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A non-invasive diabetes diagnosis method based on novel scleral imaging instrument and AI

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ABSTRACT

Type 2 diabetes mellitus is one of the most common metabolic diseases in the world. However, frequent blood glucose testing causes continual harm to diabetics, which cannot meet the needs of early diagnosis and long-term tracking of diabetes. Thus non-invasive adjuvant diagnosis methods are urgently needed, enabling early screening of the population for diabetes, the evaluation of diabetes risk, and assessment of therapeutic effects. The human eye plays an important role in painless and non-invasive approaches, because it is considered an internal organ but can be easily be externally observed. We developed an AI model to predict the probability of diabetes from scleral images taken by a specially developed instrument, which could conveniently and quickly collect complete scleral images in four directions and perform artificial intelligence (AI) analysis in 3 min without any reagent consumption or the need for a laboratory. The novel optical instrument could adaptively eliminate reflections and collected shadow-free scleral images. 177 subjects were recruited to participate in this experiment, including 127 benign subjects and 50 malignant subjects. The blood sample and sclera images from each subject was obtained. The scleral image classification model achieved a mean AUC over 0.85, which indicates great potential for early screening of practical diabetes during periodic physical checkups or daily family health monitoring. With this AI scleral features imaging and analysis method, diabetic patients' health conditions can be rapidly, noninvasively, and accurately analyzed, which offers a platform for noninvasive forecasting, early diagnosis, and long-term monitoring for diabetes and its complications.

Keywords: type 2 diabetes mellitus, shadow-free scleral images, U-net, Resnet-18, MIL

1. INTRODUCTION

1.1 Type 2 diabetes mellitus

Type 2 diabetes mellitus is the most prevalent form of diabetes, which is one of the common endocrine diseases worldwide. [1] The incidence of diabetes, especially in China, has increased in recent decades, from 0.67% in 1980 to 11.2% in 2017. At present, China has the largest population of diabetic patients in the world. [2] According to GUIDELINE for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition), fasting blood glucose, random blood glucose or OGTT(oral glucose tolerance test) 2h blood glucose is the main basis for diagnosing diabetes. If there is no typical symptoms of diabetes, the test must be repeated to confirm the diagnosis. In laboratories with strict quality control, standardized HbA1C can be used as a supplementary diagnostic criterion for diabetes. Diabetes is diagnosed based on the measurement of venous plasma glucose instead of capillary blood glucose. The classification criteria of glucose metabolism status and the diagnosis criteria of diabetes are shown in Table 1.[2]

Table 1. The classification criteria of glucose metabolism status and the diagnosis criteria of diabetes.

Diagnostic criteria	Venous plasma glucose or HbA1c level
Typical symptoms of diabetes	
And random blood sugar	≥11.1mol/L
Or fasting blood sugar	≥7.0mol/L
Or OGTT 2h blood glucose	≥11.1mol/L
Or HbA1c	≥6.5%
If there is no typical symptoms of diabetes, the diagnosis needs to be rechecked another day	

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For people at high risk of diabetes, screening should be carried out as soon as possible. The results of a number of randomized controlled studies have shown that people with impaired glucose tolerance (IGT) receiving appropriate lifestyle interventions can delay or prevent the onset of diabetes. However, the common diagnostic methods of monitoring blood glucose levels has a relatively high threshold, which leads to difficulties in early screening of type 2 diabetes mellitus with milder symptoms, and can cause sustained harm to the patients. [3-5] Therefore, there is an urgent need for a non-invasive method to diagnose diabetes, which can be quickly and easily used for early screening and risk assessment of type 2 diabetes mellitus.

1.2 The diagnostic potential of scleral features

Extensive clinical studies have revealed a close relationship between scleral features and changes in internal organs. However, the sclera, also known as the white of the eye, is the opaque, fibrous, protective, outer layer of the human eye [6]. The sclera's blood vessels are mainly on the surface [7], so they are almost the only blood vessels that can be directly observed without being covered by skin and affected by pigments. Therefore, it is expected that cancer is related to the vascular pattern of the sclera. The human eye plays an important role in painless and non-invasive approaches, because it is considered an internal organ but can be easily be externally observed [8]. The iris and sclera are two important parts of the human eye that can provide useful information about one's health status [9]. Therefore, examining the iris and sclera can reveal possible diseases or dysfunctions of specific organs [10]. Advanced image processing and data mining techniques have been utilized as a powerful disease diagnostic tool in biomedical applications [11,12]. Iris sign recognition algorithms have been used to detect cholesterol present in blood vessels [13,14], as well as definition risk factors for diabetes [15,16] and breast cancer [17]. Dilated scleral vessels have been used to assess the health status of patients suspected of having internal carotid artery occlusions [18]. Further, modeling efforts have shown that scleral stiffness [19], thickness [20], and collagen fiber structure [21], which are associated with the optic nerve head (ONH) tissues, can be used to evaluate the effects of diabetes for major ocular diseases [22]. Fundus imaging can objectively display retinal images [23] and is a common method for clinical screening of type 2 diabetic retinopathy. Coudrillier [24] found that changes in the arrangement of scleral collagen fibers are closely related to type 2 diabetes mellitus.

