, but multiple fundus diseases, including diabetic retinopathy and glaucoma, *etc*. As lesion characteristics vary from disease to disease, image optimization method aiming at AMD is pending further studies.

The purpose of our study is to develop a standard optimization software for AMD diagnosis in the Chinese population based on fundus photographs and to assess the performance of the image optimization method through a diagnostic test. Our standard optimization software is designed to use the optimal enhancement parameters to detect the soft and hard drusen, but it can also help detect late AMD lesions and other types of drusen to some extent.

SUBJECTS AND METHODS

Ethical Approval The study was compliant with the Declaration of Helsinki and approved by The Medical Ethic Committee of Zhongshan Hospital, Fudan University. Our research was accomplished by the cooperation of diabetic specialists, ophthalmologists from Zhongshan Hospital, image processing engineers, and software engineers from Pingan Technology.

Our study was part of the Shanghai Changfeng Study, which focused on multiple chronic diseases[16-18]. It contained two stages: optimization software technology development and image enhancement performance assessment.

Optimization Software Technology Development Eighty-six fundus images of AMD confirmed in the Shanghai Changfeng Study database were used as optimization development material. The study design and imaging procedure were briefly described in the previous report[17]. Our optimization method is similar to the method used in the AREDS2 study[13]. Ten images with the best quality were selected by clinicians and image processing engineers as exemplary images. Optimization parameters adjustment was using Adobe Photoshop cc2017. Fundus images were displayed in different color modes, including hue, saturation, value mode (HSV), hue, saturation, lightness (HSL), luminance, chrominance, chroma mode (YUV) and red, green, blue mode (RGB). Image processing engineers observed the information of fundus structure and compared the difference in image parameters between the exemplary images and other images through channel separation. Then, we took two areas of 3×3 pixel size in the center of the typical drusen and adjacent normal district and compared the average brightness of red channels. Optimal parameters were recorded when the brightness difference reached its maximum. Here we determined brightness as the average brightness in red channel, which is similar to the method used in the AREDS2 study[13]. Subtle adjustments were made to make sure the optimized image accorded with the reading habits of human eyes and that the images were not distorted. After multiple comparisons among the original parameters, our optimization parameters, and AREDS2 optimization parameters, we then determined the final optimization parameters after a few subtle adjustments. The optimization software was developed by software engineers through Visual C++ tools.

Image Enhancement Performance Assessment To evaluate the image enhancement software on substandard images, we conducted a paired-sample diagnostic test. Sample size calculation was performed using NCSS PASS 15.0 based on diagnostic tests for two paired samples. We took the value of *P*=0.8, α=0.05, and the sample size was finally determined to be 102. Samples used in the study were retrospectively and consecutively selected from all fundus images of patients who underwent fundus photography after mydriasis and OCT scan of the macular area in the Department of Ophthalmology, Zhongshan Hospital of Fudan University, from October 2018 to December 2018. After standard optimization of fundus images, a trained ophthalmologist performed AMD diagnosis on shuffled original images and optimized ones. In case of uncertainty, the final diagnosis was achieved after reaching a consensus with another senior ophthalmologist. Diagnosis results are compared to the OCT gold standard with fourfold tables. Patient information (gender, age, diagnosis, right/left eye, *etc*.) was also registered. Information was collected using
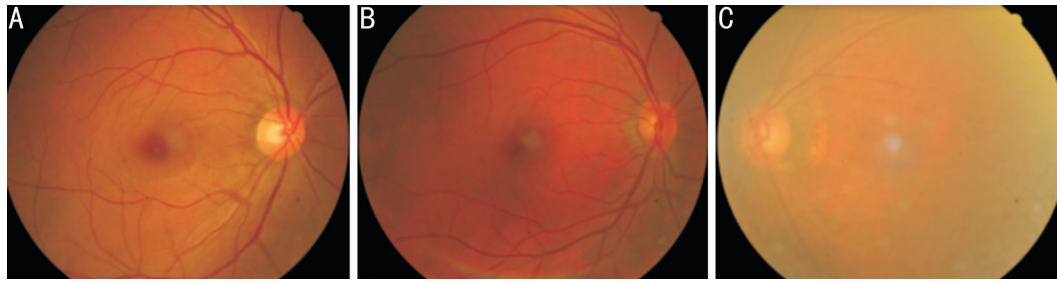
Figure 1 Standard fundus image (A), substandard fundus image due to uneven luminance (B), and substandard fundus image due to media opacity (C).

