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Automatic Analysis of Microaneurysms Turnover to Diagnose the Progression of Diabetic Retinopathy

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ABSTRACT Diabetic retinopathy (DR) is one of the most common microvascular complications and its early detection is critical for the prevention of vision loss. Recent studies have indicated that microaneurysms (MAs) are the hallmark of DR. However, the detection of MAs relies on trained clinicians and relatively expensive software. Moreover, manual errors often lower the accuracy of this detection. Therefore, an automatic analysis technique is highly demanded in the detection of DR progression. In this paper, we present a novel and complete methodology involving two different ways from the view of MAs turnover and pathological risk factors to diagnose the progression of DR. Specifically, one approach follows the traditional image analysis-based roadmap to obtain MAs turnover. The other investigates seven pathological features, related with MAs turnover, to classify the unchanged, new, and resolved MAs by means of statistical analysis and pattern classification techniques. The evaluations on Grampian diabetes database show that the proposed image analysis method could achieve a sensitivity of 94% and a specificity of 93%, while the classification model could achieve 89% sensitivity and 88% specificity, respectively. We also analyzed the potential weight of pathological risk factors leading to the MAs turnover, which could provide an alternative guidance for the progression of DR than traditional detection methods. In conclusion, this study provides a novel and noninvasive detection technique for early diagnosis of diabetic retinopathy with a competitive accuracy.

INDEX TERMS Mircoaneurysms turnover, lesion coordinates comparison, pathological risk factors.

I. INTRODUCTION

Diabetic retinopathy (DR) is the most common complication of diabetes and one of the major causes of vision impairment [1]. The early diagnosis and treatment of DR are very critical to the prevention of blindness. Microaneurysms (MAs) are the first sign of diabetic retinopathy. According to the Early Treatment Diabetic Retinopathy Study (ETDRS), the appearance of only a few MAs shows the symptom of mild non-proliferative diabetic retinopathy (i.e., ETDRS level 20) [2]. The more MAs, the higher risk of developing the diabetic retinopathy. Currently, ophthalmologists inspect the color fundus image, perform the screening and detect the MAs manually, which is a repetitive, tiring and error-prone procedure. Additionally, a manual diabetic retinopathy screening alone cannot meet the detection needs of large and increasing diabetic population. Fortunately, medical researches show that progression to vision impairment can be slowed or averted, if DR is detected earlier [3]. However, detecting DR is a time-consuming process and carried out manually, which requires a trained clinician to examine and evaluate digital color fundus photographs of the retina. Therefore, the development of automatic DR detection

techniques based on eye screening has aroused widespread interests and led to researches both academic and medical communities [4]–[6]. Thus, the majority of DR diagnostic systems are based on the image analysis methods. In this article, we propose an image analysis approach to classify MAs turnover, by combining the image registration and the lesion coordinate detection together. Importantly, we further propose a SVM (support vector machine)-based approach on classifying MAs turnover by recording the variance of pathological risk factors in-between each episode, and further predict the weight of each pathological risk factor leading to the MAs turnover. The medical contribution is to provide a referral for the ophthalmologists on controlling these high-risk factors.

The rest of the paper is organized as follows. Section 2 briefly reviews the related work. Section 3 describes the testing and training data preparation for the two paralleled methods. Section 4 details our image analysis approach, while the proposed classification model is described in Section 5. Section 6 compares the image analysis and classifier methods by referencing the gold standard confirmed from our ophthalmologists, and further investigates the potential pathological risk factors for diabetic retinopathy regression. Finally, the conclusion and future work are summarized in Section 7.

II. RELATED WORK

A. RECENT METHODS ON DIABETIC RETINOPATHY BY DETECTING MICROANEURYSMS TURNOVER

Microaneurysms (MAs) are the focal dilatation of capillaries which occurs adjacent to an occluded capillary. As further capillaries occlude, new MAs form. However, MAs attached to a capillary that subsequently occludes will thrombose and no longer be visible. Recent studies indicated that MAs are the hallmark of diabetic retinopathy [7]. Thus, most of the existing automatic methods usually treat diabetic retinopathy as MAs detection and analyze the problem on color fundus images conquering it in two consequent stages: detection and classification of MA candidates. This involves different techniques of image preprocessing, image segmentation, feature extraction and classification, such as [8] and [9]. In previous work, the software ''iGrading'' is to detect the microaneuryms and hemorrhages as described in [9]. In this article, we adopt the iGrading software to detect the MAs lesion coordinates from baseline and follow-up retinal images.