1.3 Machine and deep learning in biomedical research

In recent years, we have witnessed the significant deployment of machine and deep learning techniques used in biomedical research [25-27]. Compared to humans using experience and knowledge to analyze medical data, learning-based techniques have a key advantage in that they are capable of automatically discovering important information from raw data for further analysis. In this way, more informative features can be extracted, and more complicated but valuable patterns can be recognized. Specifically, many researchers have used Artificial Intelligence (AI) technology to increase the efficiency of scleral features-based type 2 diabetes diagnosis. Kaushal [28] developed an EyeArt system for fully automated screening of diabetic retinopathy patients, which yielded results with good sensitivity and specificity. Varun Gulshan [29] processed a huge data set (11,711 fundus images from 5,871 patients) by deep learning for the detection of diabetic retinopathy. Piyush Samant [30] analyzed 338 subjects, including 180 individuals with diabetes and 158 without diabetes and obtained infrared images of these patients, which were processed by image segmentation and feature extraction; the accuracy of classification between diabetic and non-diabetic groups was 89.63%.

2. THE INSTRUMENT AND AI MODEL

2.1 The specially developed instrument

Due to the multilayer quasi-sphere structure of eyeball, the imaging shadow from the illumination source is a challenge for scleral features imaging. To solve this problem, a slit lamp microscope was developed for ophthalmological diagnosis [31]; this facilitates the observation of flaws in the eyeball in a narrow zone using a slit light produced by the slit illumination source, free from reflection shadows due to the illumination source. However, an additional scan of slit light is required to acquire an overall image of the eyeball and it is rather time-consuming to splice images taken with a slit light scan. Moreover, slit lamp microscopes are only suitable for retinal imaging. Here, an adaptive scleral features imaging approach was proposed to avoid reflection from the illumination source, which causes disturbance (Fig. 1).

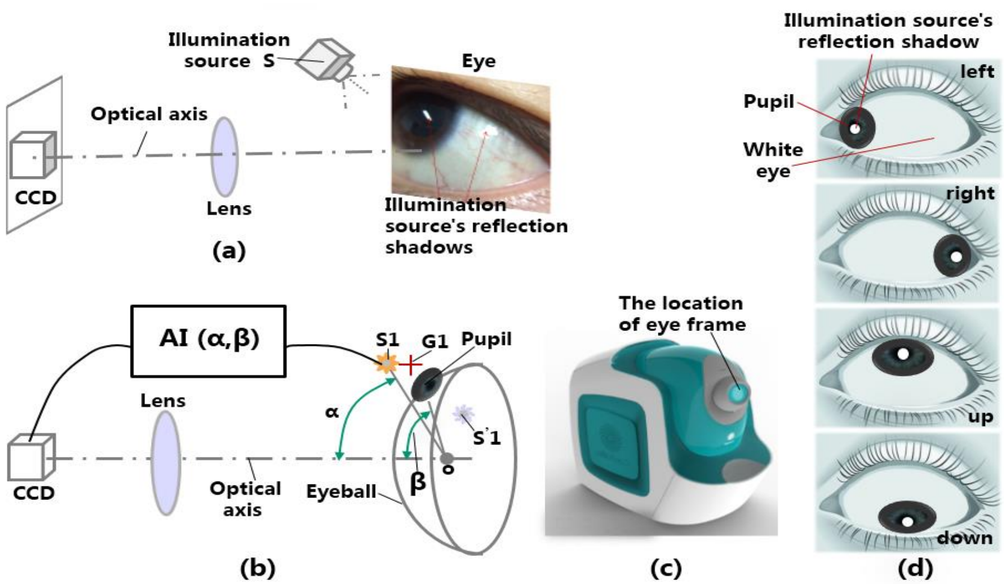


Figure 1. Schematic diagram of adaptive scleral features imaging and a photo of the system. (a) Graphical representation of conventional eye imaging, including the illumination source's reflection shadows. (b) Schematic diagram of adaptive scleral features imaging. (c) Image of the adaptive scleral features imaging system. (d) Graphical representation of shadowless white eye imaging in four directions.