Carl Zeiss CIRRUS 4000 HD-OCT 512×128 line scan mode and TOPCON TRC-50DX fundus camera.

Inclusion criteria: 1) Patients ≥45 years old; 2) Substandard quality images, defined as follows: a) The quality of the image is not as good as the ten high-quality exemplary images due to media opacity, uneven luminance, or fluctuations in focus; b) Gradable macular area ≥3/4 macular area; 3) Patients underwent the OCT scan of the macular area within one month. Examples of standard and substandard images are shown in Figure 1. In the standard image, the macular area and fundus vessels are clear. In the middle picture, there is a lack of exposure in the temporal and inferior areas. Media opacity exists in the right image, which reduces the image clarity. Exclusive criteria: 1) Extremely poor image quality: extremely overexposed or underexposed; extremely out-of-focus or blur; key areas blocked by eyelashes/hair/small pupils/other fundus diseases, and result in less than 3/4 macular area gradable; 2) Patient diagnosed with or reported having following diseases: central retinal vein occlusion, central serous chorioretinopathy, proliferative diabetic retinopathy, vitreous hemorrhage, endophthalmitis, retinal detachment, retinitis pigmentosa or retinal neoplasms within 90d before enrollment. Gold standard: OCT showed drusen in the corresponding areas, characterized as single or multiple continuous or discontinuous mound-like elevations with or without abnormal retinal pigment epithelium (RPE)[19].

Statistical Analysis IBM SPSS Version 22.0 was used to calculate diagnostic sensitivity, specificity, positive predictive value, negative predictive value, accuracy, Youden index, and other indicators of diagnostic efficacy. McNemar's test was used to compare sensitivity and specificity.

RESULTS

Image Properties of the Image Set for Software Development
In this study, we included color fundus photographs of 86 eyes of 74 subjects diagnosed with AMD, 45 (60.8%) of the participants were female. Table 1 presents the basic characteristics of the image dataset for software development. Table 2 presents the image properties of the image dataset. As shown in Figure 2A, the overall contrast values of these images are relatively small. Figure 2B indicates that the

Table 1 Basic characteristics of exemplary images   *n* (%)

Parameters	Template image
Image format and number	
JPEG	86 (100)
Gender	
Female	45 (60.8)
Male	29 (39.2)
Laterality	
OD	43 (50)
OS	43 (50)

overall brightness values of the image are relatively large and the brightness values of the three channels were dispersed in color space. We split the full RGB color image into gray-scale equivalences. By observing these gray-scale images, we found that the red channel is the optimal channel to display choroid, the green channel is the optimal channel to display retina, while the blue channel carries little information. For image optimization, we decided to increase the contrast values of the green channel and the red channel.

Brightness, Contrast, Tone Adjustment We normalize the span of pixel values from 0-255 to 0-1. As can be seen from Figure 3, the brightness difference between the lesion and non-lesion areas becomes larger in all three channels when increasing image contrast. However, excessively high contrast will introduce additional noise and may cause false positivity, and result in image distortion. We began the optimization process by using the linear transformation formula:

$$X = \frac{Contrast_n}{Contrast_a}(x - x_{min}) + X_{min} \ (\ 1\ )$$

In Formula 1, $Contrast_n$ is the span of brightness of the target optimization image, and $Contrast_a$ is the span of brightness of the original image to be optimized; x is the pixel value of a point in the original image, while x is the pixel value of the corresponding position after optimized; X_{min} is the minimum pixel value of the original unoptimized image, and X_{min} is the minimum pixel value of the target image.