An early method proposed a new constraint for optic disk detection to find the location of optic disk for lesion detection. Based on this, exudates, MAs, and hemorrhages can be detected quite accurately using different morphological operations, when they are applied appropriately [10]. Niemeijer *et al.* [11] showed that the fusion of these results of several MA detectors leads to an increased average sensitivity, measured at seven predefined false positive rates. Then, the extraction of MA candidates is accomplished by grayscale diameter closing to find all sufficiently small dark patterns on the green channel [12]. Finally, a double threshold is applied to extract MAs candidates. A simple but effective approach for detecting micro-aneurysms in retinal angiographic images was presented in [13]. The proposed scheme is based on the removal of blood vessels from the image and then classifying whether all detected circular objects are microaneurysms. In order to extract candidates, Zhang *et al.* [14] constructed a maximal correlation response image for the input retinal image. The maximal correlation response image is thresholded with a fixed cut-off value to obtain candidates. Quellec *et al.* [15] proposed a wavelet transform for the detection of microaneurysms in retina photographs, by matching a lesion template in sub-bands of wavelet transformed images. Besides, Antal and Hajdu [16] introduced an ensemble-based framework to improve MA detection. The authors proposed a combination of internal components of MA detectors, namely preprocessing methods and candidate extractors. Tavakoli *et al.* [17] also used the RetmarkerDR software to identify the early biomarkers of diabetic retinopathy by combining Radon transform (RT) and multi-overlapping windows.

After extracting the MAs from two successive images, image registration methods can be applied to both images for the detection of new, unchanged, and resolved MAs. To our best knowledge, early attempts on the image pair registration aimed to find the corresponding position in successive images to compare the changed and unchanged MAs [18]. Later, Bernardes *et al.* [19] mapped the detected MAs locations by an image registration software (named as MA-Tracker). Leicht *et al.* [20] adopted the RetmarkerDR software to analyze MAs turnover after the treatment of ranibizumab. These attempts indicate that the MAs turnover is an important biomarker for the early diagnosis on diabetic retinopathy as recorded in [21].

In our image analysis method, we adopt the Generalized Dual Bootstrap-ICP image registration (GDBICP) [22] to register the MAs candidates from baseline and follow-up images. GDBICP is an automated image registration algorithm; it extracts and matches the key points from image pair (for details, please refer to [22]).

B. RECENT CLASSIFICATION METHODS ON MICROANEURYSMS DETECTION USING PATHOLOGICAL RISK FACTORS

On the other hand, recent studies found that the pathological factors associated with diabetic retinopathy are fasting blood glucose value, blood pressure (diastolic and systolic), high and low-density lipoprotein, genetic factors, intraocular pressure, vitreous state and optic neuropathy and so on [23], [24]. Our hypothesis is that some pathological risk factors might be also related with MAs detection longitudinally.

Besides, in a recent diabetes progression research [25], SVM proves its effectiveness to perform better than traditional statistical methods, like logistic regression, especially in situations that include multivariate risk factors with small effects, limited sample size, and limited

knowledge of risk factors. This technique can be also extended to MAs detection in the large data sets, as the early biomarkers of diabetic retinopathy. Therefore, the analysis on pathological risk factors could be an effective diagnostic technique for both MAs turnover and the progression of diabetic retinopathy. It is worthy to mention that the linear SVM model has this specific indication to find feature weighs [26]. Akram *et al.* [27] presented a hybrid classifier by combining the Gaussian mixture model (GMM) and SVM in an ensemble to improve the accuracy of MAs detection. Besides, Adal *et al.* [28] adopted scale-adapted blob analysis to find the texture descriptors and semi-supervised learning to detect MAs.

The common feature of these classification models requires an image feature extraction for the pre-processing on fundus images, which needs a retinal screening in advance and could be affected by the poor image quality or clinician's error operation.

In this research, we propose a semi-supervised approach by recording the pathological risk factors after each retinal screening. After proposing an image analysis method to classify MAs turnover from each pair, their corresponding changes of risk factors were also recorded as the training features, to classify the MAs turnover from the remaining testing set. We also adopt the labeled class from the number counting of MAs turnover, to predict the MAs turnover from the testing data set. The agreement measurement between ground truth and our proposed methods proved its effectiveness in the testing data set.

C. OUR CONTRIBUTION

The contributions of this study are concluded as follows:

1. An automated image analysis method is proposed to classify the microaneurysms turnover, by combining the image registration algorithm (GDBICP) and iGrading (MAs detection) software. This image analysis method was used to detect the MAs turnover longitudinally, i.e., unchanged, new and resolved MAs.
2. By further recording the variance of the pathological risk factors in-between two consecutive episodes and assigning the label on the number of MAs turnover as the training set, the SVM classifier was also used to detect the MAs turnover longitudinally in the testing set. In this semi-supervised machine learning method, the input features are the variance of risk factors between two episodes.
3. By using the linear kernel from SVM, we can predict the weights of these pathological risk factors. The medical contribution is to monitor the high-risk factors regularly, which could control the progression of DR at an early stage.

III. TRAINING AND TESTING DATA PREPARATION

For image analysis of MAs turnover, the MA detector was applied to the baseline image and follow-up images. We therefore prepare 156 image pairs collected from 52 patients, by taking 4 episodes in both the retinal screening and risk factors recording, which means there exist 3 image pairs for each patient. By comparing two detected MAs from the baseline image and follow-up image, our method can distinguish new, unchanged and resolved MAs.

