

Quantification of Diabetic Retinopathy Lesions in DME Patients With Intravitreal Conbercept Treatment Using Deep Learning

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BACKGROUND AND OBJECTIVES: To quantitatively evaluate diabetic retinopathy (DR) lesions using the authors' validated machine learning algorithms and provide physicians with an automated and precise method to follow the progression of DR and outcome of interventions.

PATIENTS AND METHODS: Retrospective analyses were conducted of 3,496 color fundus photography images from 19 patients with clinically significant diabetic macular edema receiving conbercept treatment. The modified seven-field fundus images were obtained at baseline and at the third, sixth, and twelfth month visit, whereas the modified two-field fundus images were obtained at the other monthly visits. The area of intraretinal hemorrhage and hard exudate lesions was traced by the authors' validated algorithms.

RESULTS: The mean central foveal thickness at baseline was $459.9 \mu\text{m} \pm 127.5 \mu\text{m}$. Mean central foveal thickness was $316.5 \mu\text{m} \pm 53.0 \mu\text{m}$ at the twelfth month visit, which decreased by $143.4 \mu\text{m}$ when compared with the baseline optical coherence tomography. The mean total area of intraretinal hemorrhage in the study eye in seven fields was $5.656 \pm 1.176 \text{ mm}^2$ at baseline, $2.438 \pm 0.976 \text{ mm}^2$ at the third month, $2.901 \pm 0.521 \text{ mm}^2$ at the sixth month, and $2.122 \pm 0.582 \text{ mm}^2$ at the end of the study. The area of intraretinal hemorrhage was reduced by 62.49% from baseline to the end of study ($P < .0001$). The mean total area of hard exudates in the study eye was $2.549 \pm 0.776 \text{ mm}^2$ at baseline, $2.233 \pm 0.576 \text{ mm}^2$ at the third month, $2.710 \pm 0.621 \text{ mm}^2$ at the sixth month, and $1.473 \pm 0.564 \text{ mm}^2$ at the end of the study. The mean total area of hard exudates decreased by 41.1% at the twelfth month ($P < .0001$) compared with the first visit. Significant decrease was observed in the area of intraretinal hemorrhage during conbercept treatment. The hard exudates area fluctuated during loading then subsequently decreased at the twelfth month.

CONCLUSIONS: The present study quantitatively analyzed the change in the area change of intraretinal hemorrhage and hard exudate lesions during the course of conbercept treatment. The automated system is promising to be a precise and objective method for monitoring the progression of DR and outcomes of interventions in clinical settings.

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INTRODUCTION

Diabetic retinopathy (DR) is a common complication of diabetes mellitus (DM) and the leading cause of blindness among working-age people. Diabetic macular edema (DME) and proliferative DR are the major causes of visual loss in DR. Early detection and prompt interventions have been proven to be efficient in previous studies.¹⁻³

The pathologic changes caused by diabetes mellitus occur to most cell types of the retina.⁴ The morphological features of the inner retinal vessels are mostly used for evaluation of the disease due to its visibility. The severity of DR can be evaluated according to the International Clinical Diabetic Retinopathy Disease Severity Scale, the Airlie House classification system.⁵ A more detailed and accurate scoring system has been introduced by the Early Treatment Diabetic Retinopathy Study (ETDRS) and applies to clinical research; however, this remains a hierarchical evaluation. The development of computational image processing makes accurate quantitative lesion evaluation possible.^{6,7}

Focal or grid laser photocoagulation has been applied for the treatment of DME for several de-

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Figure 1. Image segmentation results of the automated algorithms. (A) The original image. (B) Intraretinal hemorrhage segmentation. The hemorrhage lesion pixels were marked in purple. (C) Hard exudate segmentation. The exudate lesion pixels were marked in green.

caedes.⁸ The efficacy of the intravitreal injections of anti-vascular endothelial growth factor inhibitors (VEGFs) has been confirmed by a range of randomized, control trials. Their effect on DR has also been reported, but not quantitatively.^{9,10} Their effect on the progression of DR has not come to conclusion yet. Several randomized, controlled trials have reported less DR worsening, even with the improvement in patients receiving intravitreal anti-VEGFs.^{11,12} A quantitative measurement method of lesions of DR could provide more dependable evidence for conclusion.