To eliminate the interference by reflection shadows on scleral features imaging due to the illumination source, an adaptive scleral features imaging system was developed as shown in Figure 1(b), where S1 is the illumination source of a 1-W LED white light, G1 is the cross guiding light of a 1-W green LED, the lens has a 100-mm focal length, CCD is a Canon 5D, S'1 is one of the reflection shadows of the illumination source S1, α is the angle between the optical axis and S1, and β is the angle between the optical axis and the pupil. To build the iris auto-tracking and sclera auto-focusing method, the optimum values of α and β were obtained at ~40–50° and ~65–80°, respectively, when all reflection shadows of the illumination source were focused on a small point and superimposed onto the pupil. The optimal values of α and β differ for different people. Using the cross light guide G1, the user is guided to rotate the eyeball and adjust the pupil position, and make negative feedback on the iris automatic tracking until the reflected shadows of the corresponding illumination light converge at one point and is superimposed into the pupil. The sclera can then be imaged clearly without any interference from the reflection shadows due to the illumination source, as shown in Figure 1(d) left.

Similarly, to rotate the eyeball right, up, downward, or auto-focus, and photograph the white eye synchronously, images of the entire white portion of the eye without the reflection shadows of the illumination source can be obtained as shown in Figure 1(d) right, up, and down. The above-mentioned processes can be finished within 3 min.

2.2 The AI prediction model

The AI prediction model consists of two parts, as shown in picture 2. First one is a scleral segmentation model based on the U-net, and the other one is a feature extraction and classification model based on Resnet-18 and MIL.