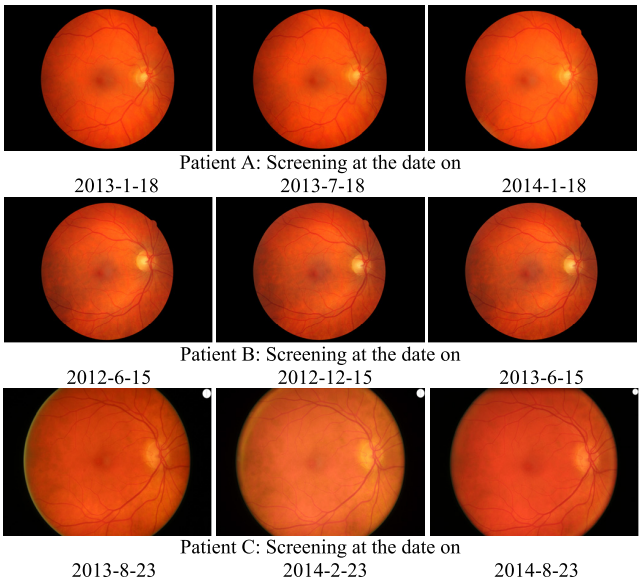


FIGURE 1. The retinal imaging data sets, with eye screening at the 6-month interval for each patient. The illustrated images indicate the right-eye screening.

For machine learning classifier using pathological risk factors, we also collected seven pathological risk factors from 52 patients during each risk factor recording.

It is worthy to note that MAs also occur in non-diabetic retinopathy (e.g., hypertension, cardiovascular disease, infection, etc), we thus only selected the data used are from DR-diagnosed persons.

A. THE TOTAL IMAGE DATA SET OF PATIENT FOR IMAGE ANALYSIS APPROACH

Longitudinal retinal imaging data was acquired retrospectively from Grampian Diabetic Research Unit, UK. A fundus camera (VISUSCOUT 100) was used to record the retinal images. A patient's images were included in the test sets if the patient had at least two digital retinal images taken between 6 months apart. Thus, an image pair was defined as two images acquired around the 6-month interval of each other.

At least one MA at the initial screening spotted all patients. The aim of this larger test set was to examine the technique's ability to perform with data representative of the screening environment.

B. TRAINING SAMPLE AND TESTING SAMPLE OF PATHOLOGICAL RISK FACTORS FOR SVM CLASSIFIER

In this study, we refer to the clinical study on pathological risk factors [29] leading to diabetic retinopathy and hypothesize these risk factors as shown in lower part of Figure 2. In our

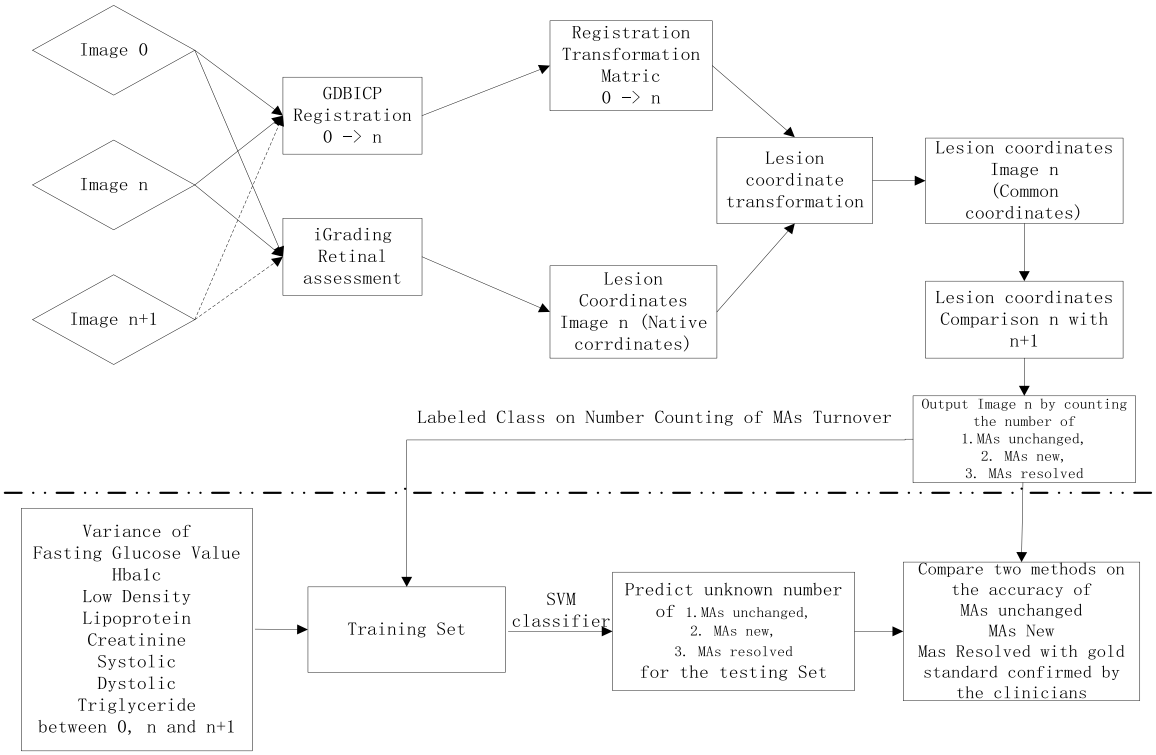


FIGURE 2. The proposed parallel framework to classify MAs turnover for each patient. The upper part indicates an image analysis approach and the lower part indicates a semi-supervised machine learning approach. The final stage is to compare the accuracy of both methods on the classification of MAs turnover.

