Research Article

Retinal OCT Texture Analysis for Differentiating Healthy Controls from Multiple Sclerosis (MS) with/without Optic Neuritis

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Multiple sclerosis (MS) is an inflammatory disease damaging the myelin sheath in the central and peripheral nervous system in the brain and spinal cord. Optic Neuritis (ON) is one of the most prevalent ocular demonstrations of MS. The current diagnosis protocol for MS is MRI; however, researchers are already looking for substitute methods to overcome MRI limitations like high cost, late-stage diagnosis, and inaccurate signs due to aging rather than MS [4]. The effects of MS on the Central Nervous System (CNS) make the retinal nerve fiber layer (RNFL) a proper candidate for being imaged instead of brain MRIs. The thickness of RNFL can be used to assess the existence of any damage in the CNS. Moreover, RNFL is

1. Introduction

Multiple sclerosis (MS) is an inflammatory disease damaging the myelin sheath in the central and peripheral nervous system in the brain and spinal cord. This disease causes the immune system to attack one or more proteins of the myelin structure and disrupts the ability of the nervous system to communicate and therefore brings about many physical signs and symptoms [1]. Those suffering from MS show neurological symptoms including disorders in the autonomic, visual, motor, and sensory nervous system [2]. Optic Neuritis (ON) is a common eye problem where inflammation or demyelination affects the optic nerve. It occurs when inflammation damages the optic nerve, a bundle of nerve fibers that transmits visual information from the eye to the brain. Signs and symptoms of ON can be the first indication of MS, or they can occur later in the course of MS. Not everyone who experiences ON goes on to develop further symptoms of MS, but a significant proportion does [3].
considered as one of the main retinal layers. The role of the remaining layers is not exactly known in the case of MS and needs more investigations.

Optical Coherence Tomography (OCT) is a noninvasive imaging modality to take cross-sectional images of biological tissues. Retinal OCT provides information on symptoms of many eye diseases such as macular degeneration, glaucoma, and diabetic retinopathy and helps ophthalmologists to diagnose and treat such diseases in a timely manner [5–7]. Parisi et al.’s study in 1998 on the diagnosis of MS using retinal OCT was the first work in this field [8]. He investigated whether there is a relationship between RNFL thickness and visual pathway function in patients with MS. Since then, a great deal of research has been done on thickness changes in different retinal layers and the possibility of their use for diagnosing MS. Petzold et al. in 2017 prepared a survey covering this topic and reviewed 110 articles from 1991 to 2016 and provided a good overview of the subject [9].

In recent years, in the field of retinal OCT image processing, much attention has been paid to extracting and using texture features of layers while these types of features have not yet been used widely for MS diagnosis and there are few works addressing this issue. As an example, Varga et al. in 2015 had a study investigating the differences in texture descriptors and optical properties of retinal tissue layers in patients with MS and evaluated their usefulness in the detection of neurodegenerative changes using OCT image segmentation [10]. The term texture in image processing and machine vision refers to the amount, type, and distribution of pixel brightness throughout the image along with the texture of the image [11]. Researchers have defined it as “A texture area in an image can be constructed with an irregular and varied spatial distribution of the intensity of the brightness or color [12].” In this regard, four general categories named statistical, structural, signal processing-based, and model-based features are usually used [11]. In this study, we want to examine the texture of OCT images, and we suspect that changes in the texture of the layers must occur before the thickness changes. It seems that the deterioration of axons in the retinal nerve fiber layer and changes in the texture layers can be determined by the non-invasive OCT method, making them possible to be used as a complementary diagnostic tool in addition to the existing methods for early detection of recurrent MS-ON and MS-None-ON [13].

Here is an overview of the literature investigating texture features in OCT images. In 2007, Baroni et al. investigated the possibility of discriminating retinal OCT image layers in texture processing using Grey-Level Cooccurrence Matrix (GLCM) feature extraction [14]. In 2014, Anantrasirichai et al. presented a new method for extracting the texture of OCT retinal images in glaucoma [15]. In 2018, Sawyer et al. examined the possibility of using texture analysis to classify ovarian OCT images [16]. In 2019, Nunes et al. used texture analysis of OCT data to define new biomarkers for MS, of course, only on one specific retinal layer [17].

The rest of this paper is as follows. The proposed method for texture extraction of retinal OCT layers is described in Section 2. The performance of the method is evaluated and discussed in Section 3. Finally, Section 4 presents the conclusions of the study.

2. Material and Method

2.1. Database. The data in this study is obtained from Spectralis Heidelberg HRA+OCT device in Faiz Hospital and Sadra Ophthalmology Center, Isfahan, Iran. The size of each B-scan is 496 × 480 pixels. For some subjects, data contains 19 B-scans, and for others, it includes 25 B-scans. OCT data includes 36 health control (HC) eyes and 39 patients suffering from MS (20 eyes suffering from MS with no history of ON (MS-None-ON) and 19 eyes suffering from MS with a history of ON (MS-ON)). HC and patient populations have matched gender and age approximately. A summary data flow diagram is presented in Figure 1.

