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Evidence-Based Patient Classification for Traditional Chinese Medicine

Guest Editors: Guo-Zheng Li, Ka-Fai Chung, and Josiah Poon

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Editorial Board

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Editorial

Evidence-Based Patient Classification for Traditional Chinese Medicine

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Some form of categorization or subdivision of disease states is inevitable in all branches of medicine. According to the traditional Chinese medicine (TCM) theory, the patterns of bodily disharmony are described in terms of eight major parameters: *yin* and *yang*, *external* and *internal*, *hot* and *cold*, and *excess* and *deficiency*. Additional systems such as *qi*, *blood*, and *body-fluid* differentiation and *zang fu* (organ) differentiation are also used. To enhance wider acceptance, these TCM categories have to have sufficient reliability and validity. There are interrater and test-retest reliability and four major types of validity: concurrent, predictive, construct, and content. As the TCM theory originated from ancient medical texts and the classification is based on symptoms and signs, the key shortcomings are the highly subjective diagnostic process and the lack of scientific support for the TCM classification. In this special issue, the evidence base of the TCM classification was investigated.

In the paper "Advances in Patient Classification for Traditional Chinese Medicine: A Machine Learning Perspective," the authors introduced the machine learning algorithms for sign classification, syndrome differentiation, and disease classification. Clinical features, as derived from inspection, auscultation, olfaction, and palpation, and patients' dataset from medical records could be analyzed by k nearest neighbor, support vector machine, linear discriminant analysis, naive bayes, decision tree, artificial neural network, graphical models, multilabel learning, deep learning, or clustering analysis. The use of machine learning algorithms is a step toward enhancing data reliability, but the accuracy, as compared to experienced TCM practitioners, is still suboptimal. We believe that the machine learning algorithms are best used to deal with large and complex dataset, while the application in sign classification merits further investigation.

With the help of computer technology, the paper "Significant Geometry Features in Tongue Image Analysis" categorized five different tongue shapes: rectangular, acute triangle, obtuse triangle, circle, and square. The authors found that tongue shape can be used to distinguish healthy and disease states, with an average accuracy of 76%. Further testing of the role of tongue shape in TCM classification is needed.

Two papers introduced novel statistical approaches to assist TCM classification. In the paper "Mining Symptom-Herb Patterns from Patient Records Using Tripartite Graph," the authors designed a data mining approach to examine the relationship between symptom, syndrome, and herb. This tripartite information network derives more accurate information than linking symptom and herb alone. In the paper "A Novel Classification Method for Syndrome Differentiation of Patients with AIDS," the authors found that a novel machine learning algorithm, minimum reference set-based multiple instance learning, was superior to other machine learning algorithms for TCM classification.

A few papers examined the clinical application of TCM classification. In the paper "Yang Deficiency Body Constitution Acts as a Predictor of Diabetic Retinopathy in Patients with Type 2 Diabetes: Taichung Diabetic Body Constitution Study," 673 patients with diabetes were examined using a body constitution questionnaire. The authors showed that *yang deficiency* was an independent predictor of a lower risk of diabetic retinopathy, suggesting that TCM classification may

have predictive validity on disease complication. As the study design was cross-sectional, the causal relationship between TCM pattern and diabetic complication should be further examined in longitudinal studies.

The paper "Cerebral Activity Changes in Different Traditional Chinese Medicine Patterns of Psychogenic Erectile Dysfunction Patients" showed that, compared to patients with *liver-qi stagnation* and *spleen deficiency*, patients with *kidney-yang deficiency* showed an increased activity in bilateral brainstem, cerebellum, hippocampus, and the right insula, thalamus, and middle cingulate cortex and a decreased activity in bilateral putamen, medial frontal gyrus, temporal pole, and the right caudate nucleus, orbitofrontal cortex, anterior cingulate cortex, and posterior cingulate cortex. As the main difference in cerebral activity between the TCM patterns is in the brain regions that are responsible for emotional modulation, the authors believed that TCM classification might help disease subclassification, which could be used to provide personalized treatment.

In the paper "Analysis and Recognition of Traditional Chinese Medicine Pulse Based on the Hilbert-Huang Transform and Random Forest in Patients with Coronary Heart Disease," the authors introduced an objective pulse measurement, which could distinguish patients with coronary heart disease and healthy controls. Further studies are needed to test the reliability and validity of the pulse characteristics. Another paper titled "Correlations between Phlegm Syndrome of Chinese Medicine and Coronary Angiography: A Systematic Review and Meta-Analysis" showed that phlegm syndrome can help to determine the severity of coronary heart disease.

Lastly, in the paper "Prescription of Chinese Herbal Medicine in Pattern-Based Traditional Chinese Medicine Treatment for Depression: A Systematic Review," the authors found that *liver qi depression*, *liver depression and spleen deficiency*, *dual deficiency of the heart and spleen*, and *liver depression and qi stagnation* were the most common TCM patterns in people with depression. The authors identified several pattern-based TCM treatments that could be further examined. Xiaoyao decoction was the most frequently used herbal formula for the treatment of *liver qi depression* and *liver depression with spleen deficiency*, while Chaihu Shugan decoction was often used for *liver depression and qi stagnation*. The authors called for more high quality studies incorporating TCM pattern differentiation and treatment principle to examine the efficacy of TCM treatments and the additional benefit of pattern differentiation. Future studies incorporating expertise in various disciplines are needed to further examine the evidence base of TCM classification in patient care.

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Research Article

Significant Geometry Features in Tongue Image Analysis

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The shape of a human tongue and its relation to a patients' state, either healthy or diseased (and if diseased which disease), is quantitatively analyzed using geometry features by means of computerized methods in this paper. Thirteen geometry features based on measurements, distances, areas, and their ratios are extracted from tongue images captured by a specially designed device with color correction. Using the features, 5 tongue shapes (rectangle, acute and obtuse triangles, square, and circle) are defined based on traditional Chinese medicine (TCM). Classification of the shapes is subsequently carried out with a decision tree. A large dataset consisting of 672 images comprising of 130 healthy and 542 disease examples (labeled according to Western medical practices) are tested. Experimental results show that the extracted geometry features are effective at tongue shape classification (coarse level). Even if more than one disease class belongs to the same shape, the disease classes can still be discriminated via fine level classification using a combination of the geometry features, with an average accuracy of 76.24% for all shapes.

1. Introduction

The human tongue contains numerous features. Traditionally, medical practitioners would examine these features based on years of experience [1–5]. However, ambiguity and subjectivity are associated with their diagnostic results. To eliminate these qualitative aspects, tongue images can be objectively analyzed, which offers a new way to diagnose disease, one that minimizes the physical harm inflicted to patients (compared with other medical examinations).

In state-of-the-art computerized tongue image analysis, color and texture features are the most prevalent [6–19]. There exists little or no literature on tongue image analysis using geometry features, whereas in traditional medicines such as traditional Chinese medicine (TCM) the shape of a tongue can be used to determine a patients' illness [3, 4, 20]. The authors in [21] proposed an approach to automatically recognize tongue shapes based on geometry features. The seven geometric features included various measurements of length, area, and angle extracted from tongue images. Using a support decision tool to weight the relative influences of the geometry features, they classified an image into one of six tongue shapes, namely, hammer, rectangle, acute triangle, obtuse triangle, square, and round (based on TCM). Experimental results conducted on 362 tongue images exhibited an accuracy of 90.3% for shape classification. Nevertheless, there was little quantitative analysis between tongue shape and the relationship to its current health state.

In this paper we thoroughly examine the aforementioned problem via geometry features in tongue image analysis. The imaging device used to capture tongue images is made up of a 3-chip CCD camera with 8 bit resolution and two D65 fluorescent tubes placed symmetrically around the camera in order to produce a uniform illumination. The images captured were color corrected [22] to eliminate any noise caused by variations of illumination and device dependency. Also, the tongue image capture device ensures that the images are properly aligned. This allows consistent feature extraction and classification in the following steps. Figure 1 shows the capture device. Using this device we form a large tongue image database consisting of 672 samples. This database is composed of 130 healthy and 542 disease samples, divided into 7 classes with at least 19 examples. Every image is segmented [19] with the background removed and tongue

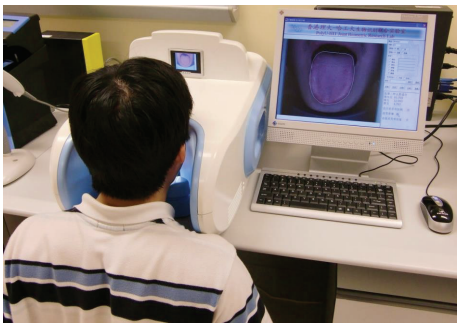

Figure 1: Tongue image capture device.

foreground remaining. From each tongue image consisting of a tip, body, and root [20], 13 geometry features derived from measurements, distances, areas, and their ratios are extracted. Using these features we define 5 tongue shapes based on TCM, rectangle, acute and obtuse triangles, square, and circle. Coarse level classification applying a decision tree [23] was used to classify a tongue into one of the shapes. Experimental results showed that a majority of the samples in the classes from healthy and disease samples tend to be one form, where healthy versus disease samples and disease versus disease are separable using fine level classification, employing a combination of geometry features. This proves the significance of the geometry features at establishing a relationship between a tongue's state and its shape.