With the implementation of machine learning algorithms, the present study team developed software focusing on the segmentation and quantitative evaluation of DR changes including microaneurysm, intraretinal hemorrhage, and hard exudate.¹³ The software achieved an area under the receiver operating characteristic curve of 0.925 on a subset of a Kaggle dataset, and 0.960 on Messidor for the detection of DR images comparing with human experts. It also achieved an F1-score of 0.924 with a sensitivity 0.995 and precision 0.863 on DIARETDB1 using the connected component-level validation for DR lesions. The details of the development and validation of our software was previously published.^{14,15}

Conbercept (KH902; Chengdu Kanghong Biotechnology Co. Ltd., Chengdu, China) is a recently developed anti-VEGF drug. Similar to aflibercept (Eylea; Regeneron, Tarrytown, NY), conbercept is an engineered protein that contains the extracellular Domain 2 of VEGF receptor 1 and extracellular Domains 3 and 4 of VEGF receptor 2 fused to the Fc portion of human immunoglobulin G1.¹⁶

In the present study, our team applied the validated machine learning algorithms to automatically detect, locate, and quantify the intraretinal hemorrhage and hard exudate lesions in color photography images of DME patients with intravitreal conbercept treatment.

PATIENTS AND METHODS

Clinical Data and Imaging Protocol

A retrospective analysis was conducted to explore the intraretinal hemorrhage and hard exudate lesion change during the course of the intravitreal conbercept treatment in patients with DME.

A total of 19 patients from our clinic with clinically significant DME receiving intravitreal conbercept treatment and monthly visits for longer than 1 year were pooled in for analysis.

The inclusion criteria mainly included the following: (1) Center-involved macular edema on optical coherence tomography (OCT) and a mean central retinal thickness of 320 μm or greater using Spectralis (Heidelberg Engineering, Heidelberg, Germany); (2) visual acuity letter score in the study eye of less than 73 and greater than or equal to 24; (4) Type 1 or type 2 diabetes; and (5) age younger than 75 years and 18 years or older.

The exclusion criteria mainly included: (1) Macular edema secondary to ocular conditions other than diabetes mellitus (eg, retinal vein or arterial occlusion, retinal detachment, macular hole, choroidal neovascularization, or uveitis); (2) myopia of 8.0 diopters or greater in the study eye; (3) panretinal photocoagulation treatment for the study eye during the study course; (4) previous history of anti-VEGF treatment for DME in the study eye; (5) previous history of intraocular surgery in the study eye within 6 months before the study or intraocular surgery taken during the course of the study; or (6) poor glycemic control ($\text{HbA1c} \geq 8\%$).

The treatment protocol was one initial injection of conbercept followed by as-need injections according to the patients' visual and morphological outcomes in the monthly follow-up visit. The retreatment criteria followed the DRCR.net anti-VEGF retreatment algorithm.¹⁷ Briefly, monthly injections followed by continued injections at monthly intervals until vision