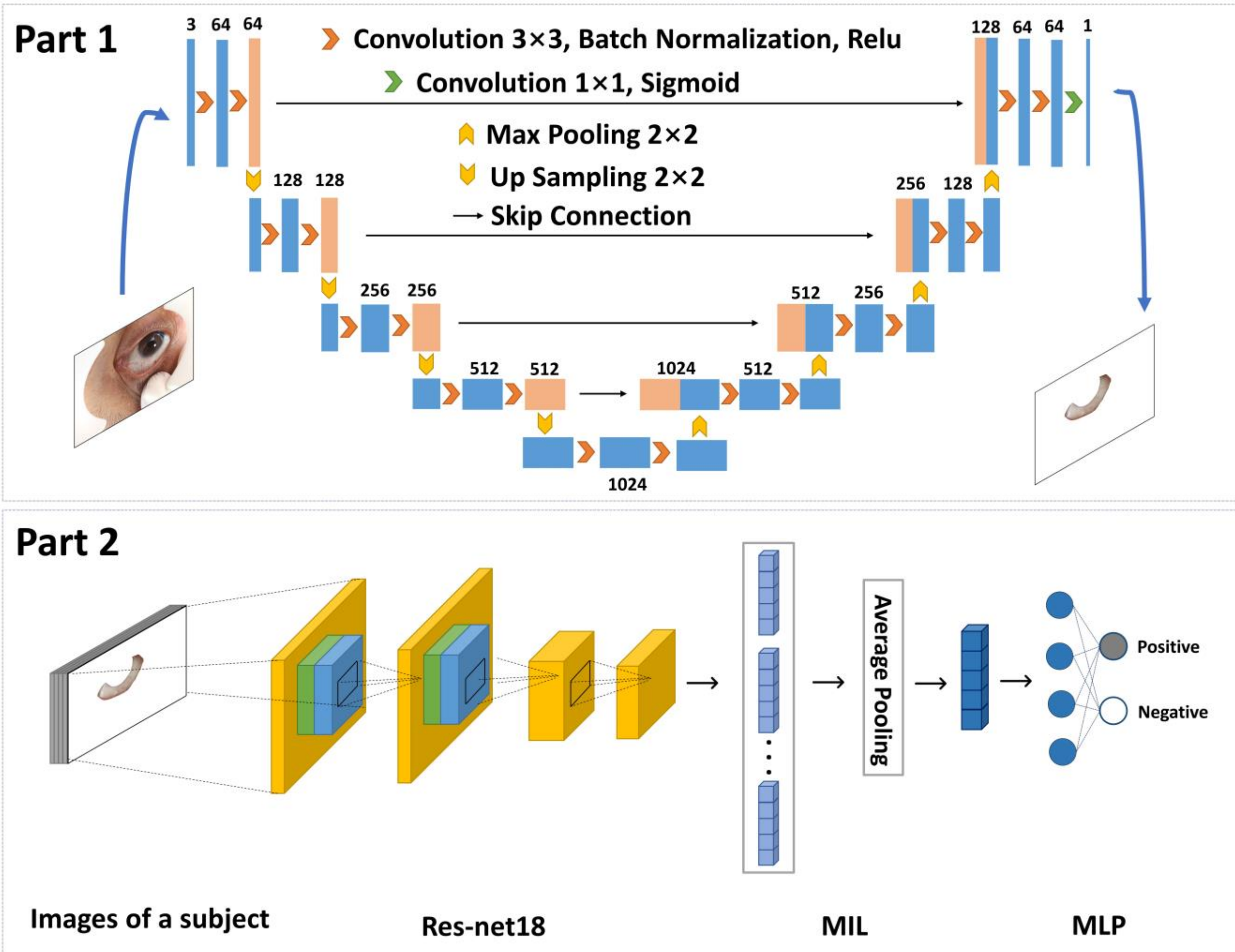


Figure 2. The AI prediction model. Part 1 is a scleral segmentation model based on the U-net, and part 2 is a feature extraction and classification model based on Resnet-18 and MIL.

The U-net structure was proposed by Olaf Ronneberger et al. in 2015 [32]. Its advantage is that it can comprehensively use deep features and shallow features to achieve more accurate target segmentation. The U-net training requires a small number of labeled samples, so It is suitable for the needs of image segmentation in the field of biomedical images. The U-net network structure is a U-shaped structure consisting of a contracting path for obtaining information and an expanding path symmetrical to it for precise positioning. The U-net network structure can combine the information of object recognition with the information of the precise position of the object, so as to realize the accurate segmentation of medical images. Now some researchers have applied U-net to the field of scleral segmentation and have achieved good results [33].

In the scleral segmentation experiment based on the U-net, we divided the training set and the test set by 7:3. Manually label the scleral area of the training set. Due to the small amount of data in the training set, in order to obtain better training results, we have expanded the training data. The optimization algorithm used in this experiment is the stochastic gradient descent method (SGD), and the momentum optimization method (Momentum) and the L2 regularization term to prevent the model from overfitting are introduced, and the adaptive learning rate method is also used. Finally, this experiment uses IoU (the ratio of the intersection and union of the two sets of Predicted Segmentation and Ground Truth), Precision, Recall, and F1-score as evaluation indicators.

The preprocessed scleral image was fed to the MIL model. For each patient, different areas of the two eyes were revealed in different images. It is better to consider all images of a patient when making a decision than to predict from a single image. This issue has been addressed by MIL.

As shown in Fig. 2, for all images $\gamma = \{x_i\}_{i=1}^{10}$ of a patient, both of them are fed into ResNet-18, which is denoted here as g. A sequence of feature vectors $\{h_i\}_{i=1}^{10}$ is extracted by ResNet-18, where $h_i = g(x_i)$ serves as the feature vectors of each scleral image. To utilize information from all images of each patient, a fusion feature vector h_{fusion} is calculated, which gathers useful information from each feature vector $\{h_i\}_{i=1}^{10}$ and serves as a reliable representation. The fusion feature vector is aggregated from feature vectors using average pooling, given by equation (1), where N denotes the number of scleral images for each patient. Finally, the fusion feature vector hfusion is fed into a multi-layer perceptron (MLP) to obtain a prediction score.

$$h_{fusion} = \frac{1}{N}\sum_{i=1}^{N} h_i \tag{1}$$

We used transfer learning techniques to improve the performance of the model. In this technique, the model is first pretrained with data from the source domain, then weights are transferred and further trained with data from the target domain. The insight in transfer learning is that the source and target domains share some basic functional patterns. To overcome the problem of class imbalance, we optimized the MIL model with the focus function as the target function. The model was optimized by Adam Optimizer.