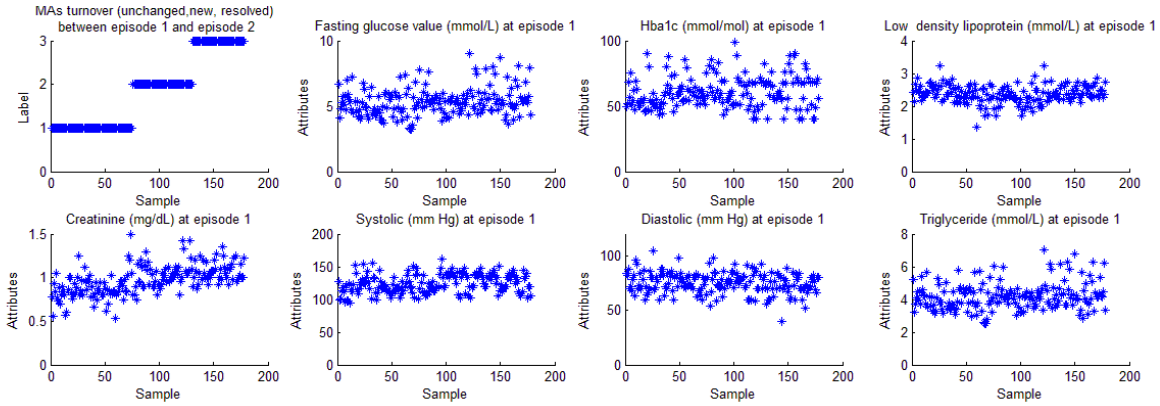
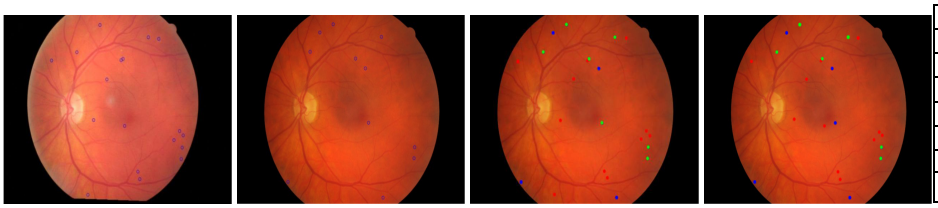


FIGURE 3. Visualization of the seven pathological risk factors.

pathological risk factors database, 7 attributes have been selected and saved into a CSV file. For each two episodes, the variance is calculated and saved into this CSV file. Totally, a 52∗7∗3 matrix is formed in our database - here 3 indicates the pathological risk factors variance between 1st to 2nd episode, 2nd to the 3rd episode and 3rd to the 4th episode, respectively, 52 indicates the total patients. The visualization of these seven pathological risk factors is shown in Figure 3.

After successfully analyzing the MAs turnover using image analysis from 30 patients, we treated their previous recorded corresponding pathological risk factors as the training sample and tested the remaining 22 patients for classifying the MAs turnover. There are many works which used the hold-out way to split the data [30]–[32]. Because we have only few samples at hand, the whole data was split via cross-validation strategy, i.e., 12 subsets for training and the remaining 1 subset for testing. Each subset contains 4 patients' pathological risk factors. In detail, the training set consisted of 7 pathological risk factors, with 3 variance in-between each episode by tracking and screening 30 patients continuously. Besides, these pathological risk factors variance from each patient are encapsulated into a



Pathological Risk Factors	Variance
Fasting glucose value	-0.073
Hba1c	0.138
Low-density lipoprotein	-0.1352
Creatinine	0.012
Systolic	-0.140
Diastolic	-0.103
Triglyceride	-0.1187

FIGURE 4. An example on MAs turnover between image n+1 and image n, and the corresponding variance on the pathological risk factors. (a) image n in sequence with iGrading software marked MAs. (b) Image n+1 (registered to the same coordinate system of image n) with iGrading software marked MAs. (c) The iGrading software output showed unchanged (green), new (blue) and resolved (red) superimposed on image n+1. (d) Shows how the expert observer classified the MAs. On the right side, the table indicates the corresponding changes from seven selected risk factors, i.e., the pathological risk factors variance between nth and (n+1)th eye screening.

training subset, and the numbers of unchanged, new and resolved MAs of each subset are also encapsulated as the training labels. Besides, the testing sample consisted of 7 pathological risk factors, with 3 variance in-between each episode by tracking and screening 22 patients continuously. Our task is to predict the unknown labels of unchanged, new and resolved MAs number in the testing sample. All pathological risk factors are collected after each episode of retinal screening, for example, after we collected the retinal imaging in Figure 1, the eye clinicians will further ask the patient to record their pathological risk factors. All imaging and pathological risk factors are collected from NHS Grampian Diabetes Centre, UK. After the preparation of all data sets, we explain our image analysis method to classify MAs turnover in Section IV.