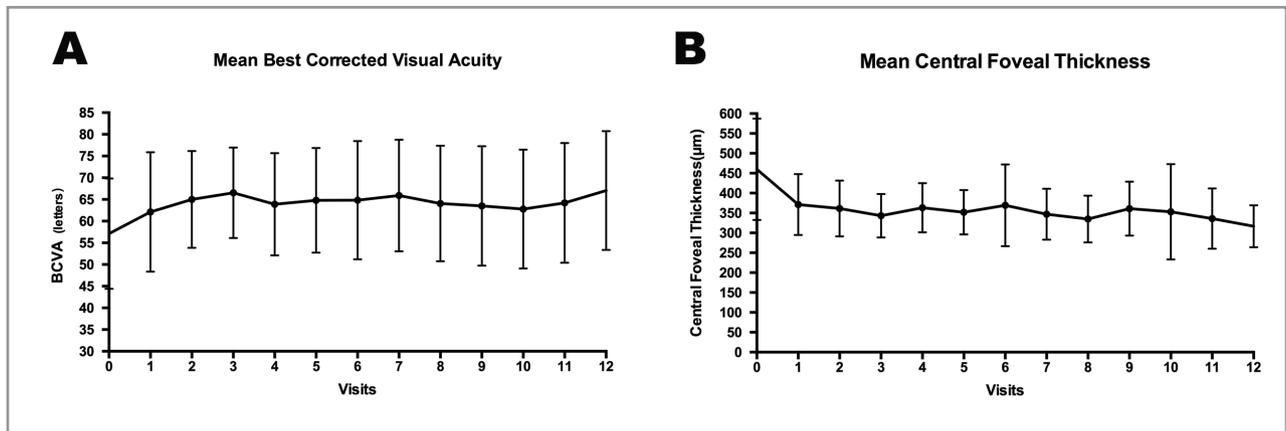


Figure 2. Best-corrected visual acuity (BCVA) and central foveal thickness change from baseline to 12 months. Vertical bars are ± 1 standard error of the mean. (A) An average 10.0 BCVA letters gained was observed from the baseline to the 12-month visit ($P < .05$). (B) An average of 143.4 μm decrease of central foveal thickness was observed from the baseline to the 12-month visit ($P < .05$).

and edema were no longer improving or can no longer improve (best-corrected visual acuity [BCVA] of 79 letters or better or central foveal thickness of 320.0 μm or less). Re-injection was at the investigator's discretion if edema recurred or worsened and was recommended if there was edema to treat.

Monthly visit was required for each enrolled patient. At each visit, refraction and visual acuity measurement, a dilated eye examination, and OCT were performed.¹⁸ The modified seven-field fundus images were obtained at baseline and at the third, sixth, and twelfth month visit, whereas the modified two-field fundus images were obtained at the other monthly visits. All color fundus images were taken from a TRC-50-DX (Topcon, Tokyo, Japan) with a Nikon D300 camera (Nikon, Tokyo, Japan). All OCT images were taken by a Heidelberg Spectralis OCT.

The study was approved by the institutional review board and ethics committee of Shanghai General Hospital. All participants provided written informed consent.

Automated Software Using Convolutional Neural Networks for Retinal Hemorrhage and Hard Exudate Lesion Detection

Our team developed algorithms based on combined neural networks for DR detection. The algorithms jointly learn the features and classifiers from data and achieve a significant improvement on detecting DR images and its typical lesions comparing with single neural network structure. The details of the development and validation of our software were previously reported and published.^{14,15}

Statistical Analysis

Color fundus photography images were analyzed by our automated software for intraretinal hemorrhage and hard exudate lesion segmentation and area measurement.

Differences in the data obtained were assessed using paired sample *t*-test. A *P* value less than .05 was considered statistically significant. All statistical analyses were performed using SPSS version 21.0 software (IBM Corp., Armonk, NY).

RESULTS

A total of 19 subjects with DME and DR were included in the present study according to the inclusion and exclusion criteria. The mean age of the subjects was 60.6 years old (standard deviation = 8.7). Nine out of the 19 subjects were female. The participants received a mean of 6.8 injections of conbercept during the 12-month follow-up period.

Modified seven-field or three-field digital color fundus images for each monthly visit were available for the included 19 patients. There were 3,496 color fundus images pooled in for intraretinal hemorrhage and hard exudate lesion area software analysis. Figure 1 is an example of the image processing results.

Change in BCVA

The mean ETDRS BCVA of the enrolled patients increased from 57.1 ± 12.7 letters to 67.1 ± 13.7 letters from baseline to the 12-month visit. There was a mean of 10.0 letters gained from the baseline to the last visit (Figure 2A).

Change in Central Foveal Thickness From OCT

The mean central foveal thickness at baseline was $459.9 \mu\text{m} \pm 127.5 \mu\text{m}$. The mean central foveal thickness was $316.5 \mu\text{m} \pm 53.0 \mu\text{m}$ at the 12-month visit, which decreased by 143.4 μm when compared with baseline (Figure 2B).