The rest of this paper is organized as follows. Thirteen geometry features extracted from tongue images are presented in Section 2 along with the tongue shape classification performed using a decision tree. Following this, experimental results using coarse and fine level classifications are given in Section 3. Finally, concluding remarks are made in Section 4.

2. Materials and Methods

The tongue image dataset is first introduced in Section 2.1. Afterwards, a detailed description of the 13 geometry features extracted from a tongue image is given in Section 2.2. How these features are then used to classify a tongue into 5 major shapes is provided in Section 2.3.

2.1. Tongue Image Dataset. The tongue image database is composed of 672 images (one image per person) divided into 130 healthy and 542 disease samples. Seven disease classes and healthy classes were captured at Guangdong Provincial Hospital of Traditional Chinese Medicine, Guangdong, China. Patients with diabetes mellitus were processed at the Hong Kong Foundation for Research and Development in Diabetes, Prince of Wales Hospital, Hong Kong. Healthy samples were verified through a blood test and other experiments. If indicators from the tests fall within a certain range they were deemed healthy. In the disease class, samples were collected from inpatients with illness determined by their admission note and diagnosed using western medical practices. Inpatients suffering from the same disease were grouped together into a single class. In total there were 7 disease groups (with at least 19 samples). A summary of the disease class breakdown is given in Table 1.

Table 1: Disease class statistics listing its name and number of samples.

Disease name	Number of samples
Diabetes mellitus (DM)	296
Nephritis (NR)	90
Gastritis verrucosa (GV)	67
Nephrotic syndrome (NS)	30
Erosive gastritis (EG)	20
Chronic gastritis (CG)	20
Coronary heart disease (CHD)	19

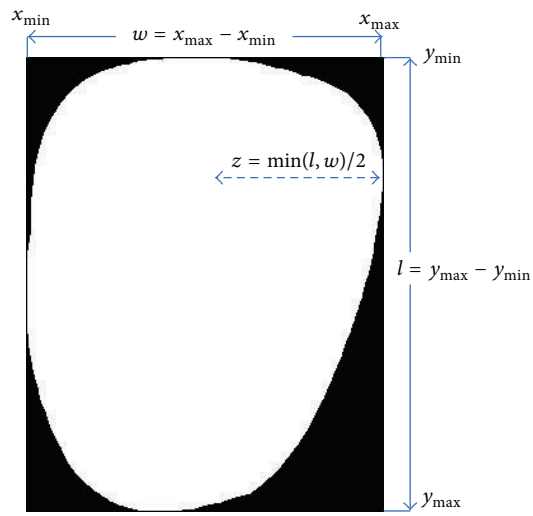

Figure 2: Illustration of features 1, 2, and 4.

2.2. Geometry Features. In the following subsection we describe the 13 geometry features extracted from tongue images (which have been converted to binary images after segmentation [19]). These features based on measurements, distances, areas, and their ratios are used in subsequent sections to define and classify 5 tongue shapes.

2.2.1. Width. The width (w) feature (see Figure 2) is measured as the horizontal distance along the x-axis from a tongue's furthest right edge point (x_{max}) to its furthest left edge point (x_{min}):

$$w = x_{max} - x_{min}. \quad (1)$$

2.2.2. Length. The length (l) feature (see Figure 2) is measured as the vertical distance along the y-axis from a tongue's furthest bottom edge (y_{max}) point to its furthest top edge point (y_{min}):

$$l = y_{max} - y_{min}. \quad (2)$$

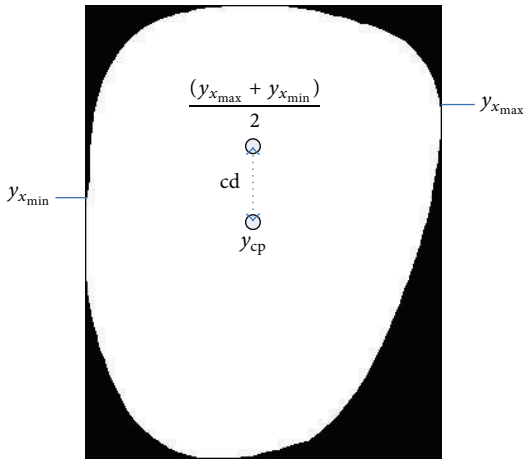

Figure 3: Illustration of feature 5.

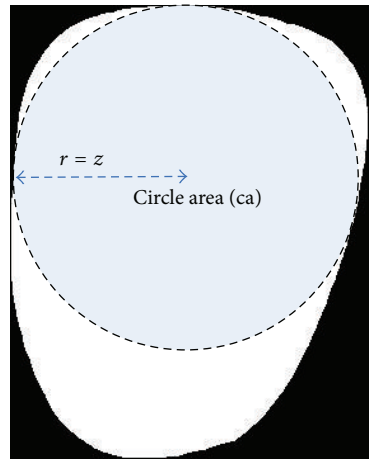

Figure 4: Illustration of feature 8.

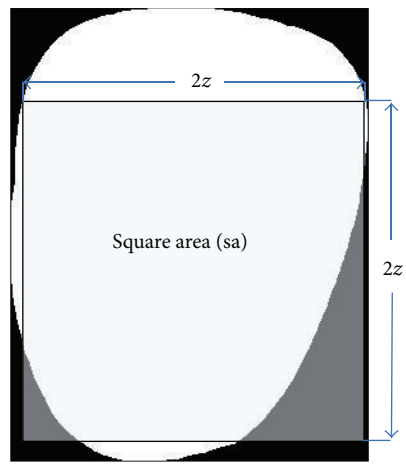

Figure 5: Illustration of feature 10.

2.2.3. Length-Width Ratio. The length-width ratio (lw) is the ratio of a tongue's length to its width:

$$lw = \frac{l}{w}. \tag{3}$$

2.2.4. Smaller Half Distance. Smaller half distance (z) is the half distance of l or w depending on which segment is shorter (see Figure 2):

$$z = \frac{\min(l, w)}{2}. \tag{4}$$

2.2.5. Center Distance. The center distance (cd) (refer to Figure 3) is the distance from w's y-axis center point to the center point of $l(y_{cp})$:

$$\text{cd} = \frac{\left(\max\left(y_{x_{\max}}\right) + \max\left(y_{x_{\min}}\right)\right)}{2} - y_{cp}, \tag{5}$$

where $y_{cp} = (y_{\max} + y_{\min})/2$.

2.2.6. Center Distance Ratio. Center distance ratio (cdr) is ratio of cd to l:

$$\text{cdr} = \frac{\text{cd}}{l}. \tag{6}$$

2.2.7. Area. The area (a) of a tongue is defined as the number of tongue foreground pixels.

2.2.8. Circle Area. Circle area (ca) is the area of a circle within the tongue foreground using smaller half distance z, where $r = z$ (refer to Figure 4):

$$\text{ca} = \pi r^2. \tag{7}$$

2.2.9. Circle Area Ratio. Circle area ratio (car) is the ratio of ca to a:

$$\text{car} = \frac{\text{ca}}{a}. \tag{8}$$

2.2.10. Square Area. Square area (sa) is the area of a square defined within the tongue foreground using smaller half distance z (refer to Figure 5):

$$\text{sa} = 4z^2. \tag{9}$$

2.2.11. Square Area Ratio. Square area ratio (sar) is the ratio of sa to a:

$$\text{sar} = \frac{\text{sa}}{a}. \tag{10}$$

2.2.12. Triangle Area. Triangle area (ta) is the area of a triangle defined within the tongue foreground (see Figure 6). The right point of the triangle is $x_{\max}$, the left point is $x_{\min}$, and the bottom is $y_{\max}$.

2.2.13. Triangle Area Ratio. Triangle area ratio (tar) is the ratio of ta to a:

$$\text{tar} = \frac{\text{ta}}{a}. \tag{11}$$

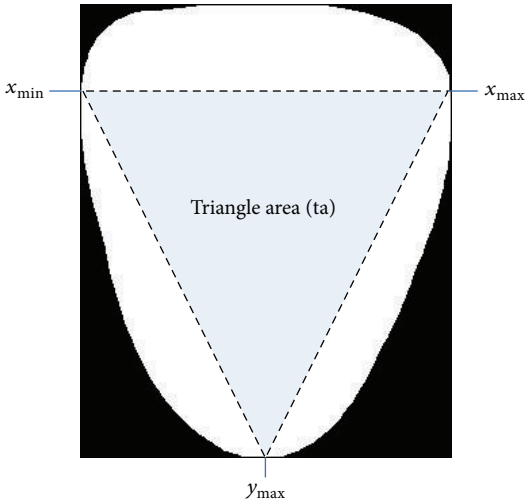

Figure 6: Illustration of feature 12.

2.3. Tongue Shape Classification. Based on TCM we define 5 tongue shapes, rectangle, acute triangle, obtuse triangle, square, and circle, which can be classified using the 13 features explained above (see Section 2.2). A rectangle tongue's vertical length is long, but its horizontal width along the tip, body, and root remains relatively constant. An acute triangle tongue's vertical length is longer than its largest horizontal width (at the root) but gradually decreases from the body down to the tip. If the tongue shape is an obtuse triangle, its horizontal width is greater than its vertical length, with the width steadily decreasing as it approaches the tip. In a square tongue shape both its horizontal width and vertical length are similar. Finally, if a tongue is circle, both the horizontal width and vertical length will be alike, but its car (8) will be closer to 1. Figure 7 depicts the 5 tongue shapes using typical samples.