IV. IMAGE ANALYSIS TO CLASSIFY MICROANEURYSMS TURNOVER

In this section, the image analysis techniques are applied to automatically classify the MAs turnover. The flowchart of this image analysis approach is illustrated in upper part of Figure 2.

A. MICROANEURYSM CANDIDATES EXTRACTION USING iGRADING

The automated extraction on MAs candidates was done using iGrading software on the unprocessed retinal image using all images from the **training** data sets. The iGrading is a CE-accredited package that detects signs of diabetic retinopathy, such as MAs (http://www.medalytix.com/). The product is the result of a collaboration with NHS Grampian diabetes center and commercial partner Medalytix Ltd (Manchester, UK). The core algorithm of this software is described in [8]. The automated grading system iGrading integrated image processing algorithms which evaluate the image quality (clarity and field definition) and detect signs of diabetic retinopathy (for example, hemorrhage or MA detection and their number counts) in retinal images. The iGrading software is currently implemented in the Grampian Diabetes Center to provide the automatic grading of retinal images and detect MAs from the images. Once an MA was identified, its coordinates, using its native image format, were also generated and recorded. The location of the MAs generated by the iGrading software for a typical image pair is shown in Figures 4.

B. IMAGE PAIR REGISTRATION USING GDBICP

The image transformation or warping is a common problem after 6-months retinal screening. Thus, the image pair registration was completed by using Generalized Dual Bootstrap-ICP (GDBICP), a fully-automated 2D image registration algorithm [23]. GDBICP was chosen over other free or commercial registration packages because it has previously been tested using retinal images [23] and found to be efficient in natural image registration testing.

For each patient, the next retinal image was registered with the previous retinal image (first episode as shown in Figure 4a) in the sequence. The transformation operation required to align the image was generated and stored (the registration transformation matrix in Figure 4b). The registration process was applied to all images for all patients. The images are shown in Figure 4a and 4b have applied this registration transformation.

C. LESION COMPARISON

The spatial coordinates of each MA detected were transformed using the generated transformation operation, therefore MAs from the same eye screening at different episodes could be compared. This comparison was implemented for all MAs detected in both training and testing sets. If the angular distance between an MA on image n+1 and that on image n was less than 0.3°, the MA was judged to be static. This value of 0.3° was chosen by comparing a pair of images in which all MAs candidates have been confirmed by an expert observer to be static(*unchanged*). An MA was defined as '*new*' if it was present in the $(n+1)^{th}$ image but no corresponding MA could be found in the n^{th} image. An MA was defined as '*resolved*' if it was present in the nth image but no corresponding MA could be found in the $(n+1)^{th}$ image. The image displayed in Figure 4c displays the output of the proposed image analysis technique with the lesions classified in different colors, while Figure 4d shows how the expert observer classifies MAs turnover from this image pair. The

number count of MAs turnover, i.e., the number count of unchanged, new and resolved MAs, is then saved into a CSV file for the labeled class in SVM classifier and the further comparison with the ground truth.

Section V describes the SVM classifier, for the same purpose of classifying the MAs turnover in a semi-supervised machine learning way.

V. SVM CLASSIFIER FOR MICROANEURYSMS TURNOVER

As depicted in the lower part of Figure 2, we further propose a classification model to detect MAs turnover on the longitudinal changes, i.e., the variance of pathological risk factors from n^{th} to $(n+1)^{th}$ eye screening. To our best knowledge, there exist recent diabetic retinopathy studies on pathological risk factors using the logistic regression model, such as [29] and [33]. Unlike fitting data to a logistic curve, the support vector machine (SVM) [34] has proved to be more effective for classification tasks in the biomedical problems, particularly in bioinformatics [35], [36]. In detail, SVM distinguishes multiple classes by transforming the input data into a high-dimensional space to find the optimized hyperplane. Because the SVM approach is data-driven and model-free, it demonstrates its effectiveness for classification study, especially in cases where sample sizes are small, and a large number of variables are involved (transforming the raw data into a high-dimensional space). This technique was used to develop the automated classification of diseases and to improve methods for detecting diseases in a clinical setting [37], [38]. Therefore, LIBSVM [39] is adopted to classify the testing data into three categories, i.e., new, unchanged and resolved MAs.

In this study, we investigated seven attributes (pathological risk factors) which are deemed to associate highly with diabetic retinopathy according to [29] and [33], with our further hypothesis leading to MAs turnover. These attributes are fasting glucose value, Hba1c, low-density lipoprotein, creatinine, systolic, diastolic and triglyceride obtained after each eye screening. The definition of these risk factors is explained below.

- Fasting Glucose Value: the blood glucose level in an individual who has refrained from eating or drinking any liquids other than water for at least 8 hours prior to the test. This test is usually carried out in the morning before breakfast.
- Hba1c: is the abbreviation of glycated hemoglobin. It refers to a form of hemoglobin which indicates the average blood glucose concentration over the course of three months.
- Low-density lipoprotein (LDL): one group of lipoproteins responsible for the delivery of cholesterol to the arteries. Higher levels of LDL can be responsible for arteriosclerosis, myocardial infarction, stroke and peripheral arterial disease.
- Creatinine: creatinine is a waste product of creatinine phosphate in muscle usually produced at a constant rate day to day.
- Systolic Blood Pressure: Pressure in the arteries during contraction of the heart which pushes the blood around the body.
- Diastolic Blood Pressure: Pressure in the arteries in the rest period of the heart between beats.
- Triglyceride: An ester which derives from glycerol and three fatty acids. Body fat in humans and other animals, as well as vegetable fat, are mainly constituted by triglycerides. Their function in the blood is to allow adipose fat and blood glucose to travel to and from the liver. They also form a major part of human skin oils.