We chose moderately higher contrast values while considering the reading habit of the visual system. The image presented
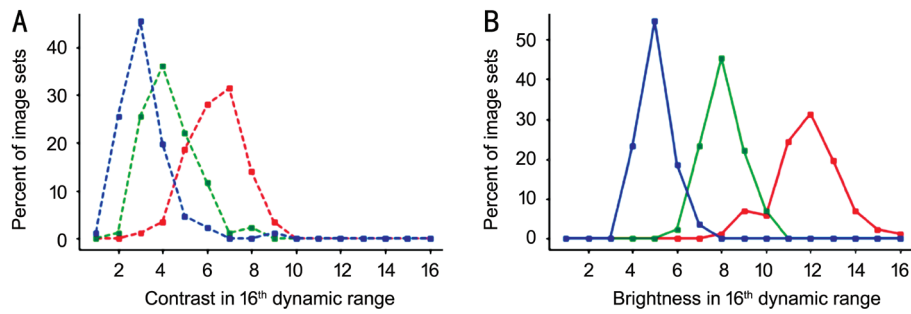
Figure 2 Contrast and brightness distribution of 86 sample images A: The overall contrast values of these image; B: The overall brightness values of the image.
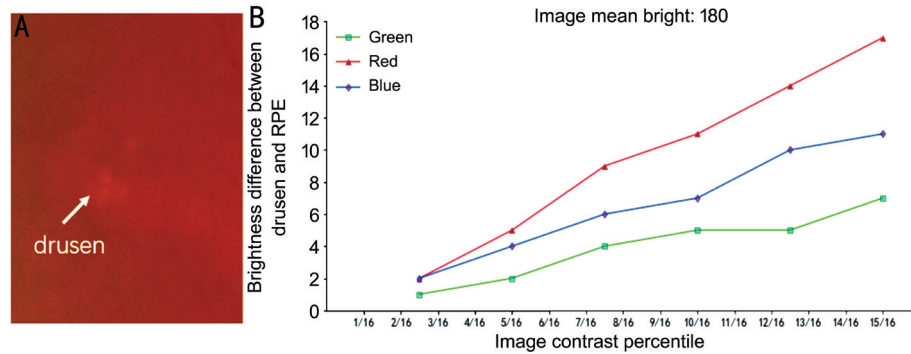

Figure 3 Difference in brightness with different contrast values A: The drusen area; B: The brightness difference between the lesion and non-lesion areas.

Table 2 Brightness, contrast, and color balance ratios for the analyzed 86 images before and after automated image enhancement   mean±SD (range)

Parameters	Before	After
Brightness		
Red brightness	169.9±21.8 (108.1-214.4)	181.1±0.7 (179.7-182.9)
Green brightness	105.0±13.2 (71.9-133.9)	90.0±0.6 (88.0-91.1)
Blue brightness	55.2±11.5 (33.3-87.3)	38.0±0.4 (37.3-39.0)
Contrast		
Red contrast	57.3±15.9 (26.0-92.0)	89.5±14.2 (54.0-121.0)
Green contrast	27.1±10.4 (12.0-52.0)	90.6±24.9 (39.0-139.0)
Blue contrast	18.9±6.4 (10.0-41.0)	34.8±6.4 (20.0-49.0)
Color balance		
Green/red ratio	0.626±0.069 (0.453-0.799)	0.496±0.010 (0.475-0.517)
Blue/red ratio	0.333±0.077 (0.183-0.541)	0.215±0.006 (0.203-0.231)

better performance when the red component is between 0.4-1 and the green component is between 0-0.8 in the color distribution histogram. Because the blue component contains less key information of the images, we only adjust the brightness and contrast of the blue channel in a small range, where a proper distribution range is 0-0.15. To explore the color balance among channels, a representative image was chosen to display the performance on typical parameters, which illustrates the selection strategy of reasonable parameter ranges. When the average brightness in the red channel exceeds 0.7, the image will be seriously overexposed. When the average brightness in the red channel is below 0.55, the image will be too dark to

display the fundus structure. Therefore, the average brightness in the red channel should be 0.55-0.7. To highlight the difference between lesions and non-lesions, and meanwhile considering the reading habit of the visual system and ensuring the image is not distorted, we chose the average brightness in the red channel to be 0.7.