2.2. Algorithm Flow. The workflow of the proposed method is shown in Figure 2. The first step is the preprocessing block in which the retinal delineation [18] is used to extract the layers. In the second block, layer-stacked (LS) images are created by stacking each specific layer from all B-scans of one subject. The third block is applied for masking the images as input to the next feature extraction block. Five different groups of texture features are utilized in this step. In the following, the most effective features are selected based on p value for distinguishing HC, MS-ON, and MS-None-ON population from retinal OCT layers around the fovea. Finally, in the last step, a classification between HC and abnormal population is performed. Each block of the proposed algorithm flow is elaborated below.

The sample output of preprocessing block is shown in Figure 3. To construct layer-stacked images, we consider that data for each subject consists of a number of B-scans, and each B-scan contains 10 layers, locations of which are obtained in preprocessing step. Accordingly, we construct 10 layer-stacked images by cutting and stacking each individual layer from all B-scans of one subject (Figures 4 and 5). A sample of layer-stacked images is demonstrated in Figure 6.

During texture calculation, boundary points in layer-stacked images have synthetic contrast which may fool the feature extraction method and lead to incorrect and outlier values. To solve this problem, an eliminating mask is developed to ignore pixels located on both sides of each individual layer.

Feature extraction is then performed on masked layer-stacked images. The features used in our work are GLCM, Local Binary Pattern (LBP), Local Directional Pattern (LDP), Local Optimal Oriented Pattern (LOOP), and fractal dimension. Finally, discriminant features are fed into

![Figure 1: Detailed structure of the data.](image-url)
Figure 2: Algorithm flow of the proposed method.

Figure 3: Interretinal layers (a sample output of preprocessing block).

Figure 4: Sample of individual layers in one B-scan.

Figure 5: Construction process for layer-stacked (LS) images.
Support Vector Machine (SVM) and Linear Discriminant Analysis (LDA) classifiers for differentiating between HC and MS cases.

2.3. Texture Feature Extraction. Investigating texture features is an efficient way to characterize various properties, such as structure, orientation, roughness, smoothness, or regularity.

Figure 6: Layer-stacked (LS) images corresponding to each retinal layer. (a) First layers of all B-scans. (b) Second layers of all B-scans. (c) Third layers of all B-scans. (d) Fourth layers of all B-scans. (e) Fifth layers of all B-scans. (f) Sixth layers of all B-scans. (g) Seventh layers of all B-scans. (h) Eighth layers of all B-scans. (i) Ninth layers of all B-scans. (j) Tenth layers of all B-scans.
of an image. Extracting features from masked layer-stacked images, we apply two categories of texture features including original and modified features.

2.3.1. Original Features. Different texture analysis methods are utilized in this research and elaborated in the next subsections. A set of features are then extracted according to Table 1.

(1) Grey-Level Cooccurrence Matrix. GLCM describes the spatial relationship between each intensity tone by considering changes between grey levels $i$ and $j$ at a particular displacement distance $d$ and at a particular angle $\theta$ [15]. Here, we use a 256 quantization level and the distance is selected as one pixel with four distinct orientations (0, 45, 90, and 135 degrees). Furthermore, conditions of those pixels with 180 degrees in difference are considered to be the same.

(2) Local Binary Pattern. LBP is a method for describing the texture characteristics introduced in 1990 [19]. LBP compares the intensity of each pixel with neighboring pixels and determines the output value based on equation (1), where $P$ is the number of neighboring points that are chosen, i.e., 8, $i_n$ is the intensity of the neighborhood points, and $i_c$ is the intensity of the central point. LBP outputs the output of LBP for $P$ neighboring points.

$$LBP_p(x_c, y_c) = \sum_{p=0}^{P-1} \text{sign}(i_p - i_c)2^p,$$

where $\text{Sign}(x) = \begin{cases} 1, & \text{if } x \geq 0, \\ 0, & \text{otherwise}. \end{cases}$

(3) Local Directional Pattern. A more robust to noise modified version of LBP is LDP which computes directional components for each pixel with Kirsch kernels and provides a measure of the strength of intensity variation in those directions [20]. For each central pixel located at $(x_c,y_c)$ with intensity $i_c$, eight rotated versions of the Kirsch edge detector should be applied on neighboring pixels with intensities $i_n$, $n = 0, 1, \cdots, 7$. Eight corresponding responses of the Kirsch masks are $m_n$, $n = 0, 1, \cdots, 7$. $m_k$ is the $k^{th}$ highest Kirsch activation, and all the neighboring pixels having Kirsch response higher than $m_k$ are assigned 1, and others 0. Then, the LDP value for the pixel $(x_c,y_c)$ is given by

$$LDP_k(x_c, y_c) = \sum_{n=0}^{7} \text{sign}(m_n - m_k) \times 2^k.$$

(4) Local Oriented Optimization Pattern. LOOP offers a non-linear combination of LBP and LDP that overcomes their individual problems while maintaining the strengths of each. Compared to LDP, LOOP assigns an exponential weight $w_n$ to each of neighboring pixels. $w_n$ is a digit between 0 and 7, according to the rank of the magnitude of $m_n$ among the 8 Kirsch mask outputs [21]. The value of the LOOP in $(x_c,y_c)$ is given by

$$\text{LOOP}(x_c, y_c) = \sum_{n=0}^{7} \text{sign}(i_n - i_c) \times 2^{w_n}. \quad (3)$$