To classify tongue images into its proper shape, a decision tree structure shown in Figure 8 is used. Given a tongue we first examine its length-width (lw) ratio. If this ratio is $t_{\text{low}}^{lw} \leq lw \leq t_{\text{high}}^{lw}$, the tongue shape must be square or circle (left branch), and if the ratio is $t_{\text{high}}^{lw} < lw$ or $t_{\text{low}}^{lw} > lw$, the shape of the tongue can be rectangle, acute triangle, or obtuse triangle (right branch). The values of t_{low}^{lw} and t_{high}^{lw} are 0.95 and 1.05, respectively.

Focusing on the left branch, the average radius (r_{avg}) of the tongue is first calculated as

$$r_{\text{avg}} = \frac{(l + w)}{4} \tag{12}$$

which is the average of $w/2$ and $l/2$. Next, the ratio T_{sc} is computed as

$$T_{\text{sc}} = \frac{a}{{r_{\text{avg}}}^2}. \tag{13}$$

If the tongue shape is approximately square, the value of $T_{\text{sc}} \approx 4$ (i.e., $4 \cdot {r_{\text{avg}}}^2/{r_{\text{avg}}}^2$), and if it is approximately circle, $T_{\text{sc}} \approx \pi$ (i.e., $\pi \cdot {r_{\text{avg}}}^2/{r_{\text{avg}}}^2$). Hence, the two shapes can be defined as

$$\begin{aligned} \text{Square} &= T_{\text{sc}} \geq \pi + \varepsilon, \\ \text{Circle} &= T_{\text{sc}} < \pi + \varepsilon, \end{aligned} \tag{14}$$

where ε is a constant equal to 0.1.

Turning our attention to the right branch, we initially calculate the ratio T_{rao}:

$$T_{\text{rao}} = \frac{a}{(l \cdot w)}. \tag{15}$$

If this ratio is greater than or equal to t_{rect}, the tongue shape is rectangle:

$$\text{Rectangle} = T_{\text{rao}} \geq t_{\text{rect}}, \tag{16}$$

where t_{rect} is 0.85 and the maximum of T_{rao} is 1. If $T_{\text{rao}} < t_{\text{rect}}$, the shape of the tongue is either acute or obtuse triangle. To determine which triangle, length-width ratio is used once again as follows:

$$\begin{aligned} \text{Acute Triangle} &= \left(T_{\text{rao}} < t_{\text{rect}}\right) \wedge \left(lw \geq t_{\text{ao}}\right), \\ \text{Obtuse Triangle} &= \left(T_{\text{rao}} < t_{\text{rect}}\right) \wedge \left(lw < t_{\text{ao}}\right), \end{aligned} \tag{17}$$

where t_{ao} is given as 1.05. The parameter values listed above to classify a tongue image were chosen empirically.

3. Results and Discussions

The following section presents the experimental results. A coarse level classification showing the results of tongue shape classification is given in Section 3.1. Classes classified into the same shape are further differentiated in Section 3.2 through fine level classification using a combination of geometry features.

3.1. Coarse Level: Tongue Shape Classification Result. By applying the tongue shape classification algorithm (described above, see Section 2.3) to every image in the dataset, its shape can be determined. This result is listed in Table 2. In the table it can be seen that the most common shapes in healthy group are circle or square, representing 86.92% (113/130) of all samples. In DM the majority shape is obtuse triangle, accounting for 86.15% (255/296). For NR, acute triangle takes the majority with 83.33% (75/90). Having 85.07% (57/67) and 83.33% (25/30), rectangle is the most prevalent shape in GV and NS, respectively. In EG the dominant shapes are circle or square, making up 85.00% (17/20). Finally, in CG and CHD acute and obtuse triangles are the most widespread, embodying 80.00% (16/20) and 84.21% (16/19) of all images correspondingly. Figure 9 depicts three typical samples from the healthy class, while Figures 10(a)–10(g) illustrate typical samples from the disease classes.

3.2. Fine Level: Classification Result within Each Shape. In the tongue shape classification results, there exists more

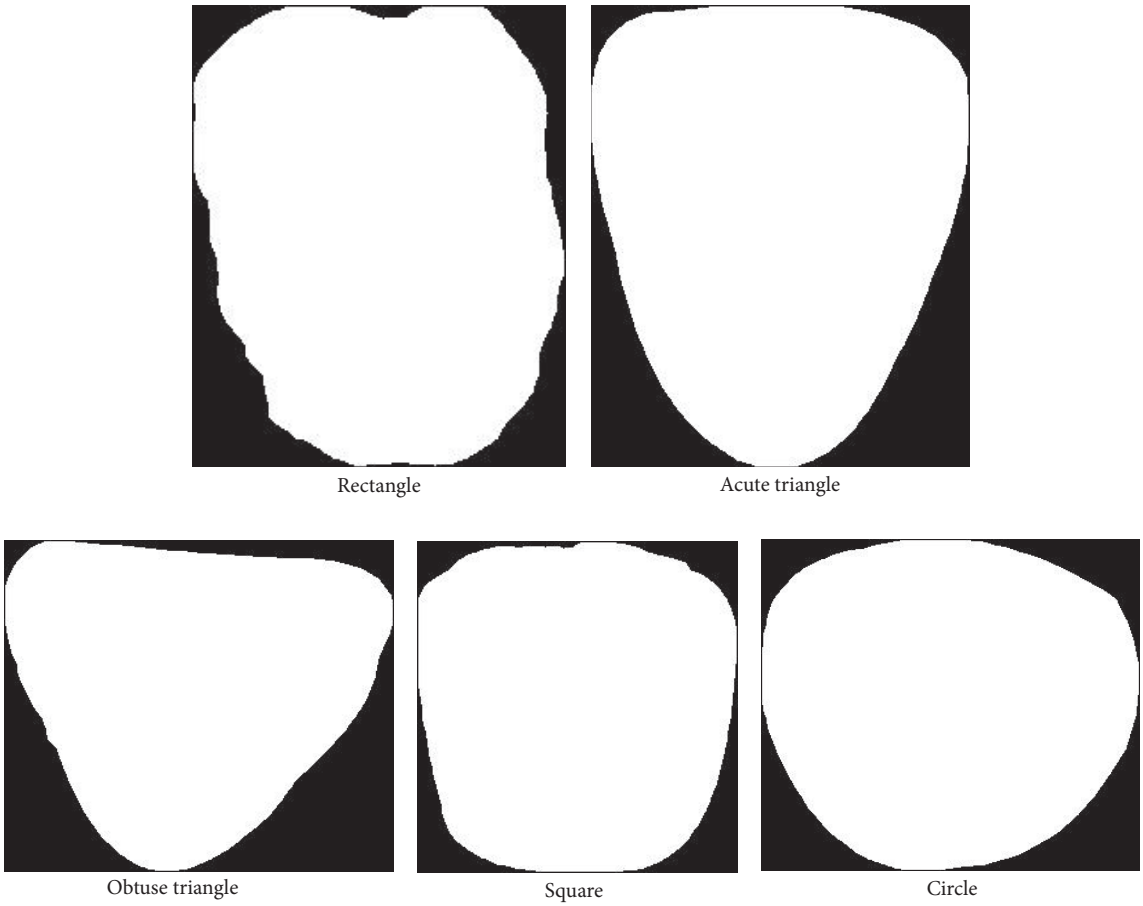

Figure 7: Typical samples to show the 5 tongue shapes.

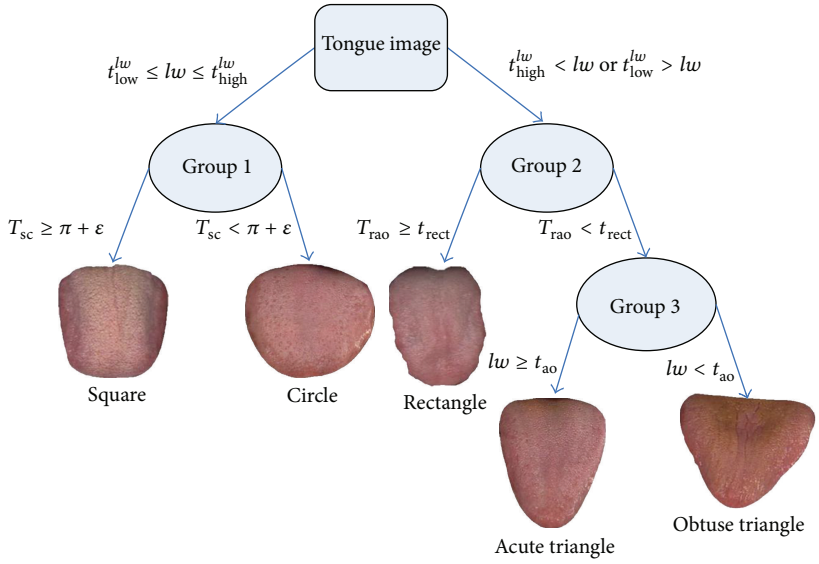

Figure 8: Decision tree to classify the tongue shapes.

