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Invited Review Article

Objective evaluation of allergic conjunctival disease (with a focus on the application of artificial intelligence technology)

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ABSTRACT

We have summarized the past efforts and results of objective measurement methods for conjunctival hyperemia classification. Severity classification using conjunctival blood vessel occupancy rate, ocular surface temperature analysis, and artificial intelligence have been reported to be clinically useful, as they have been found to correlate with the severity of conjunctival hyperemia by doctors. The AI method using slit lamp microscope images, whose main purpose is to be widely used in daily clinical practice, can be spread all over the world. As a result, it may lay the foundation for clinical research using large amounts of clinical data collected on the same basis without human bias.

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Introduction - Historical methods of the objective evaluation of conjunctival hyperemia

Expert systems have presumably driven the application of machine learning to medicine.¹ They have been structured to make a clinical diagnosis by scoring age, sex, and many other distinctive clinical findings. For example, structuring MRI images of cancer required clinicians to describe information in great detail, including anatomical location, size, stage classification, and grayscale values in black and white. This so-called rule-based method naturally declined due to the enormous data input required. Contrary to the aforementioned method, deep learning uses unstructured data.² This method is capable of identifying cancer images by merely providing cancer MRI images and normal MRI images. As the structuring and data input tasks required in the rule-base method are no longer needed, its application to medical images has been growing in all clinical areas. For example, in the area of allergies, deep learning has been used to classify whether the HE-stained slide specimens of nasal polyps in patients with chronic sinusitis are eosinophilic or non-eosinophilic. The deep learning model provided the AUC of 0.957, which is considered to be a clinically useful level.³ This review focuses on the objective allergy severity measurement studies that have been undertaken in the field of

ophthalmology. These studies show a transition from rule-based methods to deep learning methods and truly lead to an understanding of the history of problem-solving in medicine by machine learning common to all clinical areas.

Conjunctival hyperemia is one of the most common findings in ophthalmologic practice. It is routinely described in medical charts as a sign of many ocular diseases, such as conjunctivitis due to various factors, uveitis, elevated intraocular pressure due to glaucoma, and ophthalmic side effects. For example, conjunctival hyperemia is a minor side effect of glaucoma eye drops, but it becomes relatively important when medication adherence is considered. Most complaints of eye drop-related conjunctival hyperemia concern aesthetics; however, patients' dislike of their eyes' appearance can significantly impact their need to continue their medication. Several clinical studies have been conducted for conjunctival hyperemia reactions after glaucoma eye drop instillation. A critical variable in these studies is the determination of the severity of conjunctival hyperemia.

For the clinical evaluation of conjunctival hyperemia grading scales such as the McMonnies/Chapman–Davies scale, the Institute for Eye Research scale, the Efron scale, and the validated bulbar redness scale, are commonly used.

Presently, in Japan, conjunctival hyperemia is classified by severity according to the Conjunctival Hyperemia Severity Grading System, proposed by the Japan Ocular Allergy Society (JOAS).⁴

In this grading system, clinicians use standard photographs provided to grade the degree of dilation of conjunctival blood vessels, causing hyperemia on a 4-point scale that includes no

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hyperemia. This severity grading system is used in clinical studies of the aforementioned glaucoma eye drops.⁵

However, the subjective nature of the grading system has been pointed out. Yoneda *et al.* have reported a lack of consistency among experts using this grading system and invented an analytical application dedicated to conjunctival imaging to establish an objective grading system.

The hyperemia analysis software invented by Yoneda *et al.* is a type of software for quantifying the degree of hyperemia by digital processing using slit lamp photographs of the temporal bulbar conjunctiva. The resolution of the slit lamp photographs was 2000×1312 pixels, and for the region of interest (ROI), the temporal bulbar conjunctiva was selected within a range of 400×300 pixels. The method of extracting conjunctival blood vessels was analyzed by a proprietary algorithm using the RGB color model, and conjunctival hyperemia was evaluated based on the area occupied by blood vessels (%) in the ROI. They confirmed the normality and distribution of the area occupied by blood vessels in healthy individuals without conjunctival hyperemia. A total of 89 healthy adults aged 20–46 years (mean 25.4 ± 4.2 years) who had no ophthalmological diseases other than refractive errors were included in the study. The temporal conjunctiva of their right eyes was photographed, and the photographs were analyzed with the hyperemia analysis software. The mean area occupied by blood vessels of healthy adults was $4.4\% \pm 0.9\%$, indicating a normal distribution with the mean value as the peak ($P > 0.05$, Kolmogorov–Smirnov test). To evaluate the reproducibility of the results, two photographs of the temporal conjunctiva were taken for each subject, and the correlation between the analytical results were examined. The correlation coefficient was 0.79, which confirmed the reproducibility ($P < 0.01$, Pearson's moment correlation coefficient, $P < 0.01$, interclass correlation coefficient). Furthermore, bimatoprost (a prostaglandin drug used for glaucoma treatment which causes conjunctival hyperemia as a side effect) was administered to three subjects to compare the change in the degree of hyperemia before and 12 h after instillation. The mean area occupied by blood vessels was $4.4 \pm 0.8\%$ before instillation and $13.4 \pm 1.1\%$ 12 h after instillation. This means that the area significantly increased after the instillation of bimatoprost ($P < 0.001$, Wilcoxon signed-rank test). They also tested this system on three patients suffering from allergic conjunctivitis. The area occupied by blood vessels of the three patients was 23.9%, 25.3%, and 26.5%, respectively, which was approximately 5–6 times larger than values for healthy adults.