(5) Fractal Analysis. Images with self-similarity characteristics are called fractal. The box-counting analysis is an appropriate method of fractal dimension estimation for images with or without self-similarity [22]. We have a basic equation for calculating fractal dimension given by equation (4), in which $N$ is the number of boxes that cover the pattern, and $r$ is the magnification or inverse value of the box size.

$$D = \frac{\log (N)}{\log (r)}. \quad (4)$$

A higher slope means that the object is more fractal, i.e., reduction in the size of the box reveals more complexity. The lower slope means that the object is closer to the straight line, i.e., less fractal, and the amount of details does not increase rapidly with increasing magnification.

2.3.2. Modified Features. Inserting zero values by masking layer-stacked images (third block in Figure 2) causes unwanted strip artifact. In order to solve this problem, we modify the output of the abovementioned texture analysis methods, to extract more accurate features. A list of used abbreviations in this paper and their explanations is shown in Table 2.

For GLCM, the first row and column of the output matrix (which represent unwanted zero pixels) are eliminated. The GLCM features listed in Table 1 can then be calculated from

- Energy (ene) = $\sum_{i=1}^{N} \sum_{j=1}^{N} p(i,j)^2,$
- Entropy (ent) = $-\sum_{i=1}^{N} \sum_{j=1}^{N} p(i,j) \log p(i,j),$
- Contrast (con) = $\sum_{i=1}^{N} \sum_{j=1}^{N} (i-j)^2 p(i,j),$
- Homogeneity (hom) = $\sum_{i=1}^{N} \sum_{j=1}^{N} \frac{p(i,j)}{1 + (i-j)^2},$
- Correlation (cor) = $\sum_{i=1}^{N} \sum_{j=1}^{N} \left( \frac{i-\mu_x}{\sigma_x} \right) \left( \frac{j-\mu_y}{\sigma_y} \right) p(i,j),$
- Sum of squares = $\sum_{i=1}^{N} \sum_{j=1}^{N} (i - \mu)^2 p(i,j),$
- Cluster shade = $\sum_{i=1}^{N} \sum_{j=1}^{N} (i + j - 2\mu)^2 p(i,j).$
Table 1: List of utilized features.

| Texture analysis method | Features                  | Description                                                                 | Texture analysis method | Features                  | Description                                                                 |
|-------------------------|---------------------------|------------------------------------------------------------------------------|-------------------------|---------------------------|------------------------------------------------------------------------------|
| GLCM                    | Energy                    | Provides the sum of squared elements in the GLCM. It has values between 0 and 1   | GLCM                    | Difference variance        | Measures the dispersion (with regard to the mean) of the grey-level difference distribution of the image |
|                         | Entropy                   | Measure of randomness that can be used to characterize the texture of an image | GLCM                    | Difference entropy         | Measures the disorder related to the grey-level difference distribution of the image |
|                         | Contrast                  | A measure of intensity contrast between a pixel and its neighbor over the whole image | GLCM                    | Maximum probability        | Measures the maximum likelihood of producing the pixels of interest           |
|                         | Homogeneity               | Measures the closeness of the distribution of elements in the GLCM to the GLCM diagonal | GLCM                    | IMC1                      | Measure of dependency between two random variables                           |
|                         | Correlation               | A measure of how correlated a pixel is to its neighbor over the whole image   |                         | IMC2                      | Mean                                                                         |
|                         | Sum of squares            | Measures the dispersion (with regard to the mean) of the grey-level distribution |                         | LBP                       | Measures mean and standard deviation of histograms                           |
|                         | Cluster shade             | Characterizes the tendency of clustering of the pixels in the region of interest | LDP                     | Standard deviation         |                                                               |
|                         | Cluster prominence        |                                                                                | LOOP                    | Dynamic range              | Measures the ratio between the largest and smallest values                   |
|                         | Dissimilarity             | A measure of distance between pairs of pixels in the region of interest        |                         | Kurtosis                   | Measure of the “tailedness” of the probability distribution                  |
|                         | Autocorrelation           | Represents the degree of similarity between a given time series and a lagged version of it |                         | Skewness                   | Measure of the asymmetry of the probability distribution                     |
|                         | Sum average               | Measures the mean of the grey-level sum distribution of the image              |                         | Mean                       |                                                               |
|                         | Sum entropy               | Measures the disorder related to the grey-level sum distribution of the image  | Fractal dimension       | Standard deviation          | Measures mean and standard deviation of the box-counting method              |
|                         | Sum variance              | Measures the dispersion (with regard to the mean) of the grey-level sum distribution of the image |                         |                           |                                                               |
|                         | Inverse difference        | A measure of local homogeneity of an image                                     |                         |                           |                                                               |
where element \([i, j]\) of the matrix is generated by counting the number of times a pixel with value \(i\) is adjacent to a pixel with value \(j\) and then dividing the entire matrix by the total number of such comparisons made. Each entry is therefore considered to be the probability that a pixel with value \(i\) will be found adjacent to a pixel of value \(j\). \(\mu_x, \mu_y, \sigma_x, \text{ and } \sigma_y\) are means and standard deviations. \(p_x\) and \(p_y\) are partial probability density functions. \(x\) and \(y\) are the coordinates (row and column) of an entry in the cooccurrence matrix, and \(p_{x,y}(i)\) is the probability of cooccurrence matrix coordinates summing to \(x + y\). \(Hx\) and \(Hy\) are the entropies of \(p_x\) and \(p_y\). Finally, \(HXY, HXY1,\) and \(HXY2\) are shown in Table 2: A list of used abbreviations and their explanations.