The parameters of images are shown in Table 3. As shown in Figure 4, when the ratio of green and red components (G/R ratio) exceeds 0.5, the image will be greenish with some color distortion; when the G/R ratio is too small, the contrast of the lesion area will be reduced (the spectrum of drusen is mainly concentrated on the green channel). Thus, the G/R ratio was
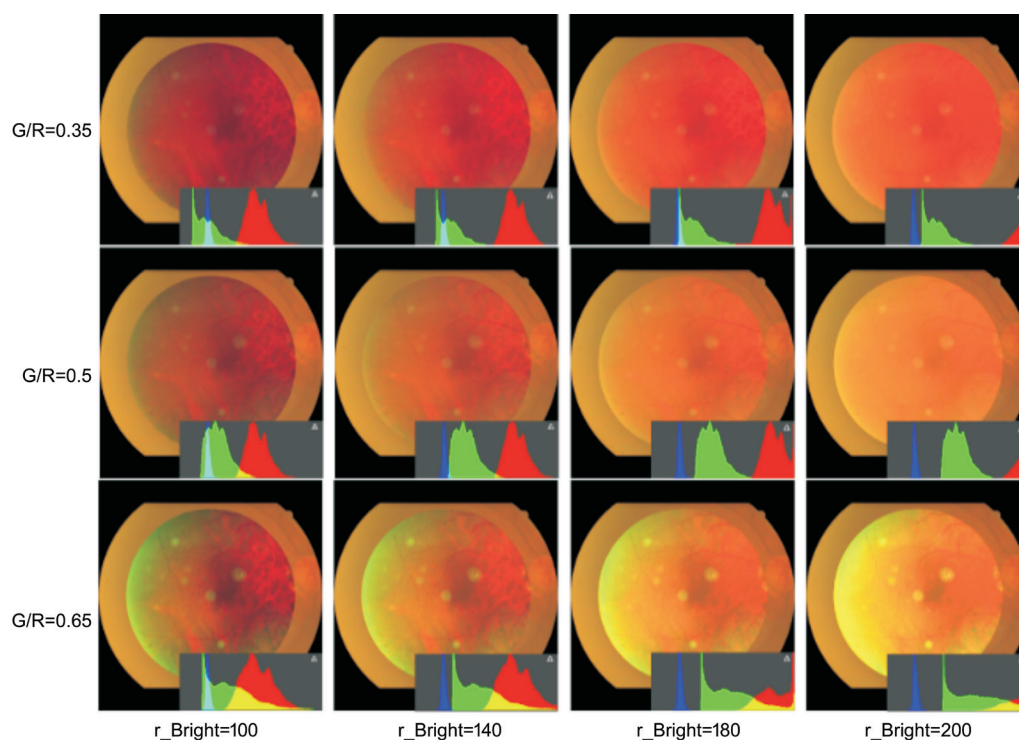
Figure 4 The effect of the software enhancement under different brightness values of the red channel and G/R ratios.

Table 3 Optimization parameters

Parameters	Red	Green	Blue
Brightness	0.7	0.35	0.15
Contrast	0.4-1	0-0.8	0-0.15

determined to be 0.5 and the average brightness of the green channel was determined to be 0.35.

Figure 5 shows the changes in the lesion and non-lesion areas with different G/R ratios and brightness values of the red channel image. By using the parameters above, we enhanced all the 86 images and calculated the brightness and contrast of all optimized images. Figure 6 shows two broken line graphs demonstrating brightness and contrast of optimized images.

In Figure 6, the overall contrast of optimized images was largely increased and the G/R ratio was maintained at approximately 0.5. Through the above procedure, we maximized the enhancement performance while maintaining the original information of the image. The optimized image is shown in Figure 7.

Image Enhancement Performance Assessment A total of 208 images of 104 participants were included in the diagnostic test. Fifty-seven (54.8%) participants were males and the mean age of all participants was 65 years old. Participants were diagnosed with AMD if at least one eye was diagnosed with AMD. The results obtained from OCT showed that 54 participants were diagnosed with AMD while 50 not. Tables 4 and 5 showed the diagnostic performance for the original images and optimized images, respectively.

Diagnostic sensitivity and specificity before and after image optimization were calculated according to the two fourfold

Table 4 Diagnostic performance of original images

Parameters	Gold standard		
	Positive	Negative	Total
Positive	40	6	46
Negative	14	44	58
Total	54	50	104

Table 5 Diagnostic performance of optimized images

Parameters	Gold standard		
	Positive	Negative	Total
Positive	48	8	56
Negative	6	42	48
Total	54	50	104

Table 6 Other indicators

Parameters	Original images	Optimized images
Positive predictive value	87.0%	85.7%
Negative predictive value	75.9%	87.5%
False positive rate	12%	16%
False negative rate	25.9%	11.1%
Positive likelihood	6.2	5.55
Negative likelihood	0.29	0.13
Accuracy	80.8%	86.5%
Youden index	0.62	0.73

tables above. The sensitivity significantly improved from 74% to 88% (χ^2=6.125, P=0.008), while the specificity slightly reduced from 88% to 84% (χ^2=0.500, P=0.500).