However, Yoneda admits that it is necessary to simplify the application before it can be used in clinical practice.⁶

Based on the slit lamp photographs, they estimated the system's success rate in grading to be 70%. Furthermore, they have admitted that the complex software operation required for grading remains an issue. Although significant improvement has been made in the objectivity of conjunctival hyperemia severity grading, Yoneda stated that further research is necessary regarding photography and analysis methods in terms of improving general clinical quality, and have continued their efforts to develop imaging equipment dedicated for the system.

There have been reports of the objective measurement of conjunctival hyperemia using Ocular Surface Thermographer (TOMEY Corporation, Nagoya, Japan). Ophthalmological applications of thermography have been reported by Hamano *et al.* in 1969⁷ regarding the temperature distribution of the anterior segment surface, and by Kayama *et al.* in 1980⁸ regarding the temperature of the ocular surface and the periocular skin of healthy individuals and those suffering various ocular diseases. Although its usefulness for glaucoma, dry eye, and ocular inflammatory diseases has been reported,^{9–14} all of these studies

have been conducted using conventional medical thermography, which has made routine thermographic testing somewhat difficult in outpatient settings. Ocular Surface Thermographer (OST, by TOMEY Corporation), a thermographer dedicated to ophthalmic testing, was developed to meet the need. OST measures ocular surface temperature and is regarded as superior to general medical thermographers for analyzing ocular diseases. In addition to an infrared camera, OST is equipped with a visible image camera that enables the operator to observe the ocular area while performing measurements. It is far superior to conventional medical thermographers in position recognition during measurement and analysis. Capable of taking a photograph every second, OST can easily capture sequential changes in surface temperature. Hara Y *et al.* conducted a CAC (conjunctival allergen challenge) test with cedar pollen using OST.¹⁵ The increase in the conjunctival surface temperature before and after instillation of the levocabastine ophthalmic solution (the levocabastine group) and artificial tears (the artificial tears group) was compared on the same individual. The conjunctival surface temperature was 0.67 ± 0.10 °C for the artificial tear group and 0.21 ± 0.06 °C for the levocabastine group; the increase was significantly smaller for the levocabastine group ($p < 0.05$). The increase in conjunctival temperature was significantly correlated with the conjunctival hyperemia severity score ($r = 0.63$, $p = 0.00058$). Despite its usefulness, OST measurements cannot be conducted without a special measuring device; therefore, its clinical application is limited to specialized clinical settings. For the purpose of using the hyperemia severity score widely in general practice, OST is not the most practical solution.

Recently, the application of automatic diagnosis methods using supervised machine learning, known as deep learning, has been widely reported in medical research. In ophthalmology, its use has been validated in reports on diabetic retinopathy, glaucoma, age-related macular degeneration, and retinal detachment.¹⁶ The imaging devices used in these studies are also diverse, including a regular fundus camera, an optical coherence tomographic system, and a wide-angle fundus camera. The benefits of diagnostic and grading systems using deep learning are broad applicability and economic efficiency. Specifically, since this system can be trained to identify somewhat unfocused or misaligned images, it is expected to be widely applicable in actual clinical settings. In addition, although a large amount of computation is required for the learning process, actual grading is performed by a simplified four-rule computation. Because such computation does not require large computing power, this system has the potential to be widely applied in clinical practice.

Although a clinically useful system that automatically performs hyperemia grading by deep learning is theoretically possible, to our knowledge, no attempts have been made except for those made by our team. In this paper, we report our initiatives to apply AI to images taken by slit lamp microscopes or anterior ocular segment measurement devices, as well as a study involving multiple facilities connected with a VPN network.