Unlike conventional machine learning methods using the *static* pathological risk factors, we investigated the variance of these selected factors from the baseline to the follow-up recording. For the example in the right table of Figure 4, fasting glucose value is 9.82 mmol/L for episode n, while it was recorded as 9.74 mmol/L for episode n+1 after 6 months, and the variance from n to n+1 is −0.08 mmol/L. Then this variance (−0.08 mmol/L) can be scaled down to −0.073 for the total variation from the maximum fasting glucose value to the minimum fasting glucose value in all sequential recordings, i.e., from 9.748 mmol/L to 8.650 mmol/L for all episodes.

TABLE 1. Pathological risk factors in patient cohort from episode 1 to episode 4.

Index	Cohort (n=52) Mean Value	SD	Min	Max	p-value
Fasting glucose value (mmol/L)	4.38	1.07	3.22	9.02	0.14
Hba1c (mmol/mol)	61.18	12.34	40.40	99.20	< 0.001
Low-density lipoprotein (mmol/L)	2.48	0.56	1.36	5.60	0.29
Creatinine (mg/dL)	0.98	0.19	0.53	1.70	0.43
Systolic (mm Hg)	99.95	14.00	70.00	162.00	< 0.001
Diastolic (mm Hg)	75.50	9.90	40.00	105.00	< 0.001
Triglyceride (mmol/L)	4.22	0.83	2.51	7.04	0.20

Further, statistical analysis was performed using SPSS 17.0 software (SPSS Inc, Chicago, IL, USA). The above pathological risk factors were all used to analyze and identify statistical differences. Detailed statistical analysis results are described in Table 1. Spearman correlation test was used for the analysis of the indicators correlating to DR patients. All analysis which had p value less than 0.05 (5% significance level) were considered to have statistical significance.

The lower part of Figure 2 plots the diagram of our classifier model on MAs turnover for the testing sample into three classes of MAs turnover (unchanged, new and resolved). In this study, the values of all kernel functions are set at the default values for fair comparison. The confusion matrix of MAs turnover classification using linear, polynomial, Gaussian RBF and sigmoid kernel functions are

TABLE 2. Confusion matrix of classification accuracy on MAs turnover with linear kernel.

	Unchanged MAs	New MAs	Resolved MAs
Unchanged MAs	**92.13%**	3.91%	3.49%
New MAs	4.05%	**92.57%**	5.13%
Resolved MAs	3.82%	3.52%	**91.38%**

TABLE 3. Confusion matrix of classification accuracy on MAs turnover with polynomial kernel.

	Unchanged MAs	New MAs	Resolved MAs
Unchanged MAs	**91.78%**	4.51%	3.71%
New MAs	4.47%	**90.19%**	5.34%
Resolved MAs	3.75%	5.30%	**90.95%**

TABLE 4. Confusion matrix of classification accuracy on MAs turnover with gaussian RBF kernel.

	Unchanged MAs	New MAs	Resolved MAs
Unchanged MAs	**91.48%**	4.24%	4.28%
New MAs	3.78%	**91.92%**	4.30%
Resolved MAs	4.74%	3.84%	**91.42%**

TABLE 5. Confusion matrix of classification accuracy on MAs turnover with sigmoid kernel.

	Unchanged Mas	New MAs	Resolved MAs
Unchanged MAs	**92.11%**	4.40%	3.49%
New MAs	3.59%	**90.63%**	5.78%
Resolved MAs	4.30%	4.97%	**90.73%**

TABLE 6. Computational time using different kernel functions.

	Linear	Polynomial	Gaussian RBF	Sigmoid
Running Time (s)	**3.82**	4.9	7.02	7.33

listed in Tables 2-5, respectively. It can be found that the classification accuracy of linear kernel is similar to Gaussian RBF kernel, and higher than polynomial and sigmoid kernel function. Additionally, we compare the computational complexity. As shown in Table 6, it is apparent that the linear kernel is much faster than using other kernel functions. Thus, we finally selected the linear kernel function for the sake of computational efficiency, and the dimension of input vector is 7 (features). The mean of the support vector (SV) numbers is 892. Both of the slack variable C and kernel width g was initialized in the range of [2^(-5), 2^5]. After using grid search with 13-fold cross validation, the optimal value of C is tuned at 0.3516 when achieving the best classification accuracy, g is not required due to our selection on linear kernel function.

The next section compares our image analysis and SVM classifier with gold standard confirmed from two expert eye clinicians by using the Bland-Altman plots.