Other indicators of diagnostic efficiency are shown in Table 6. Using the optimized images for disease diagnosis, the negative
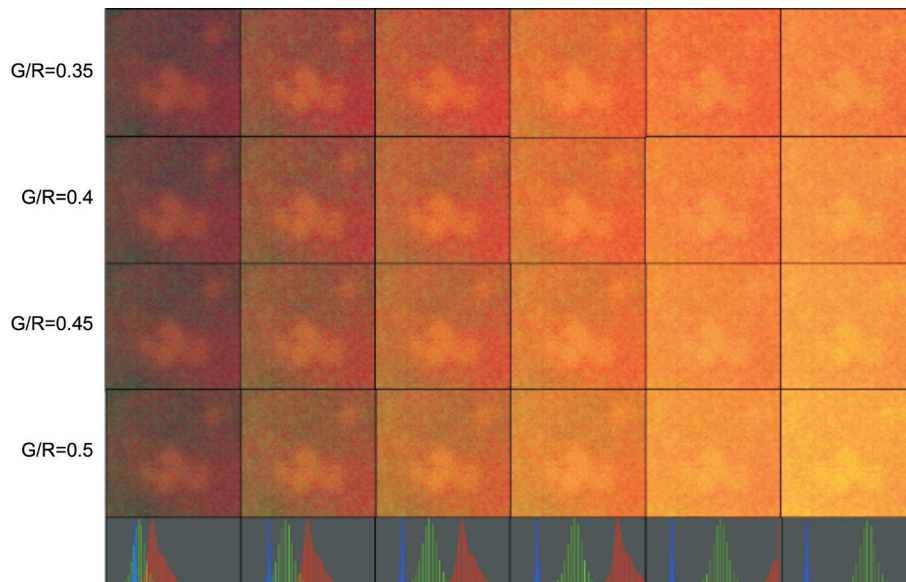
Figure 5 Changes of focus area with different G/R ratios and brightness values of the red channel.
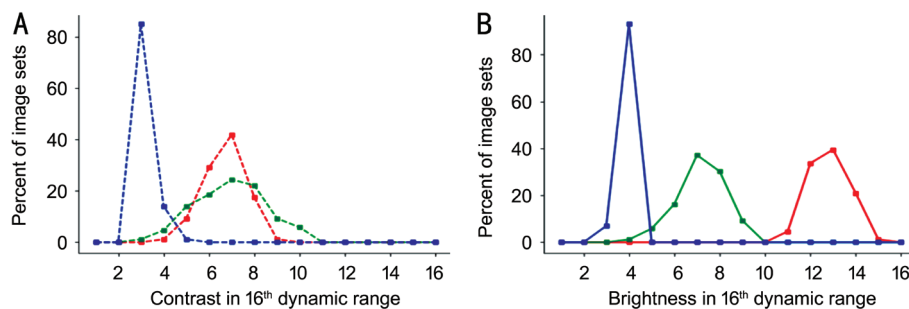

Figure 6 The distribution of brightness and contrast of optimized images A: The overall contrast values of these images; B: The brightness values.
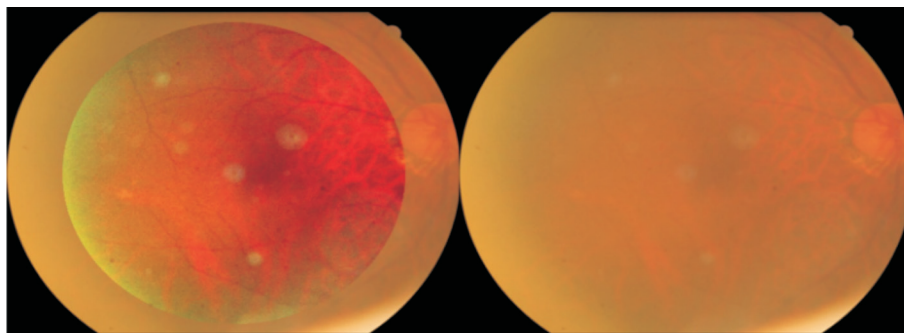

Figure 7 Image comparison after optimization (left) and before optimization (right).

predictive value increased by 11.6%, the false negative rate decreased by 14.8%, accuracy increased by 5.7%, and the Youden index increased by 0.11.