Application to the slit lamp microscopy

First, we report our attempts to develop a system that performs as well as experts using standard slit photographs to teach a deep learning network the conjunctival hyperemia severity grading of the JOAS.¹⁷ This will also help readers understand the development process of artificial intelligence applications for medical purposes.

The conjunctival hyperemia severity grading system of the Japan ocular allergy society

The Japan Ocular Allergy Society's conjunctival hyperemia severity grading system (hereafter "JOAS grading") is a system for classifying the degree of dilation of conjunctival blood vessels in spherical conjunctiva into four levels: none, mild, moderate, and advanced, using a set of standard photographs (Fig. 1).

Image data: collection and allocation for developing the AI model

From all of the slit lamp photographs taken for clinical purposes at the Ophthalmology Department of Tsukazaki Hospital, a total of 5008 photographs were extracted from the image database. To achieve consistency with the standard photographs in Fig. 1, magnifications of $4\times$ and $8\times$ were used. Slit lamp microscopes by Zeiss Corporation and Hague Straight Corporation were used, and the photographic conditions, such as the amount of light and the direction of the gaze, were not specifically defined. Figure 2 shows some of these images.

The initial 5008 images were divided into two groups: 4008 images for preparing the artificial intelligence model (hereafter "for model") and 1000 images for preliminary validation by graders and for model validation (hereafter "for validation"). For the images for validation, 128 images were excluded due to errors in ID management during the image processing; thus, the remaining 872 images were used. For the images for the model, 50 images were found non-gradable, while 92 images had errors in ID management; thus, the remaining 3816 images were used.

Selection of graders

To develop the model, a weighted kappa coefficient was used to first examine the inter-rater agreement of the 872 validation images. JOAS grading was performed on the 872 validation images independently by a physician who was a certified specialist member of the JOAS (hereafter the "specialist"), as well as by four certified orthoptists (COs). All 4 COs and the specialist graded with weighted kappa coefficients of above 0.7; (0.716599, 0.755371, 0.731601, 0.712063 respectively) therefore, they were considered grading experts (hereafter "the experts") for the purposes of reference (correct) for JOAS grading scores while developing the AI model.

(Weighted kappa coefficient is a statistic used to measure inter-rater agreement for three or more classes. For example, when there are three classes (mild, moderate, and severe), selections such as mild instead of moderate, and mild instead of severe, are weighed differently. In contrast, the standard kappa coefficient represents the degree of agreement between the two classes. Since this attempt involved four classes, the weighted kappa coefficient was used.)

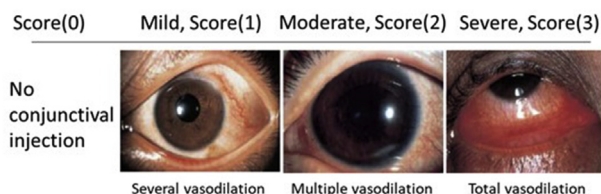


Fig. 1. Standard photographs of the severity of conjunctival hyperemia by Japan Ocular Allergy Society grade.

Grading by the experts for training the artificial intelligence model

The 4008 images for the model were divided into two sets of images. Two COs, Mat and Nis (hereafter the "Expert 1"), graded the first set of 2004 images with smaller study IDs, and other two COs, Ohi and Oka (hereafter the "Expert 2"), graded the second set of 2004 images with larger study IDs using JOAS grading. During the grading process, 92 images were excluded from grading due to data management errors such as misassignment, overwriting, or deletion of internal IDs. For the remaining 3916 images, both graders were in agreement for 2707 images; this set was then used for the training data. The remaining 1209 images, which were inconsistent in grade, were graded again by the specialists. A total of 90 images were graded as ungradable by the specialists.

Building the artificial intelligence model

The image data was equally divided into five blocks. Four of the five blocks were used for training, and the remaining one block was used for validation (K-Fold Cross Validation). Image processing was performed on the training data, which was amplified 18 times. The image amplification processing performed included contrast adjustment, γ correction, histogram equalization, noise addition, and inversion. With the amplified images, we trained six types of deep neural networks (VGG16, VGG19, ResNet50, InceptionV3, Inception ResNet V2, Xception) to build models. Using each model, we tested the validation data and evaluated the model. All of the blocks were readied for validation by repeating this process five times.