Table 2: Tongue shape classification result for the dataset.

	Rectangular	Acute triangle	Obtuse triangle	Circle	Square
Healthy	5	4	8	**50**	**63**
DM	7	22	**255**	2	10
NR	5	**75**	4	0	6
GV	**57**	5	4	0	1
NS	**25**	1	1	1	2
EG	1	1	1	**5**	**12**
CG	4	**16**	0	0	0
CHD	0	3	**16**	0	0

Figure 9: Three typical samples from healthy samples.

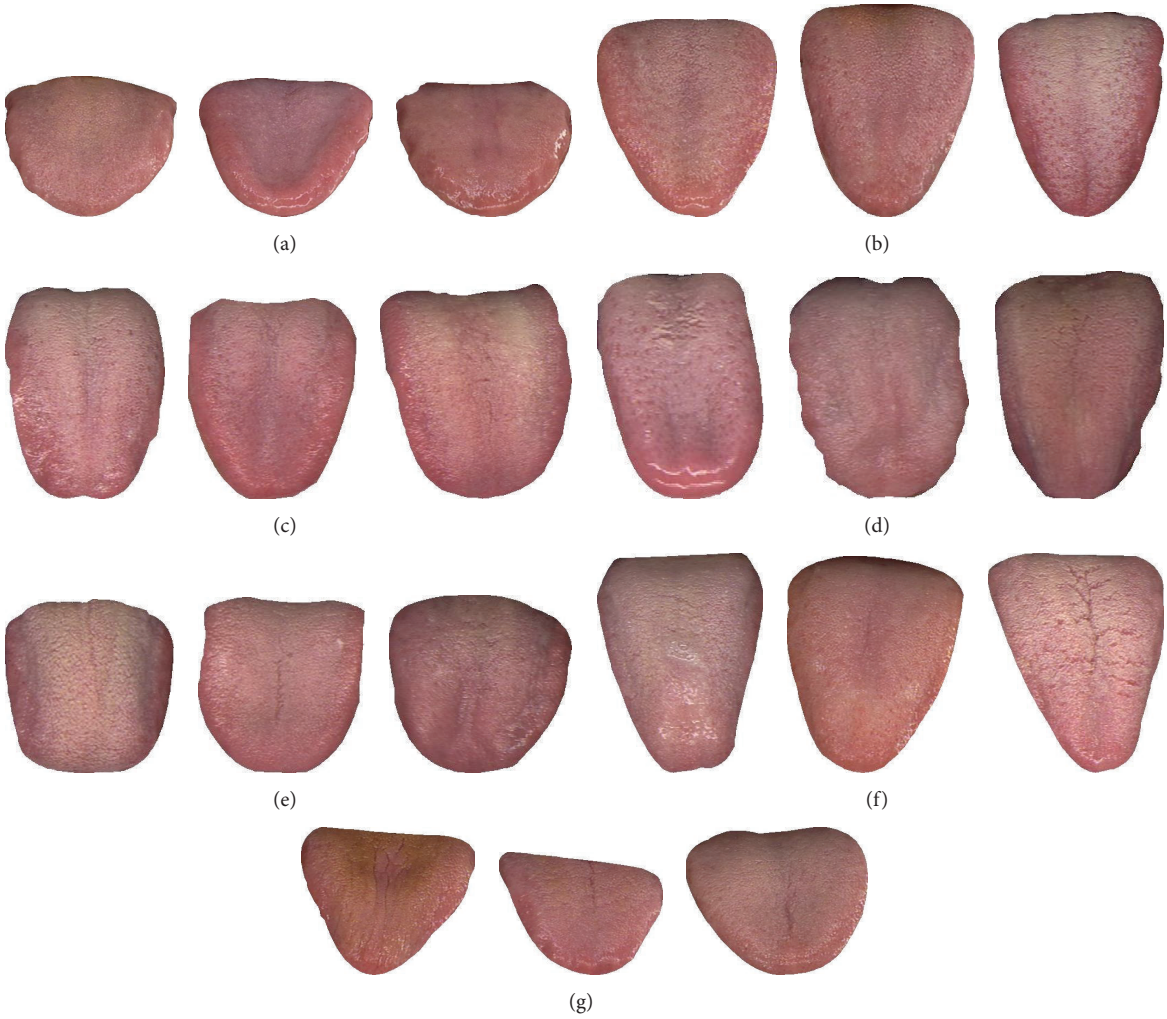

Figure 10: Three typical samples from (a) DM, (b) NR, (c) GV, (d) NS, (e) EG, (f) CG, and (g) CHD.

Table 3: Optimized classification result between various classes having identical tongue shape.

Tongue shape	Class comparison	Optimal feature(s)	Average accuracy
Circle or square	Healthy versus EG	1, 7	88.65%
Obtuse triangle	DM versus. CHD	1, 7, 4, 11, 13, 2	76.23%
Acute triangle	NR versus CG	2	70.00%
Rectangle	GV versus NS	9, 4, 7, 8, 2, 13, 12, 1	70.07%

than one class for each shape (see Table 2). To distinguish between classes with the same shape, a set of geometry features were selected and applied to SVM. Half the images in each class were randomly selected for training, while the other half was used as testing. To measure the performance, average accuracy was employed. The linear kernel function (dot product) was used to map the training data into kernel space, while a quadratic kernel produced similar classification results. k-NN was also tested but did not perform as well.

Utilizing a grouping of the features is logical, since not every feature can have a positive contribution to the final result, as is the case here where 13 features used for classification produced poor results. Therefore, an optimization of the features is necessary. To reduce the number of features, sequential forward selection (SFS) [23] was implemented. SFS is a feature selection method that begins with an empty set of features. It adds additional features based on maximizing some criterion function J and terminates when all features have been added. In our case J is the average accuracy of SVM. Below, each tongue shape is examined in detail.

3.2.1. Rectangle. Both GV and NS were classified into this shape. Applying SFS with SVM to separate the two classes, the highest average accuracy of 70.07% was achieved using features 9, 4, 7, 8, 2, 13, 12, and 1.

3.2.2. Acute Triangle. For this shape NR and CG were classified together. l (feature 2) attained the best average accuracy of 70.00%.

3.2.3. Obtuse Triangle. DM and CHD were assigned to obtuse triangle. Through a combination of features consisting of 1, 7, 4, 11, 13, and 2, the highest average accuracy of 76.23% was achieved.

3.2.4. Circle or Square. The maximum average accuracy of 88.65% was obtained using w (feature 1) and a (feature 7) to classify the two classes (healthy and EG) appointed to circle or square.

Table 3 summarizes the results for each tongue shape. For completeness, the average accuracy of healthy samples versus NR, GV, NS, CG, DM, and CHD is shown in Table 4. From this result, it can be seen that healthy samples are distinguishable compared to others, given their different tongue shapes.

Table 4: Optimized classification result between healthy versus NR, GV, NS, CG, DM, and CHD groups.

Classes compared with healthy	Optimal feature(s)	Average accuracy
NR	1, 7, 12, 8, 4	82.09%
GV	1, 8	86.72%
NS	7, 4, 1, 8	85.26%
CG	1	75.19%
DM	12, 1, 13, 9, 11	69.09%
CHD	8, 6, 4, 10, 13, 9, 2	80.89%

4. Conclusions

In this paper we thoroughly examined tongue shape and its relation to a patients' state (either healthy or diseased) using geometry features through computerized methods. With tongue images captured by a specially designed device that accounts for image correction and a large dataset labeled according to western medical practices, we have a solid foundation to carry out this objective study. Thirteen geometry features including measurements, distances, areas, and their ratios were extracted from each tongue image. The features helped define 5 tongue shapes rooted upon TCM and classified using a decision tree. In the experimental results, coarse level classification first showed that the tongue classes belong to different shapes. Although more than one class occupies the same shape, in fine level classification they are still distinguishable, when employing SFS with SVM (using a grouping of geometry features). This validates the significance of geometry features at shape classification, as well as healthy versus disease/disease versus disease classifications. With tongue shape and a persons' health state now established using computer-based methods, this potentially provides a new painless and efficient way to diagnose patients. A continuation of this work will investigate the fusion of all possible tongue features including color and texture in order to better determine a patients' state.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Advances in Patient Classification for Traditional Chinese Medicine: A Machine Learning Perspective

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As a complementary and alternative medicine in medical field, traditional Chinese medicine (TCM) has drawn great attention in the domestic field and overseas. In practice, TCM provides a quite distinct methodology to patient diagnosis and treatment compared to western medicine (WM). Syndrome (ZHENG or pattern) is differentiated by a set of symptoms and signs examined from an individual by four main diagnostic methods: inspection, auscultation and olfaction, interrogation, and palpation which reflects the pathological and physiological changes of disease occurrence and development. Patient classification is to divide patients into several classes based on different criteria. In this paper, from the machine learning perspective, a survey on patient classification issue will be summarized on three major aspects of TCM: sign classification, syndrome differentiation, and disease classification. With the consideration of different diagnostic data analyzed by different computational methods, we present the overview for four subfields of TCM diagnosis, respectively. For each subfield, we design a rectangular reference list with applications in the horizontal direction and machine learning algorithms in the longitudinal direction. According to the current development of objective TCM diagnosis for patient classification, a discussion of the research issues around machine learning techniques with applications to TCM diagnosis is given to facilitate the further research for TCM patient classification.