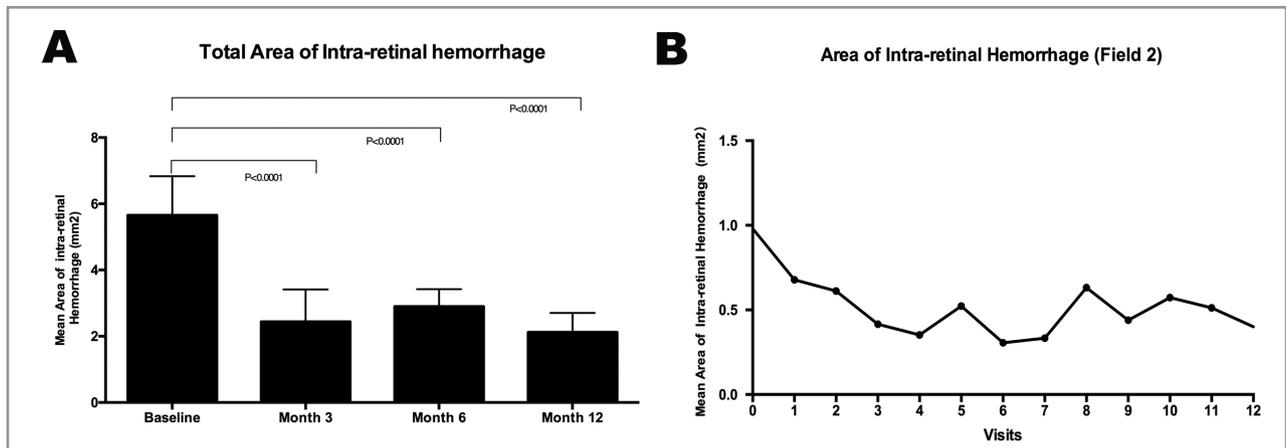


Figure 3. The area changes of intraretinal hemorrhage lesions over time. (A) Total area of intraretinal hemorrhage lesions in all seven fields at baseline, Month 3, Month 6, and Month 12. (Area changes comparing with baseline: $P < .0001$ at Month 3, $P < .0001$ at Month 6, and $P < .0001$ at Month 12. (B) The area of intraretinal hemorrhage lesions in Field 2 at each monthly visit.

Area Change of Intra-retinal Hemorrhage Lesions

The mean total area of intraretinal hemorrhage in the study eye in the seven fields at baseline was $5.656 \pm 1.176 \text{ mm}^2$ at baseline, $2.438 \pm 0.976 \text{ mm}^2$ at the third month visit, $2.901 \pm 0.521 \text{ mm}^2$ at the sixth month visit, and $2.122 \pm 0.582 \text{ mm}^2$ at the twelfth month the end of the study visit. The area of intraretinal hemorrhage was decreased and reduced by 62.49% from baseline to the end of the study ($P < .0001$; Figure 3A). The monthly area change of intraretinal hemorrhage in the macular field (Field 2) is presented in Figure 3B.

Area Change of Hard Exudate Lesions

The mean total area of hard exudates in the study eye in all seven fields at baseline was $2.549 \pm 0.776 \text{ mm}^2$ at baseline, $2.233 \pm 0.576 \text{ mm}^2$ at the 3-month visit, $2.710 \pm 0.621 \text{ mm}^2$ at the 6-month visit, and $1.473 \pm 0.564 \text{ mm}^2$ at the 12-month end-of-study visit. The area of hard exudates slightly increased by 6.3% at the 6-month visit ($P = .4849$) and subsequently decreased by 41.1% at the 12-month ($P < .0001$) when compared with the first visit (Figure 4A). The monthly area change of hard exudates lesion in Field 2 is presented in Figure 4B.

DISCUSSIONS

The efficacy of intravitreal injections of anti-VEGFs on DME has been well established through multiple randomized, controlled clinical trials including RESOLVE, RIDE, and RISE.¹⁸⁻²¹ The clinically significant benefits on prohibiting DR severity from progressing has also been reported previously in the RIDE and RISE open-label extension period data using ETDRS scoring.^{22,23} The results of our study are

consistent with previous studies but presented by a novel quantitative method.

Intraretinal hemorrhage in DR is considered the eruption of the enlarged microaneurysms in outer retinal layers including the inner nuclear layer and outer molecular layer. These lesions appeared in various shapes, such as punctate, blot, or linear, with the color of venous blood or paler.^{5,22} Hence, it is difficult to quantify these lesions manually.