Deep learning model and training the model

Among the various DNNs used in this study, we will explain VGG-16, which is a typical deep learning model. The VGG-16 can be divided into five bidding blocks composed of convolution layers and max-pooling layers, as well as the fully connected layer. First, all the input images were converted to 256×192 pixels in advance, read in RGB ranging from 0 to 255, which were then divided by 255 to normalize to the range of 0–1. The convolutional layer recognizes features of the target through convolutional filters. The max-pooling layer was placed at the end of each block. It reduces the position sensitivity of a feature output from a convolutional layer so that more general recognition can be performed. Finally, after flattening the three-dimensional matrix, we arranged two layers of the fully connected layer and classified them into two classes by a softmax function. The purpose of the fully connected layer is to remove spatial information from extracted features and to distinguish the target from other feature vectors statistically. Dropout processing was applied to the first fully connected layer to mask out with 25% probability. The purpose of dropout processing is to improve generalization performance and prevent over-learning during training. We used a method called fine-tuning, which uses already learned parameters with different data. Its objective is to increase training speed and easily obtain high performance even with a small amount of data. The parameters obtained from learning Imagenet were used, fixating blocks 1 to 4, and only block 5, and all the fully connected layers were adjusted. The initial weight update was performed according to an optimization algorithm called Momentum SGD (learning coefficient = 0.001, inertia term = 0.9), which is one of the stochastic gradient descent methods. The construction and validation of the model were carried out using Keras (<https://keras.io/en/>), which runs Python's TensorFlow backend (<https://www.tensorflow.org/>).

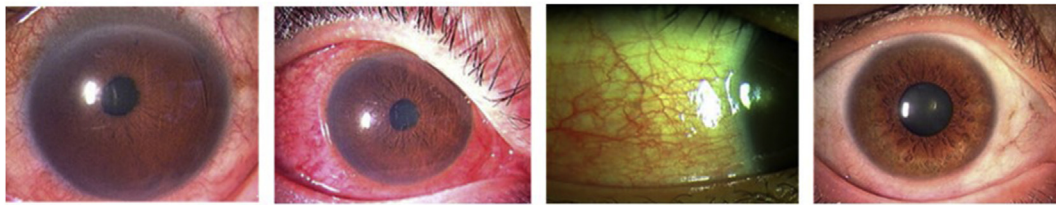


Fig. 2. Slit photographs for grading conjunctival hyperemia extracted from the database of the Ophthalmology Department of Tsukazaki Hospital.

Multimodel evaluation using artificial intelligence models (ensemble method)

The six types of learning models were combined to grade 872 images for validation to examine the degree of agreement in grading with the experts' responses. The mean grade provided by the experts was used. If half of the six DNN models gave the same grade as the experts, we counted it as a correct answer. By this standard, the correct answer rate was 83.5%.

The weighted kappa coefficients between the grades given by the typical model VGG16 and Expert 1 and Expert 2 were 0.76 and 0.78, respectively, whereas the weighted kappa coefficient between Expert 1 and Expert 2 was 0.73. This means that the grade discrepancies between the AI model and the experts were smaller than those found between the experts. In other words, the AI's learning ability was closer to each of the experts than the other human counterpart.

Correlation with objective indicators

What is the correlation between the AI grading results and the objective indicators developed by Yoneda *et al.*, which is based on the area occupied by blood vessels in the bulbar conjunctiva. Our study's results were favorable, showing a high correlation of 0.74.

Attempts to incorporate the AI application into the anterior eye measurement device

We attempted to apply the above-mentioned AI model for slit lamp to images taken with the anterior segment measuring device (MR-6000) from the TOMEY Corporation.¹⁸ When the AI model for slit lamp was directly applied to the MR-6000 images, the mean weighted kappa coefficient between the AI model and the experts was 0.47, which represents a low degree of agreement. In order to improve the performance to the level of the slit lamp AI model, the parameters of the slit lamp AI model were optimized using 421 images for additional learning. As a result, the mean weighted kappa coefficient between the AI and the three experts increased to 0.647. The images used for additional learning accounted for 11% of the 3816 images required for the slit lamp model, which suggested that fine-tuning AI applications for different devices requires much less effort than creating the original model. We believe that this result is useful information for developing medical AI applications in the future.

The use of an AI application in multiple facilities

The study was conducted at three facilities: Ophthalmology Department of Tsukazaki Hospital, Niimi Ophthalmology Clinic, and Yamaike Ophthalmology Clinic, which were networked with a secure VPN. All the facilities have the same image filing system installed, and a total of about 1.55 million images registered in the image database of these facilities were included in the

study.¹⁹ Of all of the images, only photographs taken by slit lamps were selected using our own AI model that automatically identifies the images taken by a specific imaging device. Similarly, using our own AI model (which excludes images with subconjunctival hemorrhages), we excluded images with subconjunctival hemorrhages and post-operative eyes. As a result, a total of 1,0186 images were included in the study. For these images, we applied the AI model for slit lamp, and extracted the distribution of images graded 0 to 3. It took three days from the time when the plan was confirmed to the time when it was implemented (excluding the time required for registering with the ethics committee). The images graded as 2 or 3, which indicates a pathological sign, accounted for 8.8% and 0.9% of the images, respectively. This result was consistent with the clinical judgement of the collaborating experts.