1. Introduction

Traditional Chinese medicine has been used for treatment and prevention of diseases and healthcare for thousands of years in China. To some extent, TCM has also been treated as a popular complementary and alternative medicine in medical field. This is due to the fact that western medicine generally focusing on prescribing medication to deal with the patient's symptoms as effectively as possible. However, TCM theory is based on philosophical frameworks such as the Yin-Yang and five elements theory, the human body meridian systems, and the Zang Fu theory [1, 2], wherein TCM treatments intend to restore the Yin-Yang balance of patient's body and then eliminate the causes of the diseases [3]. To be more detailed, according to the Ying-Yang balance theory, everything consists of five elements: wood, fire, earth, metal, and water. Based on this theory, TCM interprets that the physiology and pathology of human body and the natural circumstance have some relationships which shows the visceral organs having similar properties with the five elements [3]. Thus, diseases would occur if the Ying-Yang balance is disturbed in our body system. Meanwhile, the visceral organs are affected and some clinical manifestations and pathological conditions will appear on some parts of the body or sometimes throughout the whole body.

Then, in order to examine these human pathological conditions in practice, TCM ancient specialists establishe four main TCM diagnostic methods as commonly called inspection (observation), auscultation and olfaction (listening and smelling), interrogation (inquirying or questioning), and palpation (pulse examination). The inspection is to observe all the visible signs and external conditions of the patients which mainly include the vitality, color, appearance, secretions, and excretions. Auscultation and olfaction refer to utilizing the auditory and olfactory sense to gather information about the patient's voice, breathing, coughing, and odor. Interrogation is a way to ask various questions about patients' family history, major complaints, living states, diets, sleeping habits, and such like these physical conditions. Palpation always examines patients' pathological changes

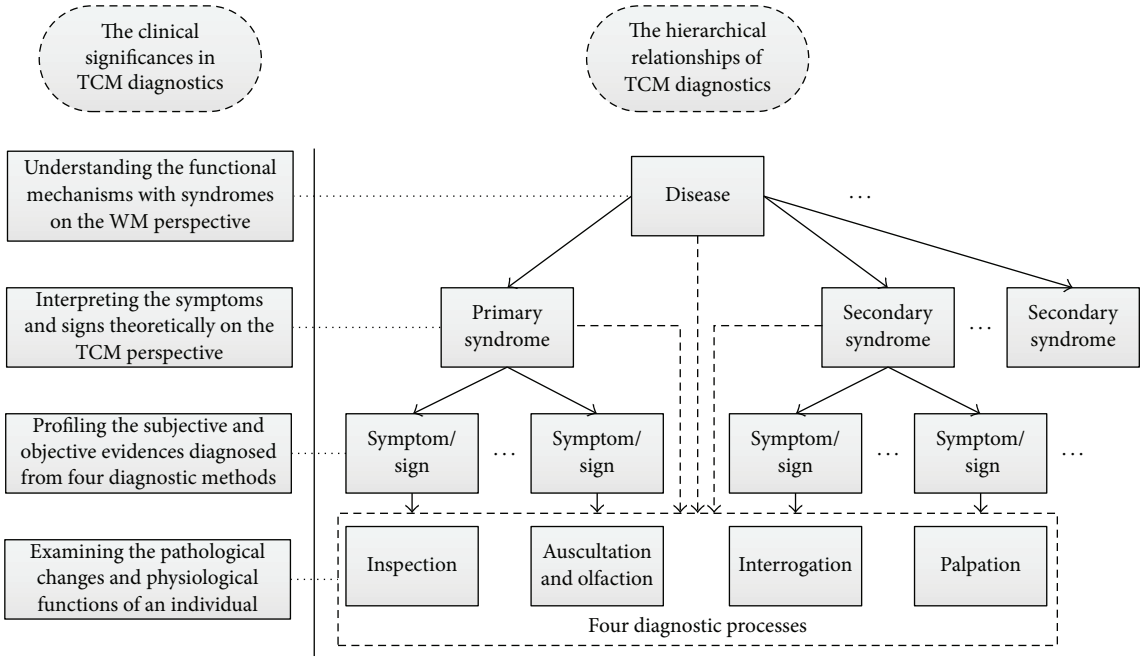

Figure 1: The hierarchical relationships and corresponding clinical significance of TCM diagnostics.

of internal organs by doctors' three fingers touching three special positions of radial artery pulse. All these diagnostic methods require considerable skills which would spend many years for beginners to understand the complicated relationships between symptoms and different diseases, even learnt knowledge from distinguished TCM veteran doctors.

Furthermore, apart from the above four diagnostic methods, TCM diagnostics involves another critical component which is known as the differentiation of syndromes (also known as pattern classification or ZHENG differentiation). This concept is established on the four main diagnostic TCM procedures, which is different from the conventional diagnosis approach as western medicine. Figuratively speaking, it is like a bridge to make a comprehensive analysis from four diagnostic methods and then guide the choice of TCM treatment with acupuncture and herbal formula based on TCM diagnostics and treatment theory. In practice, the mentioned four diagnostic methods would derive two critical cues used for syndrome differentiation, which are called symptoms and signs. A symptom is identified as a subjective experience changes in the physiological and psychological functioning, sensations, and cognition of an individual. Oppositely, a sign is referred to as any abnormality indicative of disease which is examined by TCM practitioners [4].

From the perspective of TCM practitioners, both syndromes and diseases should be diagnosed upon the patients' symptoms and signs. This is due to both syndromes and diseases can providing information for making a prescription on the Chinese medical treatment. In particular, a disease indicates pathological changes of patients' body whereas a syndrome reflects the status of a disease at a certain period. Therefore, in general, the relationships among those diagnostic methods and disease can be delineated by a unified framework as shown in Figure 1.

Seen from the hierarchical diagram, it is easy to know that a patient who suffers from a WM disease is a mixture of one primary syndrome with several secondary syndromes on the TCM perspective. And all syndromes are the theoretical profiles of several symptoms/signs (i.e., manifestations) but not only a simple assemblage of symptoms/signs. Moreover, each symptom is a diagnostic conclusion based on the four main diagnostic methods. In particular, the dotted arrow in this diagram is also outlined due to some patient classification studies which focus on syndrome differentiation or disease classification without using all the diagnostic methods. This is reasonable because some syndromes or diseases of TCM reflect apparent and distinct pathological changes on certain aspects, which makes it possible to classify patient only by one or several diagnostic methods, even regardless of the differentiation process of syndrome. In addition, a patient may suffer from several diseases at the same time and one disease can reflect several syndromes, and, furthermore, one syndrome could be transformed during the TCM treatment of the illness, so the syndrome differentiation is also dynamic simultaneously. So in a more comprehensive view, the relationships between TCM diagnostics with diseases should be multidimensional, which has been exhibited in [5].

As one of the main aspects of complementary and alternative medicine throughout the whole medical field, the practice of TCM has been studied extensively for a long time. However, some serious challenges are still hindering the development of TCM diagnosis and treatment. For example, the basic methodology of TCM diagnostic methods is still mainly based on the observation with practitioners' nude eyes or clinical experience knowledge for thousands of years.

This is likely to get inconsistent diagnostic results due to the large dependence of practitioners' subjective experiences and personal knowledge. What is more, different patients with the same disease may be subjected to different TCM syndromes; conversely, different diseases may contain the same TCM syndrome. This makes TCM diagnostics difficult to be put into practice, even done by distinguished TCM practitioners. Therefore, it is worthwhile for TCM doctors and scholars to develop an objective and reliable computer-assisted system for clinical diagnosis.

In recent decades, computational methods for TCM have been developed to allow experts to identify and diagnose pathological information and also explore these potential relationships which are unknown between current TCM and western medicine. For these methods, the ultimate purpose is to classify patients with different diseases or syndromes and investigate their potential relationships. Then, on the basis of clinical manifestations, effective TCM treatments could be formulated to restore the balance of patients' body. However, in practice, the successful and appropriate treatments would require accurate syndrome differentiation or ZHENG classification based on the diagnostic symptoms and signs. Thus different TCM treatments could be applied to their corresponding patients classes. Generally, patient classification is critical not only for clinical uniformity and efficacy diagnosed by different TCM experts, but also for the development of TCM objectification which could consummate the understanding of the relationships among different syndrome types, symptoms/signs, and diseases.

The remainder of this paper is organized as follows: Section 2 describes the related works on the survey of TCM modern researches. Section 3 briefly introduces some classic and advanced machine learning algorithms for researchers' understandings of the characteristics of those techniques. Extensive works on patient classification issue are presented in Section 4, including four main diagnostic approaches, syndrome differentiation from medical records, and some miscellaneous aspects of TCM. Then, we discuss current status and main problems of patient classification with machine learning techniques in Section 5. Finally, Section 6 draws some conclusions for the whole paper.

2. Related Works

For the related summarization studies in modern researches of traditional Chinese medicine, a large amount of works has been carried out previously in terms of different aspects of TCM (syndrome differentiation, medical records analysis, four diagnostic methods, treatment, and a mixture of them) [1, 3, 5–15]. In view of practice and applications, machine learning can be derived with two aspects: pattern recognition and data mining. The pattern recognition technology is more commonly used for inspection, auscultation and olfaction, and palpation which attempts to recognize the correct pathological information such as facial complexion, pulse condition, acoustic features, and the chemical components of odor of an individual. Data mining technology, mainly used for text mining and knowledge discovery in machine learning field, focuses on finding out various kinds of hidden knowledge relationships such as symptom and symptom, symptom and syndrome, and syndrome and disease.