In the present study, the area of intraretinal hemorrhage decreased significantly during the course of the follow-up. The area of intraretinal hemorrhage decreased by 56.9% at the 3-month visit after one or three initial monthly injections and decreased by 48.7% at 6 months and 62.5% at the end of the year compared with the baseline visit. Similar results have been presented in several randomized, controlled trials in a hierarchical manner including VIVID, VISTA, RISE, and RIDE etc.^{11,12} In the present study, data were delivered in a more precise and quantitative approach.

The area change over time of hard exudate during the course of course of the conbercept treatment was more interesting. When the blood-retinal barrier was damaged, serous liquids leaked from the vascular structure. They were absorbed during the course of time, and the process may be accelerated with prompt treatment. However, lipoproteins remained to form hard exudate mostly located in the outer layers of the retina. Different descriptions of the change of HE during the resolution of diabetic macular edema have been reported. In our study, the area of hard exudate grew during the loading phase of treatment and increased by 8.9% at the sixth month. But by the end of the study, the study eye resulted in significantly

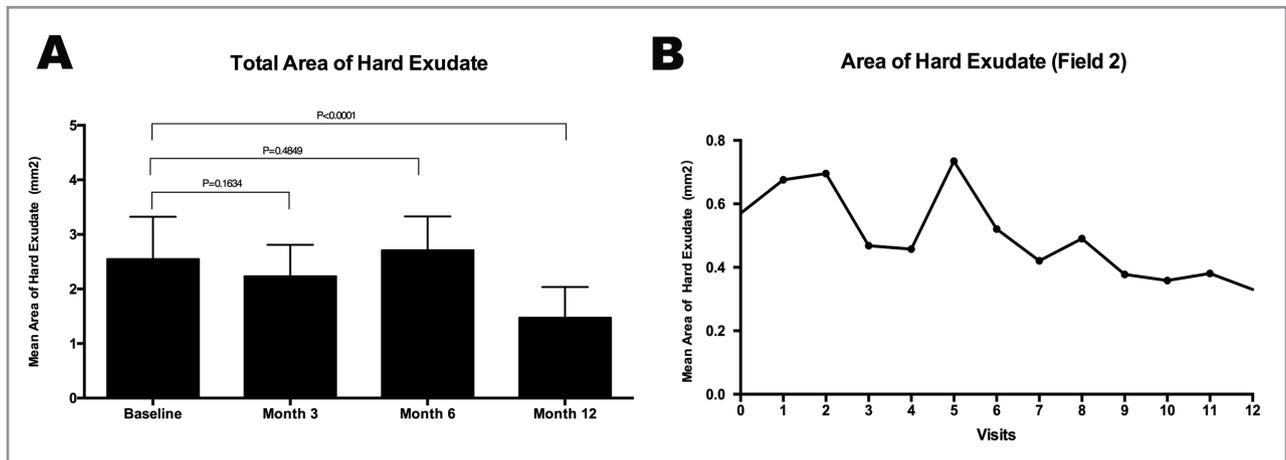


Figure 4. The area changes of hard exudate lesions over time. (A) Total area of hard exudate lesions in all seven fields at baseline, Month 3, Month 6, and Month 12. (Area changes comparing with baseline: $P = .1634$ at Month 3, $P = .4849$ at Month 6, and $P < .0001$ at Month 12. (B) The area of hard exudate lesions in Field 2 at each monthly visit.

greater reduction of HE area comparing with baseline. This supports the conclusion that macular edema is the first to resolve, followed by a later resolution of hard exudate lesions.^{23,24}

Certain limitations existed in the present study. The wrong judgment of the automated software occurred in some of the images. Localized depigmented areas such as choroid atrophy and laser scars were mistaken for hard exudate when they appeared to be morphologically similar. A few vascular segments were misjudged as intraretinal hemorrhage. The related classifiers are under development to exclude those false-positive lesions.

The follow-up time could be extended to better observe the lesion change over time. In addition, as a single-center study, the number of subjects included in the present study was limited. Large-scale, randomized, multicenter clinical trials with central reading center are proposed for further clinical evidence. Furthermore, novel modules of our software system to locate, segment, and quantify other typical lesion types of DR are under development.²⁵⁻²⁷

The automated software is a promising to be a precise and objective method for evaluating the progression of DR and the outcomes of interventions.

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