### Table 2: A list of used abbreviations and their explanations.

| Abbreviation | Explanation |
|--------------|-------------|
| MS           | Multiple sclerosis |
| ON           | Optic neuritis |
| OCT          | Optical coherence tomography |
| CNS          | Central nervous system |
| LSI          | Layer-stacked images |
| MS-ON        | Multiple sclerosis with optic neuritis |
| MS-None ON   | Multiple sclerosis without optic neuritis |
| MRI          | Magnetic resonance imaging |
| RNFL         | Retinal nerve fiber layer |
| GLCM         | Grey-level cooccurrence matrix |
| HC           | Health control |
| LBP          | Local binary pattern |
| LDP          | Local directional pattern |
| LOOP         | Local optimal oriented pattern |
| SVM          | Support vector machine |
| LDA          | Linear discriminant analysis |
| FD           | Fractal dimension |
| LS image     | Layer-stacked image |

\[
HXY = -\sum_{i,j} p(i,j) \log (p(i,j)),
\]

\[
HXY1 = -\sum_{i,j} p(i,j) \log \left\{ P_X(i)P_y(j) \right\},
\]

\[
HXY2 = -\sum_{i,j} p_x(i)p_y(j) \log \left\{ P_X(i)p_y(j) \right\}.
\]

In LBP, LDP, and LOOP methods, the features in Table 1 should be extracted from the histogram of the output. To solve the same problem of unwanted strip artifact, the first column of the histogram (which represent unwanted zero pixels) is eliminated. Finally, five statistical features including mean, standard deviation, dynamic range, kurtosis, and skewness are extracted.

The last category of texture analysis methods to be considered is fractal analysis. Here, we remove the background above the layer-stacked images before performing the masking step. The mean and standard deviation of the fractal dimensions for each image is then reported.

2.4. Feature Selection and Classification. To handle the course of dimensionality problem caused by small number of available data compared to bunch of calculated features, more significant features are selected based on \(t\)-test and Bonferroni correction. The Bonferroni correction is an adjustment made to \(p\) values when several dependent or independent statistical tests are being performed simultaneously on a single data set. To perform a Bonferroni correction, the critical \(p\) value (\(\alpha\)) is divided by the number of comparisons being made.

Here, considering that the majority of the features have been extracted from the GLCM matrix and this matrix has produced the features in four different angles, according to
Table 3: Evaluation of statistical significance of the extracted features, before feature selection. The t-test was used to identify which features show significant differences between healthy and MS (ON and None-ON) cases. The p values indicate the test rejection of the null hypothesis at 5% significance level, considering the Bonferroni correction (p value < 0.001).