3. DATA

3.1 Subjects and biochemical indicators

This study randomly selected 177 subjects (including 50 ordinary people and 127 people with type 2 diabetes mellitus) from residents of Shanghai and Chongqing community, China, from April 10–20, 2016. They were examined using novel optical instrument and other biochemical test. We retrospectively collected patient data from the novel optical instrument and hospital records, including scleral pictures and physiological indicators. Subjects were excluded from insulin treatment. This study was approved by the Ethics Committee of Tsinghua University School of Medicine. This is a retrospective study, and it is difficult to contact each subject and obtain informed consent, therefore the research notice and contact information of relevant staff were posted publicly at School of Medicine, Tsinghua University.

In addition, we also counted other biochemical indicators of 127 patients with type 2 diabetes, as shown in Table 2.

Table 2. Information on video and audio files that can accompany a manuscript submission.

Subjects	Biochemical indicators	Mean ± S.D.
Ordinary people	Fasting blood glucose	5.024 ± 0.477
people with type 2 diabetes mellitus	Fasting blood glucose	8.081 ±1.764
	Triglycerides	1.775 ±1.346
	Total cholesterol	5.896 ±1.062
	High density lipoprotein	3.439 ±0.875
	Low-density lipoprotein	1.291 ±0.311
	Alanine aminotransferase	20.984 ±12.104
	Aspartate aminotransferase	22.307 ±8.274
	Creatinine	64.315 ±16.118
	Urea	5.767 ±1.539

3.2 Scleral images

Scleral images were recorded for each eye of the 177 subjects, including center, up, down, left, and right images Thus, a total of 17770 scleral images were used in the subsequent AI analysis. The typical scleral images are shown in Fig. 3. In these images, scleral area is reflection- and shadow-free, so that the reflection shadows are focused on pupil. The distribution of capillaries and abnormal patterns are clearly visible even by naked eye.

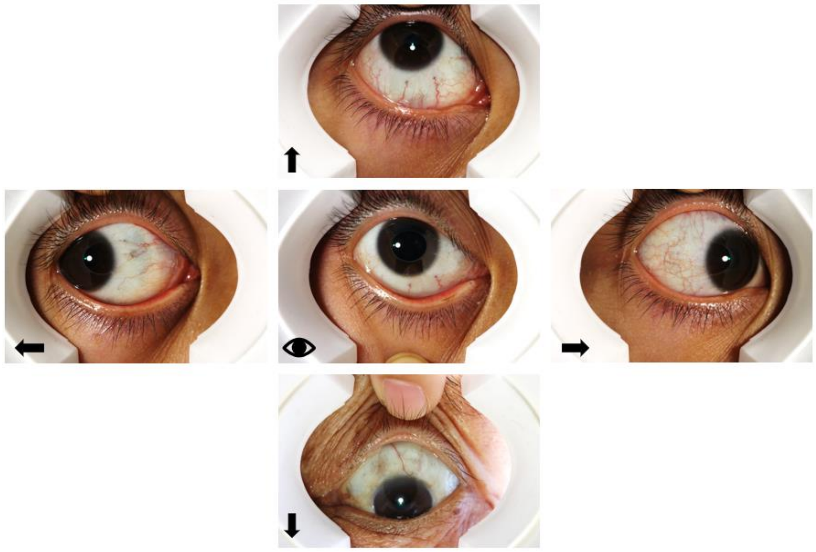
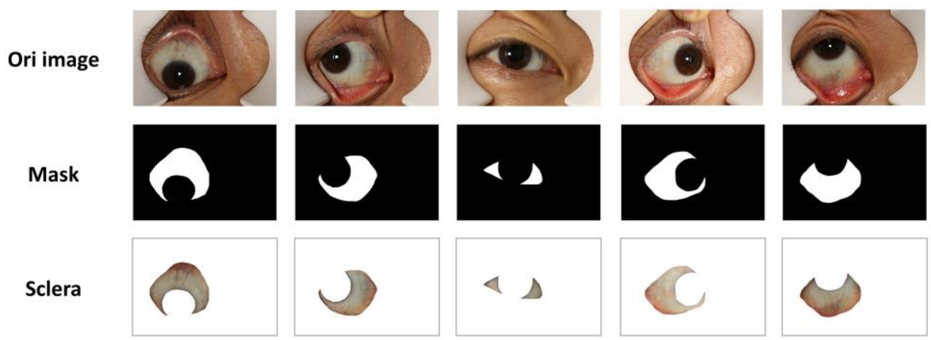
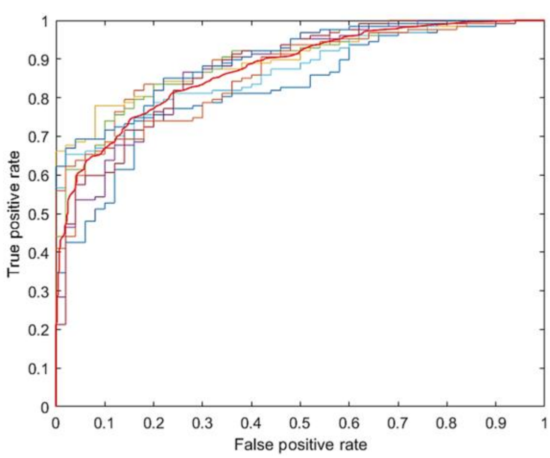