VI. COMPARISON BETWEEN TWO METHODS ON THE CLASSIFICATION OF MICROANEURYSMS TURNOVER

Two expert eye clinicians were asked to examine the retinal images for the confirmation of the ground truth (gold standard). The location of the MAs identified by the automated image analysis approach was indicated in each image and the expert observer identified whether the lesions were new, resolved or unchanged. The aim was to assess how well the relative positions of MAs in the sequential images were identified by the image analysis algorithm and hence its ability to assess turnover. The algorithm was applied to all of the image pairs in the testing sample and the number of new, static and resolved MA's for each pair was summarized.

We compare the image analysis and the SVM classifier with gold standard confirmed by two clinicians, by using the Bland-Altman plot for the agreement measurement [40]. Here, each dot represents a patient from testing sample, with totally 22 patients for the comparison. X-axis indicates the mean value of MAs between the automated methods and the gold standard, Y-axis represents the difference of MAs between the automated methods and the gold standard. Note there exists the overlapping dots in the new and resolved MAs number counts in this agreement measurement.

As demonstrated in Figure 5, the standard deviation (SD) and mean (Bias) among unchanged, new and resolved MAs are very close for two methods. For example, the bias of unchanged MA using image analysis is -0.13 and bias for SVM classifier is 0.24, whilst SD is 0.91 and 0.88, respectively. The agreement measurements of unchanged, new and resolved MAs indicate a similar performance between two methods in terms of classification accuracy.

VII. DISCUSSION

Based on the agreement measurement using Bland-Altman plot, both methods proved to classify MAs turnover effectively. In this section, we further predict the weights of the pathological risk factors from this SVM classifier model.

A. FURTHER INVESTIGATION ON PATHOLOGICAL RISK FACTORS

We predict the weights of pathological risk factors of MAs turnover by recalling the SVM linear kernel function. The weights of each risk factor are listed in Table 7 with the variation after ten trials. After adopting the linear kernel form SVM classifier, each weight from these risk factors can estimate the relevance of MAs turnover. A higher weight indicates that the corresponding risk factor plays a more important role leading to MAs turnover. As referred [24], the linear SVM model has this specific indication to find feature weights.

TABLE 7. Predict weights of pathological risk factors of MAs turnover.

Diastolic	Systolic	Fasting Blood Glucose	Hba1c
0.0994±0.0027	0.0948±0.0017	0.2125±0.0052	0.0974±0.03
Creatinine	Triglyceride	Low-Density Lipoprotein (LDL)	
0.0738±0.0014	0.2382±0.0064	0.2021±0.0021	

Table 7 indicates that the cause of MAs turnover coincides with our hypothesis at the beginning. Regarding MAs

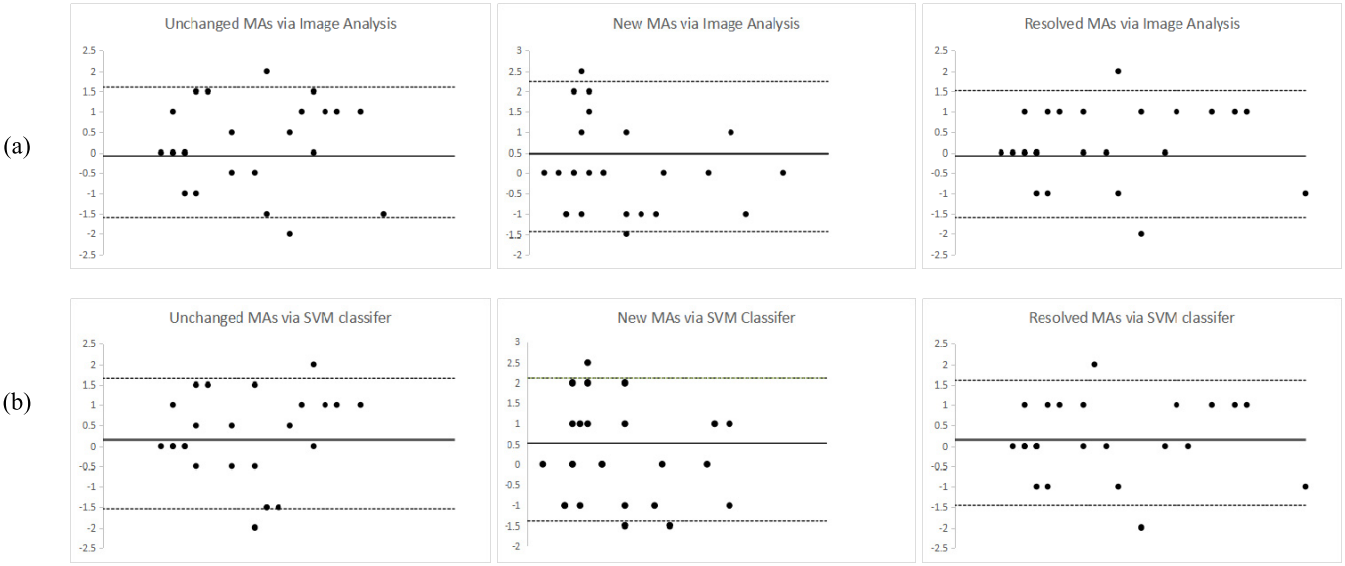


FIGURE 5. Comparison of the Bland–Altman plot on unchanged, new and resolved MAs number counts between two proposed methods and the gold standard confirmed by two expert clinician observers. The x-axis indicates the mean value between the clinician and our proposed method using image analysis (above) and SVM classifier (below), respectively. (a) the top row is to measure the agreement between the image analysis on unchanged, new and resolved MAs with the ground truth, (b) the bottom row is to measure the agreement between SVM classifier on unchanged, new and resolved MAs with the ground truth.