| Features      | Layer | \( p \) (HC vs. MS-None-ON) | \( p \) (HC vs. MS-ON) | \( p \) (MS-ON vs. MS-None-ON) | \( p \) (HC vs. MS) | Features      | Layer | \( p \) (HC vs. MS-None-ON) | \( p \) (HC vs. MS-ON) | \( p \) (MS-ON vs. MS-None-ON) | \( p \) (HC vs. MS) |
|---------------|-------|-----------------------------|------------------------|-------------------------------|-------------------|---------------|-------|-----------------------------|------------------------|-------------------------------|-------------------|
| Autocorrelation | 2     | <0.001                      | <0.001                 | 0.966                         | <0.001            | Fractal mean | 1     | <0.001                      | <0.001                 | 0.832                         | 0.051              |
| Autocorrelation | 3     | <0.001                      | 0.101                  | 0.092                         | 0.003             | Fractal mean | 4     | <0.001                      | <0.001                 | 0.799                         | 0.955              |
| Autocorrelation | 4     | <0.001                      | 0.026                  | 0.222                         | 0.008             | Fractal mean | 5     | <0.001                      | <0.001                 | 0.862                         | 0.896              |
| Cluster prominence | 3    | <0.001                      | 0.086                  | 0.033                         | <0.001            | Fractal mean | 8     | <0.001                      | <0.001                 | 0.339                         | 0.785              |
| Cluster prominence | 4   | 0.002                      | 0.057                  | 0.525                         | <0.001            | Fractal mean | 9     | <0.001                      | <0.001                 | 0.964                         | 0.710              |
| Cluster shade   | 2     | 0.038                      | <0.001                 | 0.209                         | 0.044             | Fractal mean | 10    | <0.001                      | <0.001                 | 0.514                         | 0.408              |
| Cluster shade   | 3     | <0.001                      | 0.025                  | 0.054                         | <0.001            | Fractal Std. | 5     | <0.001                      | <0.001                 | 0.744                         | 0.014              |
| Cluster shade   | 4     | <0.001                      | 0.015                  | 0.298                         | <0.001            | Fractal Std. | 8     | 0.113                       | 0.001                  | 0.276                         | <0.001            |
| Contrast        | 1     | 0.341                      | <0.001                 | 0.058                         | 0.012             | Fractal Std. | 9     | <0.001                      | <0.001                 | 0.751                         | <0.001            |
| Contrast        | 2     | <0.001                      | <0.001                 | 0.944                         | <0.001            | Fractal Std. | 10    | <0.001                      | <0.001                 | 1.000                         | <0.001            |
| Contrast        | 3     | <0.001                      | 0.005                  | 0.150                         | 0.001             | LBP mean     | 2     | 0.001                       | 0.003                  | 0.981                         | <0.001            |
| Contrast        | 4     | <0.001                      | 0.001                  | 0.398                         | <0.001            | LBP mean     | 3     | 0.001                       | <0.001                 | 0.950                         | 0.017              |
| Correlation     | 1     | <0.001                      | <0.001                 | 0.999                         | 0.927             | LBP mean     | 4     | <0.001                      | <0.001                 | 0.127                         | 0.024              |
| Correlation     | 2     | <0.001                      | 0.004                  | 0.029                         | 0.546             | LBP mean     | 5     | <0.001                      | <0.001                 | 0.353                         | 0.061              |
| Difference entropy | 2    | <0.001                      | <0.001                 | 0.929                         | 0.951             | LBP mean     | 6     | <0.001                      | <0.001                 | 0.941                         | 0.335              |
| Difference entropy | 3   | <0.001                      | <0.001                 | 0.513                         | 0.677             | LBP mean     | 7     | <0.001                      | <0.001                 | 0.908                         | <0.001            |
| Difference entropy | 4   | <0.001                      | <0.001                 | 0.546                         | 0.263             | LBP mean     | 9     | <0.001                      | <0.001                 | 0.251                         | 0.068              |
| Difference entropy | 5   | <0.001                      | 0.004                  | 0.413                         | 0.733             | LBP Std.     | 4     | <0.001                      | <0.001                 | 0.409                         | 0.319              |
| Difference variance | 2   | <0.001                      | <0.001                 | 0.999                         | 0.001             | LBP Std.     | 5     | <0.001                      | <0.001                 | 0.456                         | 0.645              |
| Difference variance | 3   | <0.001                      | 0.001                  | 0.169                         | <0.001            | LBP Std.     | 6     | <0.001                      | <0.001                 | 0.905                         | 0.234              |
| Difference variance | 4   | <0.001                      | <0.001                 | 0.523                         | <0.001            | LBP Std.     | 7     | <0.001                      | <0.001                 | 0.205                         | 0.116              |