Figure 3. Different directions scleral images of one eye.

4. RESULTS

4.1 Performance of the AI prediction model





U-net	
Precision	0.943
Recall	0.922
IoU	0.825

Resnet-18 & MIL	
Precision	0.841±0.025
Recall	0.902±0.022
Accuracy	0.808±0.023
AUC	0.876±0.022

Figure 4. Performance of the AI prediction model. The upper part and the first table in the lower right corner of this picture show the performance of U-net for segmenting sclera; the picture in the lower left corner of this picture and the second table in the lower right corner show the prediction performance of Resnet-18 and MIL .

It can be seen from Figure 4 that the accuracy and recall rate of the U-net model applied to the sclera segmentation are relatively high, and IoU also meets the requirements. It should be pointed out that there is no other public data set to compare the performance of the scleral segmentation algorithm.

Furthermore, when Resnet-18 and MIL are used to predict type 2 diabetes based on scleral images, the classification accuracy is 0.808, precision is 0.8567, recall is 0.902, and AUC is 0.876. The results indicate that the model has learned to distinguish features related to type 2 diabetes on the scleral images of subjects, and has a good predictive performance.

4.2 Model score and complications

Through the correlation analysis between biochemical indicators and the scores of our AI prediction model for type 2 diabetes, we found that the model is not sensitive to diabetes-related diseases such as hyperlipidemia and nephropathy. This further shows that our AI prediction model specifically recognizes the characteristics of diabetes and has the ability to resist interference from complications.

Table 3. Correlation coefficient of model score and complications.

Biochemical indicators	**Correlation coefficient**	**Biochemical indicators**	**Correlation coefficient**
Triglycerides	0.048219	Alanine aminotransferase	0.080244
Total cholesterol	0.085137	Aspartate aminotransferase	-0.08684
High density lipoprotein	0.08376	Creatinine	-0.08684
Low-density lipoprotein	-0.08684	Urea	0.110006

4.3 Discussion

The novel scleral imaging instrument solves the problem of artifacts during scleral imaging, making scleral imaging a high-quality and standardized operation. The AI model based on U-net and MIL can segment and classify scleral images relatively accurately. From a point-of-care perspective, the non-invasive AI method has various advantages such as simplicity, ease of use, low cost, no reagent required, and almost real-time(<3min), making it suitable for large-scale community early screening. More importantly, due to its painless and non-invasive nature, we believe our assessment system for lung cancer at an early stage may have chance to simplify physical examination processes and improve patients' medical experiences.

Many aspects are worth exploring further in our research. First, the outpatients participating in the experiment are all from only two centers, which may limit the mobility of the algorithm. Thus, further external multi-center validation is warranted. Second, the non-invasive AI method could be used to detect type 2 diabetes mellitus, whether it could distinguish other diseases requires more samples and data.Furthermore, even though AI applied to biomedical research is a powerful tool to analyze deep features and connections among type 2 diabetes and scleral images, it is still should concerned about privacy protection and improper use in social implications.

5. CONCLUSIONS

In summary, we have developed a non-invasive AI method to predict the risk of type 2 diabetes: We have developed a MIL model that predicts the probability of lung cancer through scleral images taken by a specially developed instrument, which can conveniently, quickly acquire complete scleral images in four directions, complete AI analysis within 3 minutes, without any reagent consumption, and no laboratory. The average AUC of the binary classification results of the MIL model is 0.876, indicating that there is great potential for early screening of type 2 diabetes in regular physical examinations or daily family health monitoring.

Our results suggest a new concept that in this innovative study, the use of deep learning to analyze scleral images can help detect type 2 diabetes. This work supports a potential step towards the development of deep learning-based tools for pre-screening diabetes probability assessment in outpatient clinics or diabetes screening in the community, which may help guide further diagnostic tests or visits.

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