From machine learning perspective, several works paid more attentions on surveys about using pattern recognition approaches to perform TCM researches. Lukman et al. [1] presented briefly on TCM elements and reviewed various computational approaches on TCM herbs and formulations, TCM diagnosis, and other biomedical mining systems for TCM. Finally, they concluded that the development of standards for evaluating various computational methods for TCM is urgent and significant. Jokiniemi [3] not only surveyed the TCM herbs, formulations, and diagnosis, but also focused on the expert systems, knowledge acquisition, and sharing systems in TCM. In particular, he also presented some famous corporations deploying technology to help hospitals standardize their patient records in China on the health-care issues, such as IBM, Dell, and Microsoft. This showed that TCM has been paid attentions and has spread worldwide. Jiang et al. [5] focused their survey on syndrome differentiation and pharmacological evaluation of TCM herbal formulary for drug discovery. Several general and impressive frameworks have been summarized based on the current modern researches of TCM. Gu and Chen [6] discussed the relationship between modern bioinformatics and TCM and concluded that the major focuses of current TCM researches are to understand the pathological mechanisms of TCM from the systems biology perspective and facilitate novel drug design based on the analysis of TCM herbal medicine. Ferreira [7] introduced the validation methods of computational models for diagnostic assessment and also analyzed some potential reasons of misdiagnosis results. In another work [10], Ferreira and Lopes reviewed pattern classification researches regarding specific disorders such as genitourinary, cardiovascular, neurologic, surgical, and the like. Lu et al. [8] described historical evolution on the syndrome differentiation, the methodology of syndromes differentiation, and the efficacy of TCM practice with syndromes and diseases. Guo et al. [13] illustrated the methods and status of current objective researches of TCM diagnosis according to the modern TCM diagnostic processes, which contains platform of software and hardware construction, data acquisition, feature extraction from sample data, and syndrome classification. Sá Ferreira [14] evaluated the diagnostic accuracy of Pattern Differentiation Algorithms (PDA) with different combinations of four diagnostic methods, and finally he suggested that both explained and available information should be used as objective criteria for PDA evaluation.

On the other hand, some works provided surveys mainly on data mining methods for TCM. Zhang et al. [9] discussed the data mining methods used on real-world clinical diagnosis and treatment. Lan et al. [11] investigated current data mining applied in TCM clinical diagnosis, syndrome standardization and prediction, and investigation of herbs and formulations. Zhou et al. [12] made a comprehensive overview of the basic TCM concept and a series of theories, related information sources (such as bibliographic literature databases and annotated ancient literature databases) and text

mining methods to TCM. They also compared the differences between modern biomedicine and TCM on the viewpoint of methodology. Feng et al. [15] reviewed the knowledge discovery in database for medical formula, herbal medicine, syndrome research, and clinical diagnosis. In addition, they discussed several important issues on where is gold standard, what kind of gold standard is hidden, and how we can mine for the gold standard.

Throughout all the above reviews on the TCM researches, summarizing and inducing the different types of machine learning techniques applied to TCM patient classification on different applications still have not been investigated explicitly. To do this review, valuable information would be beneficial to TCM in several aspects: (1) It could guide TCM practitioner, who expects just to apply machine learning algorithms for specific applications, to choose more general and effective method. (2) TCM researchers could also discover machine learning algorithms which have not yet been studied or used for specific applications. (3) We could understand some domain-related characteristics of TCM clinical data for patient classification problem from a machine learning perspective. In this regard, we aim to review the advanced researches for TCM patient classification according to different machine learning types.

3. Preliminary Knowledge for Machine Learning Algorithms

In this section, in order to do preliminary understanding of machine learning algorithms, we will firstly introduce several approaches frequently used for patient classification in TCM. Nevertheless, it is almost impossible to elaborate all machine learning algorithms in this paper, and also not what we should consider to do. So we only describe briefly several classic algorithms and some advanced approaches raised recently. Moreover, those methods are the foundations of most current machine learning algorithms, which can explain the core idea of the majority of other later proposed methods.

k Nearest Neighbor (k-NN). A type of lazy learning, which is regarded as the simplest machine learning algorithm, is implemented by computing the closet training samples in the test samples. It is modeled without any training phase, just only to store the feature (or attributes/variables) vectors and their corresponding labels. In addition, the commonly used distance metric is Euclidean distance and the only parameter is the k value.

Support Vector Machine (SVM) [15]. A supervised machine learning algorithm constructs a hyperplane or a set of hyperplanes in feature space. It can be often used as classification or regression model. By applying the kernel trick, nonlinear SVM can be derived from the original linear SVM. The effectiveness of SVM depends on the kernel function and several parameters selection like the kernel's parameters and soft margin parameter.

Linear Discriminant Analysis (LDA). It is related to another method called Fisher's linear discriminant which attempts to discover a linear combination of features for classification. It can be used as classification or dimensionality reduction. So it is also similar to principle component analysis (PCA) from the dimensionality reduction perspective.

Naïve Bayes (NB). It is a simplified probabilistic model based on Bayes' theorem but assumes strong independence among all features. The parameter estimation for naive Bayes models always uses maximum likelihood in most cases. Even this algorithm makes a strong independence assumption between the features, it still can achieve excellent classification performance in most practical applications.

Decision Tree. A predictive model maps samples' features to class labels which can be built as classification trees or regression trees. It is called tree because the labels are represented as trees' leaves and the conjunctions of features are represented as trees' branches. The tree can be learnt by repeating on different subsets of original feature sets in a recursive manner. Some notable decision-tree algorithms are ID3 (Iterative Dichotomiser 3), C4.5 (successor of ID3), and CART (Classification And Regression Tree). In addition, based on decision tree, some advanced techniques are derived, which is known as ensemble classifier, such as Random Forest.

Artifical Neural Network (ANN). It is inspired by an animal's central nervous system and referred to computational model in machine learning field. It builds a system with a large number of neurons from input to output. The connections of neurons on neighbor layers are modeled by activated functions. Its learning algorithms are common using backpropagation with gradient descent. Common neural networks are Backpropagation Neural Network (BP-NN) and Radial Basis Function Neural Network (RBF-NN).

Graphical Models. A probabilistic model which uses graph representation to denote the conditional dependence structure among various features. It can be used to discover the features relationships and analyze the complex distribution of features in feature space. Bayesian networks (BNs), conditional random fields (CRFs), and Hidden Markov Model (HMM) are some famous types of graphical models.

Multilabel Learning. It is phrased as a problem of modeling multiple input features mapped into multiple output labels for each sample. So it is opposite to single-label learning and completely different to multiclass learning which outputs different labels for different samples but only one label for each sample. Some famous algorithms are binary relevance (BR), multilabel k-NN (ML-kNN), Rank SVM (Rank-SVM), and so on.

Deep Learning. A recent advanced machine learning technique which contains a set of algorithms, such as Deep Belief Networks (DBNs) and Deep Convolutional Neural Networks (DCNNs). It attempts to build a highly nonlinear transformation to map raw data into high-level abstractions with a large deep network. In particular, it can learn feature

representation automatically based on the given raw data. It has achieved great success in recent years on fields of computer vision, automatic speech recognition, and natural language processing.

Clustering Analysis. An unsupervised machine learning technique aims to aggregate a set of samples into different groups (clusters). In the same group, all samples are similar but distinct with samples in the other groups based on the specified metric: well known algorithms like k-means and fuzzy logic based version known as fuzzy C-means (FCM).

4. Machine Learning Approaches for TCM Patient Classification

This section gives detailed overview of current researches on TCM patient classification. But firstly, it should be noted that large works focus on symptoms/signs diagnosis using machine learning methods and do not directly carry out the syndrome differentiation or patient classification. So in consideration of the significance of those studies, the survey in this paper for patient classification would be more generalized than previous studies which also contains the symptoms/signs classification based on TCM diagnostics and relationships among symptom, syndrome, and disease. Therefore, patient classification problem will be generalized into three aspects with respect to specific TCM diagnostic data: sign classification (SC), syndrome differentiation (SD), and disease classification (DC) issues. In addition, for the medical records data collected from the four diagnostic methods, most works focus on the SD issue with common machine learning algorithms or their proposed methods. But in fact, there are some researches exploring other aspects from the perspective of data mining technique. Those works attempt to discover some relationships of medical records without conducting syndrome differentiation in TCM: symptom and symptom, symptom and syndrome, and syndrome and disease relationships.

4.1. Machine Learning Approaches for Inspection. As mentioned earlier in Section 1, the diagnostic method inspection is to observe some visible signs from patients. Those signs contain various aspects that appeared on the appearance of an individual or excretions from patients. Seen from the current literatures studied on the inspection issue, most works emphasize on the tongue information, lip color, and facial complexion analysis. Classic machine learning algorithms and their modified versions have been proposed to different inspection problems. Table 1 summaries some of recent studies for TCM inspection, where the number in each table cell indicates the corresponding reference.