| Dissimilarity   | 2     | <0.001                      | <0.001                 | 0.790                         | 0.010             | LBP Std.     | 9     | <0.001                      | <0.001                 | 0.417                         | 0.150              |
| Dissimilarity   | 3     | <0.001                      | 0.001                  | 0.271                         | 0.030             | LBP dynamic range | 3 | 0.525 | 0.002 | 0.088 | <0.001 |
| Dissimilarity   | 4     | <0.001                      | 0.001                  | 0.380                         | 0.013             | LBP dynamic range | 5 | <0.001 | 0.004 | 0.567 | 0.164 |
| Dissimilarity   | 5     | <0.001                      | 0.035                  | 0.274                         | 0.302             | LBP dynamic range | 6 | <0.001 | 0.006 | 0.675 | <0.001 |
| Energy          | 2     | <0.001                      | <0.001                 | 0.999                         | <0.001            | LBP kurtosis | 2     | <0.001                      | <0.001                 | 0.804                         | 0.968              |
| Energy          | 3     | <0.001                      | <0.001                 | 0.921                         | <0.001            | LBP kurtosis | 3     | <0.001                      | <0.001                 | 0.941                         | 0.048              |
| Energy          | 4     | <0.001                      | 0.001                  | 0.528                         | 0.861             | LBP kurtosis | 4     | 0.001                       | <0.001                 | 0.805                         | 0.001              |
| Energy          | 5     | <0.001                      | 0.019                  | 0.329                         | 0.008             | LDP mean     | 2     | 0.459                       | 0.659                  | 0.961                         | <0.001            |
| Entropy         | 2     | <0.001                      | <0.001                 | 0.896                         | 0.903             | LDP mean     | 4     | <0.001                      | <0.001                 | 0.564                         | 0.067              |
| Entropy         | 3     | <0.001                      | <0.001                 | 0.446                         | 0.765             | LDP mean     | 5     | <0.001                      | <0.001                 | 0.555                         | 0.035              |
| Features                        | Layer | \( p \) (HC vs. MS-None-ON) | \( p \) (HC vs. MS-ON) | \( p \) (MS-ON vs. MS-None-ON) | \( p \) (HC vs. MS) | Features | Layer | \( p \) (HC vs. MS-None-ON) | \( p \) (HC vs. MS-ON) | \( p \) (MS-ON vs. MS-None-ON) | \( p \) (HC vs. MS) |
|--------------------------------|-------|-----------------------------|------------------------|-----------------------------|------------------------|----------|-------|-----------------------------|------------------------|-----------------------------|------------------------|
| Entropy                        | 4     | <0.001                      | <0.001                 | 0.453                       | 0.274                  | LDP mean | 6     | <0.001                      | <0.001                 | 0.121                       | 0.799                  |
| Entropy                        | 5     | <0.001                      | 0.029                  | 0.222                       | 0.871                  | LDP mean | 7     | <0.001                      | <0.001                 | 0.883                       | 0.047                  |
| Homogeneity                    | 2     | <0.001                      | <0.001                 | 0.942                       | 0.900                  | LDP mean | 8     | <0.001                      | <0.001                 | 0.808                       | 0.055                  |
| Homogeneity                    | 3     | <0.001                      | <0.001                 | 0.681                       | 0.690                  | LDP mean | 9     | <0.001                      | <0.001                 | 0.219                       | 0.037                  |
| Homogeneity                    | 4     | <0.001                      | <0.001                 | 0.504                       | 0.201                  | LDP mean | 10    | <0.001                      | <0.001                 | 0.834                       | 0.782                  |
| Homogeneity                    | 5     | <0.001                      | 0.006                  | 0.396                       | 0.680                  | LDP skewness | 2 | <0.001 | <0.001 | 0.813 | 0.530 | | |
| IMC1                           | 2     | <0.001                      | <0.001                 | 0.862                       | 0.017                  | LDP skewness | 3 | <0.001 | <0.001 | 0.930 | 0.085 | | |
| IMC2                           | 9     | 0.004                       | <0.001                 | 0.619                       | 0.043                  | LDP skewness | 4 | 0.004 | <0.001 | 0.633 | 0.002 | | |
| Inverse difference moment      | 1     | 0.319                       | <0.001                 | 0.063                       | 0.011                  | LDP Std.  | 2     | <0.001                      | <0.001                 | 0.276                       | 0.018                  |
| Inverse difference moment      | 2     | <0.001                      | <0.001                 | 0.920                       | <0.001                 | LDP Std.  | 4     | <0.001                      | <0.001                 | 0.652                       | 0.083                  |
| Inverse difference moment      | 3     | <0.001                      | 0.006                  | 0.154                       | 0.001                  | LDP Std.  | 5     | <0.001                      | <0.001                 | 0.882                       | 0.025                  |
| Inverse difference moment      | 4     | <0.001                      | 0.001                 | 0.381                       | <0.001                 | LDP Std.  | 6     | <0.001                      | <0.001                 | 0.093                       | 0.597                  |
| Maximum probability            | 2     | <0.001                      | <0.001                 | 1.000                       | <0.001                 | LDP Std.  | 7     | <0.001                      | <0.001                 | 0.554                       | 0.310                  |