DISCUSSION

The improvement of medical image processing technology makes it possible for cooperation among doctors, image processing engineers, and software development engineers. The uniform quality of fundus images is of great significance to the accurate detection and classification of AMD. In the present study, 86 fundus images diagnosed with any stage of AMD in the Shanghai Changfeng Study have been used for optimization technology development[17]. By comparing

exemplary images with other images and observing features of typical AMD lesions under different brightness and contrast parameters, the optimal parameters were finally obtained. After multiple times of adjustments, we developed software that enables rapid and accurate enhancement of fundus images for AMD diagnosis in the Chinese population. The diagnostic test results showed that after optimization the sensitivity of fundus image diagnosis can be significantly improved without significantly reducing the specificity. The improvement in image parameters and the diagnostic test provided evidence that the fundus image optimization software can help accurate screening, detecting, and grading of AMD.

Previous studies have explored various methods of retinal image enhancement, including histogram equalization, but few studies have focused on AMD diagnosis[11-13]. Through standardized optimization of fundus images in the Caucasian population, the AREDS2 team demonstrated the effect of fundus image optimization for AMD, indicating extensive application prospects in image optimization for AMD grading. Compared with the optimization parameters for the Caucasian subjects in the AREDS2 study, lower brightness in the red channel, higher brightness in the blue channel, higher contrast in the blue and green channel were adopted in our study. This might be partly due to the racial difference in fundus pigments. Caucasians have lighter fundus pigmentation than Chinese, thus the basic tones of their fundus images may be bluish or purplish compared with the Chinese population. In AREDS2 research, the proportion of bluish or purplish images in all digital photographs is as high as 33.6%, but the same problem did not present in our study[13]. However, differences in camera properties, photographer techniques and other factors in the two studies may also result in the disparity in image performance. Large-scale studies that include multi-ethnic populations are needed. In 2018, some researchers proposed an image optimization method for retinal diseases, where the AUC of the optimized images was increased from 0.918 to 0.975[15]. However, the optimization method they proposed targeted at a variety of retinal diseases, including diabetic retinopathy, glaucoma, not only for AMD[15]. Characteristics and parameters of typical lesions vary among different retinal diseases; therefore, disease-specific optimization parameters should be a better choice for a specific fundus disease. The optimization parameters developed by the current study may not be applicable to other fundus diseases or other racial groups.

In our study, there is a significant increase in sensitivity from 74% to 88% by using optimized images. Our optimization may facilitate better screening, detecting and classifying AMD and reduce the probability of missed diagnosis. AMD is most commonly seen in the elderly, and meanwhile a large proportion of them present with cataract, vitreous opacity and other diseases that result in degradation of fundus image quality, making images optimization essential for diagnosis and classification of AMD. Furthermore, our diagnostic test was based on mydriatic fundus images collected in the clinical setting, which may have better image quality than those taken in the community and without mydriasis. Therefore, we may underestimate the improvement of sensitivity when generalizing it to the disease screening based on non-mydriatic fundus photographs in community settings.

The strengths of our research are as follows: First, we developed an automated fundus image optimization software for the Chinese population for the first time and assessed the performance of optimization software by a diagnostic test. Second, our research was a multidisciplinary research achieved by the multi-sectoral collaboration of ophthalmologists, image processing engineers, and software development engineers. Possible limitations of this study are the following: first, the specificity of the optimized images decreased slightly from 88% to 84%. However, the difference is not significant. In previous studies, the sensitivity of AMD diagnosis grading by fundus images ranged from 50% to 90%, and the specificity ranged from 63% to 90%[15,20]. Compared with previous results, our study showed an overall good performance. Second, the number of fundus images in our study was not large and may introduce potential bias. Due to the variety of the characteristics of late AMD lesions, using a single set of parameters to increase the detection rates of late AMD lesions to the maximum level is not realistic and feasible. Our enhancement procedure does not focus on late AMD lesions or other types of drusen such as the cuticular drusen and the reticular pseudo drusen. However, it can help detect late AMD lesions and other types of drusen to some extent. Furthermore, our optimization software may need further assessments on larger populations and different camera manufacturers.

In conclusion, in the current study, we developed an automated fundus image optimization software for the Chinese population and assessed the performance of optimization software by a diagnostic test. Our fundus image optimization software increased diagnostic sensitivity and may help ophthalmologists and researchers in AMD diagnosis and screening.

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