TABLE 8. Sensitivity and specificity on the classification of MAs turnover.

Nearest Neighbor [43]	Naive Bayesian [44]	PCA+ANFIS [45]	LDA [46]	CNN	SVM
81%/ 79%	77%/ 73%	82%/ 78%	79%/ 80%	85%/ 87%	89%/ 88%

turnover, the triglyceride, LDL and fasting blood glucose are probably the high-risk factors with a close relationship to the MAs turnover. The traditional diagnosis of diabetic retinopathy (DR) is routine to control blood glucose, however, this is a generalized method for the prevention of further development of DR. Our analysis provides a deeper understanding of the pathological factors is critical for the early detection of DR.

Three high-risk factors (fasting blood glucose, triglyceride, and LDL) demonstrate their close relationship with MAs turnover. Our findings are consistent with the results of epidemiological investigations on DR. For example, recent research has proved that severe DR is closely related to the higher value of triglyceride [41]. Latest findings demonstrated that the levels of triglyceride and cholesterol are largely varied between DR and non-DR patients [42]. The findings on triglyceride also apply to the analysis of MAs turnover as shown in the above table. Our study also suggests that fasting glucose and low-density lipoprotein could play a key role in MAs turnover. However, the experiments demonstrated that creatinine, Hba1c (glycated hemoglobin), diastolic and systolic are less critical to MAs turnover, which contradicts our hypothesis at the very beginning.

B. COMPARISON WITH OTHER CLASSIFIERS FOR MAs TURNOVER

Several state-of-the-art classification models were proposed to predict diabetic retinopathy in recent studies [43]–[46]. To our best knowledge, there is still limited analysis on the pathological factors with a specific aim on MAs turnover. We also attempted above classification models to compare the best performance by adopting the ''sensitivity vs specificity'' curve. We still adopt the variance of pathological factors and the training labels of the unchanged, new and resolved MAs numbers from the training data set. In detail, Nearest Neighbor Classifier [43], Bayesian Classifier [44], PCA+ANFIS [45], LDA [46], and Convolutional Neural Network in TensorFlow Toolbox are compared with our SVM classifier on the testing data set. The performance comparison in Table 8 proved the SVM classifier outperforms other machine learning methods regarding to this testing data set, probably due to the small size of all pathological risk factors.

C. COMPARISONS WITH OTHER MAs DETECTION METHODS

Based on the literature significance on recent MAs detection approaches [18]–[20], [47]–[52], we compared the sensitivity and specificity of the longitudinal changes for the comparison on unchanged MAs. Table 9 is the comparative results with other methods on detecting the unchanged MAs longitudinally. For example, 100%/98% indicates the sensitivity vs specificity obtained from two expert observers as the golden standard, respectively. Comparing with our retinal image analysis approach by combining iGrading and GDBICP toolbox, the proposed classification model also proves its

TABLE 9. Comparison on unchanged MAs detection using sensitivity and specificity metrics.

Goatman et al. [18]	Bernardes et al. [19]	Leicht et al. [20]	Zhang et al. [47]	Cree et al. [48]	Pereira et al. [49]
62%/ 75%	69%/ 83%	78%/ 85%	83%/86%	82%/84%	87%/75%
Peng et al. [50]	Rosas-Romero et al. [51]	Dai et al. [52]	Image Analysis	SVM	Gold standard
73%/71%	85%/86%	86%/82%	94%/ 93%	89%/ 88%	100%/98%

potential effectiveness in identifying the MAs turnover. As the classification model is free of purchasing and maintaining the image processing software, it would be a promising approach for automatic analysis on the progression of diabetic retinopathy, considering that MAs turnover is the early biomarker of diabetic retinopathy.

VIII. CONCLUSION

In this paper, we proposed a parallel framework to classify MAs turnover based on the sequential retinal images and longitudinal pathological factors. This study is a valuable step towards the intelligent diagnosis on the progression of diabetic retinopathy, in both health and medical communities. The proposed automated analysis on MAs turnover combining two different approaches presented can significantly improve this situation, and therefore is fundamental for the screening of a large diabetic patient population for diabetic retinopathy. Both two methods can effectively classify the MAs turnover. Importantly, our automated analysis tool can make the DR detection process more reliable and cost-effective. As a result, it can greatly reduce the burden on health care systems while providing improved care to the DR population.

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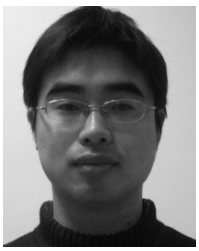

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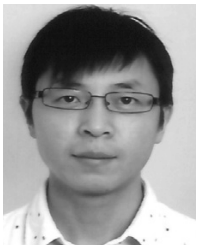

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