| Maximum probability            | 3     | <0.001                      | <0.001                 | 0.876                       | <0.001                 | LDP Std.  | 8     | <0.001                      | <0.001                 | 0.989                       | 0.870                  |
| Maximum probability            | 4     | <0.001                      | 0.068                  | 0.293                       | 0.430                  | LDP Std.  | 9     | <0.001                      | <0.001                 | 0.629                       | .882                   |
| Maximum probability            | 5     | <0.001                      | 0.062                  | 0.222                       | 0.647                  | LDP Std.  | 10    | <0.001                      | <0.001                 | 0.901                       | 0.792                  |
| Sum average                    | 2     | <0.001                      | <0.001                 | 0.814                       | 0.005                  | LDP dynamic range | 1 | 0.188 | 0.219 | 0.999 | <0.001 | | |
| Sum average                    | 3     | <0.001                      | 0.013                  | 0.194                       | 0.028                  | LDP kurtosis | 2 | <0.001 | <0.001 | 0.998 | <0.001 | | |
| Sum average                    | 4     | <0.001                      | 0.006                  | 0.383                       | 0.048                  | LDP kurtosis | 3 | <0.001 | <0.001 | 1.000 | <0.001 | | |
| Sum entropy                    | 2     | <0.001                      | <0.001                 | 0.953                       | 0.708                  | LDP kurtosis | 4 | <0.001 | <0.001 | 0.801 | 0.466 | | |
| Sum entropy                    | 3     | <0.001                      | 0.002                  | 0.402                       | 0.938                  | LDP kurtosis | 5 | <0.001 | <0.001 | 0.781 | 0.001 | | |
| Sum entropy                    | 4     | <0.001                      | 0.001                  | 0.514                       | 0.384                  | LOOP mean  | 2 | 0.459 | 0.659 | 0.961 | <0.001 | | |
| Sum entropy                    | 5     | <0.001                      | 0.064                  | 0.182                       | 0.806                  | LOOP mean  | 4 | <0.001 | <0.001 | 0.564 | 0.067 | | |
| Sum of squares                 | 2     | <0.001                      | <0.001                 | 0.528                       | 0.001                  | LOOP mean  | 5 | <0.001 | <0.001 | 0.555 | 0.035 | | |
| Sum of squares                 | 3     | <0.001                      | 0.014                  | 0.092                       | <0.001                 | LOOP mean  | 6 | <0.001 | <0.001 | 0.121 | 0.799 | | |
| Sum of squares                 | 4     | <0.001                      | 0.003                  | 0.262                       | <0.001                 | LOOP mean  | 7 | <0.001 | <0.001 | 0.883 | 0.047 | | |
| Sum variance                   | 2     | <0.001                      | <0.001                 | 0.400                       | 0.002                  | LOOP mean  | 8 | <0.001 | <0.001 | 0.808 | 0.055 | | |
| Sum variance                   | 3     | <0.001                      | 0.016                  | 0.087                       | <0.001                 | LOOP mean  | 9 | <0.001 | <0.001 | 0.219 | 0.037 | | |
| Sum variance                   | 4     | <0.001                      | 0.004                  | 0.248                       | <0.001                 | LOOP mean  | 10 | <0.001 | <0.001 | 0.834 | 0.782 | | |
| LOOP Std.                      | 2     | <0.001                      | <0.001                 | 0.964                       | 0.013                  | LOOP skewness | 2 | <0.001 | <0.001 | 0.998 | <0.001 | | |
| LOOP Std.                      | 3     | <0.001                      | <0.001                 | 0.202                       | 0.021                  | LOOP skewness | 3 | <0.001 | <0.001 | 1.000 | <0.001 | | |
| Features    | Layer | $p$ (HC vs. MS-None-ON) | $p$ (HC vs. MS-ON) | $p$ (MS-ON vs. MS-None-ON) | $p$ (HC vs. MS) | Features    | Layer | $p$ (HC vs. MS-None-ON) | $p$ (HC vs. MS-ON) | $p$ (MS-ON vs. MS-None-ON) | $p$ (HC vs. MS) |
|-------------|-------|-------------------------|-------------------|---------------------------|----------------|-------------|-------|-------------------------|-------------------|--------------------------|-------------------|
| LOOP Std.   | 4     | $<0.001$                | $<0.001$          | 0.800                     | 0.218          | LOOP skewness | 4     | $<0.001$                | $<0.001$          | 0.818                    | 0.641             |
| LOOP Std.   | 5     | $<0.001$                | $<0.001$          | 0.830                     | 0.019          | LOOP skewness | 5     | $<0.001$                | 0.002             | 0.769                    | 0.001             |
| LOOP Std.   | 6     | 0.014                   | $<0.001$          | 0.091                     | 0.548          | LOOP Std.    | 9     | $<0.001$                | $<0.001$          | 0.538                    | 0.390             |
| LOOP Std.   | 7     | $<0.001$                | $<0.001$          | 0.576                     | 0.425          | LOOP Std.    | 10    | $<0.001$                | $<0.001$          | 0.786                    | 0.799             |
| LOOP Std.   | 8     | $<0.001$                | $<0.001$          | 0.463                     | 0.316          |              |       |                        |                   |                          |                   |
Bonferroni correction, the value of meaningful p value ($p < 0.005$) is divided by 4 and $p < 0.001$ is considered as a significant level for cut-off. After Bonferroni adjustment for multiple comparisons, features with $p < 0.001$ are selected as significant features. Then, two classification models, SVM and LDA, are utilized for differentiating between four possible groups including HC vs. MS, HC vs. MS-ON, HC vs. MS-None-ON, and MS-ON vs. MS-None-ON. A 10-fold cross-validation is used to evaluate accuracy, for each classification model.