Table 1: Overview of machine learning algorithms for patient classification using inspection (SC_Inspection: sign classification based on inspection; SD_Inspection: syndrome differentiation based on inspection; DC_Inspection: disease classification based on inspection).

Algorithms	Applications		
	SC_Inspection	SD_Inspection	DC_Inspection
K-nearest neighbor	[16–18, 29, 32, 33, 35, 43]		[19, 21, 34, 38, 138]
Naïve Bayes	[35, 43]	[22]	
Decision tree		[20, 22]	
Support vector machine	[35, 36, 39, 42, 43]	[20, 22]	[21, 37, 38]
Neural network	[23]	[20]	[21]
Graphical models	[26]	[22]	[24, 25]
Miscellaneous	[29–31, 35, 40]	[27]	[28, 41]

Based on this table, it is easy to find that the SVM and k-NN methods are more commonly used in the SC issue based on inspection data. Except these algorithms, some other classic algorithms are also utilized to TCM inspection, such as naïve Bayes, decision tree, and neural networks. In particular, several graphical models have been studied and introduced on different TCM diagnosis, such as Bayesian Networks and Hidden Markov Model.

For the specific application on tongue diagnosis, Huang and Li [16] reported that we could use all pixels in tongue surface to analyze tongue color categories, so they proposed a tongue color analysis scheme based on a reduced k-nearest neighbor algorithm. Chiu [17] employed feature matching based on k-NN metrics to identify the colors of the tongue and the thickness of its coating. Wang et al. [18] showed that regional information is more essential than pixel-wise based tongue color classification. They used Earth Mover's distance algorithm to classify different categories of colors of substances and coatings on tongue. Zhang et al. [19] studied normal health, appendicitis, and pancreatitis diseases classification problem by extracting the chromatic and textural features. Combining feature selection procedure and nearest neighbor classifier, they validate the significant role of tongue inspection for these diseases diagnosis. Kanawong et al. [20] proposed a ZHENG classification system which extracts the coating information as features on modified specular-free tongue images. Different syndrome differentiation issues from gastritis versus healthy volunteers database are built and evaluated upon several classification algorithms including Support Vector Machine, Multilayer Perceptron Networks, and Random Forest. Another similar work [21] compared linear SVM, nonlinear SVM, Radial Basis Functions (RBF) neural network, and k-NN to analyze chronic cholecystitis patients and healthy volunteers classification based on hyperspectral medical tongue images. The experimental results manifested nonlinear SVM is more appropriate to their data. Siu et al. [22] derived 24 tongue classes from syndrome perspective and compared five algorithms supported by Weka software: two decision tree-based, two Bayesian-based, and SVM algorithms. As a result, SVM achieved best performance in terms of accuracy and Receiver Operating Characteristics Curve (AUC) evaluation metrics.

All the above studies mainly considered a simple classifier as k-NN or a more powerful classifier as SVM. There are

also some sparse researches that brought in other machine learning algorithms and models. In the early stages, Jang et al. [23] have introduced neural network to analyze the color of tongue body. Afterwards, neural network has been also employed in [20, 21] as mentioned before. Graphical model, such as Bayesian networks, has been compared to other methods in [22]. Zhang et al. [24] proposed a computer aided tongue diagnosis system (CATDS) which contains acquisition module, image processing module, and diagnosis module. The Bayesian networks classifier is integrated for 9 diseases and healthy subjects diagnosis, similar as [25]. Li et al. [26] focused on the tongue fissure extraction and classification problem, where a Hidden Markov Model is utilized to classify tongue fissures into 12 typical categories. TCM diagnostics is characterized by subjective experience and fuzzy definition in a long period, so fuzzy theory-based algorithms and frameworks may be suitable to explain the potential links of TCM. Hence, the state-of-the-art researches have been studied for TCM in recent decades. Watsuji et al. [27] early built a tongue inspection diagnosis system based on fuzzy rules of TCM items and logic to make different syndromes classification. Pham and Cai [28] introduced some visualization techniques and processes to analyze interactive tongue inspection data. And, also, they discuss how fuzzy set theory can be integrated into visualization techniques to improve perception and understanding of tongue inspection data. More recently, Huang et al. [29] performed tongue shape classification by geometric features. A fuzzy fusion framework was combined with 7 Analytic Hierarchy Process (AHP) modules. This method validated that it can represent the uncertainty and imprecision between quantitative features and tongue shapes. Chiu et al. [30] considered the inspection of the sublingual veins of tongue for blood stasis classification using logistic regression, which is a type of probabilistic statistical classification model. Another tongue color classification model [31] applied spectral angle mapper (SAM) algorithm to discriminate different categories of substances and coatings. This method compares image spectra to known spectra which is applied to hyperspectral tongue images.

Indeed, tongue diagnosis has been studied for a long time. But some recent reports showed that facial diagnosis and lip diagnosis were also considered on the agenda. Preliminary works have been carried out for facial color classification (five morbid color and healthy color) using k-NN classifier [32, 33]. They also designed a device for facial image acquisition which aims to overcome the unstable natural light in an open environment. Liu and Guo [34] built an automatic facial color diagnosis system for hepatitis disease; k-NN with Euclidean distance is employed as their classifier. Liu et al. [35] compared various supervised learning algorithms on five different facial parts, respectively. The color recognition performance demonstrated that SVM with fusion of five facial parts is more superior than k-NN, naïve Bayes, and Adaboost. This conclusion is also similar to another work reported in [36]. The difference is that the facial parts are finer than [35] according to another facial partition TCM theory. Wang et al. [37] investigated normal health and icterohepatitis classification based on facial color by fuzzy clustering and SVM. Zhang et al. [38] not only studied the disease classification based on facial color, but also found that facial gloss information is important to health versus disease classification. They compared SVM with k-NN in their experiment, but results showed that k-NN is performed slightly better than SVM. Furthermore, Zhao et al. [39] proposed a novel chromatic feature for facial color recognition and gloss analysis based on SVM, which can represent the chromaticity and luminance distribution with facial regional prior knowledge. Zhou et al. [40] focused their work on facial gloss recognition and compared various discriminant analysis methods on different color spaces. The linear discriminant analysis was proved to be more superior competing with others. A more recent study on facial diagnosis has been reported in [41]. This research addressed diabetes mellitus via a more advanced approach than previously, namely, Sparse Representation Classifier (SRC). Based on their method, the average accuracy can reach to 97.54% on the diabetes mellitus versus health classification issue with their facial images database. Moreover, the model based on SRC is more powerful than classic approaches like k-NN and SVM. Other than the above researches, Zheng et al. [42] employed SVM to classify different lip color categories with histogram statistical features on various color spaces. Li et al. [43] established an automatic lip color recognition system on a well-designed acquisition device. Different supervised learning algorithms and feature selection algorithms are extensively compared on their database. The conclusion is that SVM with recursive feature elimination for feature selection is the best model for lip color classification.

Throughout all the mentioned works on the inspection issue, we note that a large amount of works focuses on the tongue diagnosis. Meanwhile, the facial diagnosis and lip diagnosis have been reported and studied recently. The popular machine learning algorithms, such as k-NN and SVM, are still the first choice seen from the current literatures. Besides, the nonlinear model may be more appropriate to inspection data in most cases according to the above reviewed literatures, which indicates that the spatial structure of inspection data is nonlinear distribution. Furthermore, more advanced machine learning algorithm is also necessary to be studied for TCM, which may improve the previous system performances as shown in [41].

4.2. Machine Learning Approaches for Auscultation and Olfaction. In this section, we review another important diagnostic method which contains two subjects: auscultation and olfaction. Auscultation is to examine the voice changes through physician's auditory sense, and olfaction is to check the odor changes through physician's smell sense. Their theoretical foundation is that TCM believes the speech sound and body odor produced by patients can reflect the physiological and psychological conditions of Zang Fu organs. So auscultation and olfaction have caused great attention during a long period in TCM field. However, related works on objective auscultation and olfaction are still sparse and rarely studied. This may be due to the complex acoustic characteristics of sound including massive noises and similar acoustical signals in the nature, and diverse chemical compositions of exhaled

Table 2: Overview of machine learning algorithms for patient classification using auscultation or olfaction (SC_Aus-Olf: sign classification based on auscultation or olfaction; SD_Aus-Olf: syndrome differentiation based on auscultation or olfaction; DC_Aus-Olf: disease classification based on auscultation or olfaction).

Algorithms	Applications		
	SC_Aus-Olf	SD_Aus-Olf	DC_Aus-Olf
K-nearest neighbor			[55, 64]
Naïve Bayes			
Decision tree			
Support vector machine		[45–47]	[56–58, 60]
Neural network	[61]		
Graphical models			
Miscellaneous		[48–50]	[54, 59, 62, 63, 65]

breath containing thousands of volatile organic compounds (VOCs). All these factors hinder the development of the research of objective auscultation and olfaction in TCM. To our best endeavors, a minority of preliminary researches have been studied on this issue. Even so, we list related works in Table 2. Besides, detailed descriptions are presented in objective auscultation and olfaction perspective, respectively. In addition, although some works did not even learn a machine learning model for objective auscultation-olfaction diagnosis, we will still review them briefly because their fundamental works would be a valuable reference for further researches in the future.