Our team would like to highlight two things from this study. The first thing to note is the outstanding speed of the networked database study. This study took only three days to complete. This type of database study would provide quality information required for decision making on fluid policies, such as gaining insight into allergy trends. Faster speeds mean less human involvement. The ability to acquire mass data without compromising routine clinical practice is a benefit of networked environments. The second element worth underscoring is artificial intelligence, which is the theme of this paper. AI should be able to logically perform a more stable classification of hyperemia severity than the doctors at the three facilities. Though further study is necessary to prove the grading accuracy of AI, we believe that the implications of AI grading would be significant in large-scale clinical studies, and this study's results did not refute this perspective.

Summary of the development of the AI-based hyperemia severity grading system

We developed a deep learning-based hyperemia severity grading system that was accurate and highly consistent with grading by clinical experts. The mean weighted kappa coefficient, an indicator of the degree of agreement between the experts, was 0.74, which represents the clarity of the grading criteria employed by the severity grading system itself. Furthermore, the weighted kappa coefficient of the typical AI model was 0.78, which was higher than the degree of agreement between the experts, indicating that grading by AI is clinically highly acceptable. This is because the grades given by AI fall within the range of variation in grades given by experts.

Another notable benefit of this system for slit lamp is that it was built using images obtained in routine clinical practice. The system does not require imaging methods intended only for hyperemia grading, nor a special imaging device; instead, it uses images acquired using standard slit lamp microscope with necessary angle and magnification, suggesting that it is highly suitable for routine clinical application.

The study also suggested that this system can be incorporated into another device, such as an anterior ocular segment photographing device with relatively little effort. If this AI grading system is used on the same device in multi-centered studies, the problem of inter-rater grade discrepancies can be minimized as this system would remove background variations in the imaging conditions. If the application of this system becomes widely accepted, hyperemia severity grading may be used to assess therapeutic effects and side effects for many types of ocular disease. The resulting clinical progress is that for which our development team aspires.

We would like to develop this system by improving the problematic aspects, utilizing it in actual clinical settings, and adding necessary functions to gain widespread use.

Conclusion

Conjunctival hyperemia is a critical finding that supports clinicians' decision-making in routine ophthalmologic clinical practice. There have been many studies on the classification of hyperemia severity. In Japan, the grading system formulated by JOAS has been used to develop objective evaluation methods. The reduction of variations in subjective grading based on reference pictures is the primary goal of developing an objective evaluation method. At the same time, it is also important that such a method can be easily used by general ophthalmologists. Objective hyperemia grading capability is likely to be particularly useful for general as well as for specialized clinics. The system application using the area occupied by blood vessels developed by Yoneda *et al.*, the hyperemia degree measurement system using thermography developed by Hara *et al.*, and our AI-based hyperemia severity grading system have been successful to a certain extent; however, none of these systems have been put into general use. The system developed by Yoneda *et al.* is highly accurate and credible and is academically extremely useful, but its measurement process is too complex to be commonly used. The method developed by Hara *et al.* is also attractive for its excellent visibility; however, the necessity of a special measuring device is an unavoidable bottleneck preventing general use. We believe that our system is the most likely to become available for general use; however, the results we have at this time arise from a small-scale experiment. In order to achieve social implementation, all necessary steps must be taken, including testing by a certification body.

In other words, further research and development are needed in this area in order to achieve social implementation of the system, which was our initial intention. For example, if the AI-based hyperemia severity grading system becomes widely used in medical institutions without an ophthalmologist, this will certainly mark a medical advance. If such a system is utilized in emergency medical care, internal clinics, or geriatric healthcare facilities to detect anterior segment hyperemia, it will help assist in making emergency referrals to ophthalmologists. To this end, we are working earnestly to add this AI-based hyperemia severity grading system to a handheld anterior segment imaging device currently under development.

The objective hyperemia severity grading system will become useful for large-scale disease analysis if the system is widely used in general ophthalmology practice, not only in Japan but throughout the world. Furthermore, we believe that the usefulness of conjunctival hyperemia as a critical ophthalmological finding will be reaffirmed by the medical community.

Conflict of interest

Both HT and HM are main members of Thinkout Corporation which has various patents of AI. The company owns the rights of the hyperemic AI mentioned in this article.

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