3. Result

3.1. Feature Analysis. To evaluate the statistical significance of the extracted features, the $t$-test is used to identify which features show significant differences between healthy and MS (ON and None-ON) cases (Table 3). The $p$ values indicate the test rejection of the null hypothesis at the 5% significance level, considering the Bonferroni correction ($p < 0.001$). Frequencies of significant selected features for each retinal layer are also presented in Table 4.

3.2. Classification Result. According to Tables 3 and 4, 15 common significant features between three groups (HC, MS-ON, and MS-None-ON) are selected as input of each classifier. However, no significant feature is found for the last group (MS-ON vs. MS-None-ON). Then, the classification step is done to discriminate between four target groups including HC vs. MS, HC vs. MS-None-ON, HC vs. MS-ON, and MS-ON vs. MS-None-ON. The accuracy results obtained from our classifiers in different groups are shown in Table 5.

In addition, to prepare a fair comparison with the previous studies, we also test the performance of the two classification models using thickness features as input. As above-mentioned, utilizing texture features for our intended goal is totally novel and previous researches were only relying on thickness as discriminant features. Therefore, the thickness features are calculated as the average value of distance between two consecutive boundaries, which lead to 10 thickness values out of 11 retinal layer boundaries, and this thickness feature vector is fed also to each classifier. In summary, the following set of information are utilized as input of each two classifiers:

(I) 15 common selected texture features based on $t$-test and Bonferroni correction

(II) Thickness features

(III) Combination of I and II

As it can be found in Table 5, in cases I and II, SVM outperforms LAD. In analyzing the effect of texture and thickness features separately, it has to be mentioned that the best accuracy result for groups HC vs. MS and HC vs. MS-ON is found using texture features and SVM classifier. Meanwhile, for groups HC vs. MS-None-ON and MS-ON vs. MS-None-ON, thickness features and SVM classifier obtain the best accuracy.

| Layers | HC vs. MS | HC vs. MS-ON | HC vs. MS-None-ON | MS-ON vs. MS-None-ON |
|--------|-----------|--------------|------------------|---------------------|
| 1      | 1         | 4            | 2                | 0                   |
| 2      | 10        | 22           | 22               | 0                   |
| 3      | 10        | 11           | 21               | 0                   |
| 4      | 7         | 15           | 24               | 0                   |
| 5      | 0         | 8            | 18               | 0                   |
| 6      | 1         | 5            | 5                | 0                   |
| 7      | 1         | 6            | 6                | 0                   |
| 8      | 1         | 5            | 5                | 0                   |
| 9      | 1         | 9            | 8                | 0                   |
| 10     | 1         | 5            | 7                | 0                   |
| Total  | 33        | 90           | 117              | 0                   |

Furthermore, the impressive point is that in case III and with the combination of texture and thickness features as input of the classifiers, the result improved considerably and also the performance of the LDA classifier is superior to the SVM performance in most of the conditions.

4. Conclusion

There are no specific tests for MS detection. Instead, a diagnosis of MS often relies on ruling out other conditions that might produce similar signs and symptoms, known as a differential diagnosis. Blood tests, spinal tap (lumbar puncture), evoked potential tests, and MRI are the conventional MS diagnosis methods. The first MR images of MS were produced in the early 1980s [23]. In most people with relapsing-remitting MS, the diagnosis is fairly straightforward and based on a pattern of symptoms consistent with the disease and confirmed by brain imaging scans such as MRI; however, MS diagnosis can be more difficult in patients with unusual symptoms or progressive disease.

MRI-based methods have been indeed the most successful techniques to estimate CNS damage up to the present, although it is becoming increasingly clear that due to the ability of direct visualization of retinal axons, OCT has become an extremely sensitive method for
imaging neurodegeneration in MS patients. Studies show thickness reduction in retinal layers of MS patients with and without history of ON by OCT image analysis [4, 9, 24–28]. Hence, OCT is suggested as an important tool for monitoring MS and also as a complementary method for MRI-based diagnosis techniques [29–32]. However, as mentioned above, the majority of previous works are on the thickness analysis of retinal layers. Here, by combining the information of thickness and texture of retinal layers, we prepared a more comprehensive analysis of OCT imaging performance in the diagnosis of MS with or without ON.

Indeed, texture analysis is a novel strategy for studying intrinsic changes in retinal layers during neurodegenerative diseases. MS, as one of the famous neurodegenerative disorders, is investigated in this research.

After performing a vast survey on available texture analysis methods, a treasury of powerful features is collected in this paper. As a primary work, this paper shows the ability of such features in discrimination of HC and MS (ON and None-ON) cases. Even with simple classification methods, the texture features are powerful to diagnose MS cases (from HC ones) with accuracy of 85.3% and 72% with SVM and LDA classifiers, respectively.

Another valuable point is that adding information of conventional thickness values to texture features improves the discrimination between most of the target groups including HC vs. MS, HC vs. MS-None-O, and HC vs. MS-ON. It should be noted that the results of the last group (MS-ON vs. MS-None-ON) are generally weaker than other groups due to the lack of significant discriminant texture features for this group.

Furthermore, the findings show that some layers like 2, 3, and 4 carry more texture information useful in separation of HC from MS cases. Such finding can be a start point for further investigation in this area.

Data Availability

The data will be available upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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