For the objective auscultation analysis, Wang et al. [44] have reviewed some digital techniques in recent years. But almost all of the related works on auscultation diagnosis are reported before the 21st century, where the researches are preliminary and immature. More recently, some auscultation signals analysis works in TCM have been reported. Yan et al. [45] introduced wavelet packet energy entropy for decomposing auscultation signals to split more elaborate frequency bands. Then SVM is utilized to classify patients into their respective categories: health, Qi-vacuity, and Yin-vacuity. In another work, Yan et al. [46] considered the nonstationarity information of the auscultation signals to automatically recognize healthy individuals from the one with Qi-deficiency or Yin-deficiency. By means of SVM and a feature selection method conditional mutual information maximization criterion, they obtained 80% classification accuracy based on their experimental results. Furthermore, one improved feature extraction work on auscultation signals has been studied in [47]. The combination of wavelet packet transform and two different entropy methods (sample entropy and approximate entropy) was computed to quantize all audio signals. And, likewise, they performed classification with SVM on the same issue. Finally, the recognition accuracy was improved and approaching 90% with approximate entropy scheme, and even higher than 90% with sample entropy compared to the previous works.

Different from the above works, Chiu et al. [48] proposed four novel acoustic parameters to form signal features: two temporal parameters (the average number of zero-crossings, the variations in local peaks and valleys) and two other parameters (the variations in first and second formant frequencies, and the spectral energy ratio). The classification purpose is tha same as the above works, but another machine learning algorithm logistic regression was introduced to build the recognition model. Considering the speech characteristics related to production irregularities, Chiu et al. [49] also utilized the fractal dimension parameter. Experimental results with logistic regression showed the classification rate was better than their previous work. Yan et al. [50] found that most existing approaches were limited to analyze a single vowel, so they introduced multi-instance multilabel learning framework in order to make a comprehensive analysis with five vowels. The experiment results reveal that this method is effective in identifying the health, Qi-deficiency, and Yin-deficiency auscultation data of TCM. The remainder works we retrieved and did not build a diagnosis model for auscultation diagnosis, such that Yan et al. [51] utilized independent component analysis to noise reduction. Yan et al. [52] introduced the delay vector variance method for detecting the nonlinearity of the time series. Two novel parameters, energy ratio and max power ratio, are proposed to study the objective auscultation in [53].

For the objective olfaction analysis, there are almost no recent works with respect to TCM perspective. Most researches for exhaled breath analysis are carried out for disease diagnosis from the western medicine perspective. Based on this situation, we still review several recent works as a reference for TCM olfaction diagnosis. In disease diagnosis, most works focus on the diabetes identification from healthy volunteers. Ping et al. [54] introduced a nonsupervised fuzzy clustering algorithm for diabetes based on electronic nose in early time. Yu et al. [55] developed a portable gas analysis system by using conducting polymer sensor array. The diabetes patients were discriminated from normal persons by the principle component analysis (PCA) with k nearest neighbor classifier. Another breath analysis system [56, 57] was established for two purposes: diabetes diagnosis and blood glucose levels prediction. Their diagnosis models were built by support vector classifier and support vector regression, respectively. Guo et al. [58] applied a novel regression algorithm named support vector ordinal regression to perform classification with four ordinal categories marked with well controlled, somewhat controlled, poorly controlled, and not controlled.

Other researches paid attentions to diverse diseases diagnosis with various machine learning algorithms. Dragonieri et al. [59] used electronic nose to collect exhaled breath for different levels of asthma patients diagnosis and was classified by linear discriminant analysis. An ensembling decision method was established based on soft-margin SVM with Gaussian kernel in [60], and then this model was applied to ten different bacteria cultures captured from electronic nose. Saraoglu et al. [61] used RBF neural network for HbA1c parameter predictions and glucose parameter predictions based on quartz crystal microbalance sensor.

Patients with lung cancer could have accelerated catabolism of volatile organic compounds by the induction of high-risk cytochrome p450 genotypes. Therefore, based on this fact, Phillips et al. [62, 63] constructed a predictive model and a fuzzy logic model, respectively, for lung cancer detection and prediction, both with volatile markers. A breath analysis system [64] was built for diabetes, renal disease, and airway inflammation classification based on a simple classifier, known as k nearest neighbor. Lin et al. [65] concerned the uremia diagnosis by electronic nose. They collected exhaled breath from normal subjects, uremic, renal insufficiency, and chronic renal failure patients. Final signals analysis was carried out by a standard technique referred to as discriminant analysis.

As can be seen from Table 2 and reviewed researches on the objective auscultation and olfaction diagnosis, the works focused on the TCM are not so many and preliminary. On the contrary, quite a few reports have been studied on the olfaction but were carried out from the disease diagnosis of western medicine perspective. Several common machine learning algorithms are also taken into account on the various disease classification issues, such as SVM, k-NN, and ANN. Meanwhile, we find that there are sparse works concerning the issue of sign classification by using auscultation or olfaction data. Although the objective auscultation and olfaction diagnosis from TCM perspective has been seldom put into practice, the above studies could be a knowledge worth learning and exploring.

4.3. Machine Learning Approaches for Palpation. Palpation diagnosis (or called pulse diagnosis), another important diagnostic method in TCM, is also a noninvasive and effective way to examine the location and extent of an individual's health conditions. The traditional examined methods in Chinese medicine are feeling three measurement positions on the radial artery defined in TCM theory, where they are known as Cun, Guan, and Chi in Chinese. Several different palpation data acquisition systems have been developed using various signal sensors [66–70]. According to the retrieved papers, we produce the rectangular reference list for the recent machine learning approaches for palpation, as listed in Table 3.

Seen from the table, it is obvious that the sign classification and disease classification based on palpation are the main focus in TCM. However, to our best knowledge, syndrome differentiation by palpation data using computational methods has not been studied yet. This is not as the inspection data for syndrome differentiation which has been investigated as shown previously. On the other hand, commonly used algorithms like SVM and k-NN are also the first choice to analyze pulse signals as well as the inspection data. It is worth noting that some advanced machine learning algorithms that caused a great attention recently are also employed to solve pulse waveform classification or disease classification. Therefore, we will overview most works in this part from different aspects including the same issue solved by different machine learning algorithms and different issues solved by same machine learning algorithms.

Table 3: Overview of machine learning algorithms for patient classification using palpation (SC_Palpation: sign classification based on palpation; SD_Palpation: syndrome differentiation based on palpation; DC_Palpation: disease Classification based on palpation).

Algorithms	Applications		
	SC_Palpation	SD_Palpation	DC_Palpation
K-nearest neighbor	[71, 76]		[79–83]
Naïve Bayes			
Decision tree	[72, 76]		
Support vector machine	[73, 76]		[83–93]
Neural network	[74, 75, 139]		[84, 140]
Graphical models	[77, 78]		
Miscellaneous	[76, 95]		[79, 83, 94–96]

As for the pulse waveform type classification, Zhang et al. [71] proposed two novel k nearest neighbor-based approaches using edit distance with real penalty. Then, those methods were applied to recognize five pulse patterns, including moderate, smooth, taut, hollow, and unsmooth. Compared with other recent literatures, the proposed methods performed better with the accuracy criterion. A decision tree method is introduced in [72] to pulse strength types classification from four hundred pulse signal samples. Due to the imbalanced classes of this dataset, they undersampled the majority class and built a balanced pulse subset. Experimental results on normal strength pulse (NS-pulse) versus feeble pulse (F-pulse) and overall samples classification were both obtained over 90%. Jia et al. [73] recognize five distinct pulse patterns from 2470 pulse waveforms. They provided a novel elastic metric for SVM to perform pulse waveforms classification. Experiments were carried out on two aspects: metrics comparisons and classifiers comparisons. All results demonstrated the proposed metric is appropriate to represent the pulse waveforms data. Xu et al. [74] and Wang et al. [75] all proposed the combination of fuzzy theory and neural networks to address pulse patterns recognition issue. Compared with back propagation network, the fuzzy logic was proved more useful to pulse analysis in TCM. Ling et al. compared various neural networks with the improved Echo State Network (ESN), which is based on the chaos theory, validated the effectiveness, and superiority of ESN neural network. Ma et al. [76] proposed an improved two-step classification method to classify seven common pulse patterns. They first compared eight discriminant functions including SVM, k-NN, and decision tree. Then a coarse-to-fine hierarchy classification model is built with optimal classifier in corresponding domains. Final results showed that the improved method could obtain good performance on the overall classification accuracy.

Bayesian networks, a probabilistic graphical model, could build the mapping relationships between pulse types and pulse signals. Wang and Zhang [77] presented a model using

Bayesian networks to identify depth, frequency, rhythm, strength, and shape of human pulse signals, respectively. Thus, five graphical structures are established to realize the automatic identification of different parameters of pulse signals. The confusion matrix and accuracy criteria demonstrated the powerful modeling ability of Bayesian networks. Wang and Cheng [78] claimed that the pulse types can be classified into eleven types according to seven factors. They considered that the architecture of the pulse diagnosis system based on BNs should consist of three steps: discovering dependency relationship module, parameter learning, and reasoning module. So modified Greedy Bayesian Pattern Search algorithm (GBPS*) was used for the first two steps; Clique Tree Propagation algorithm (CTP) was implemented for the reasoning module. In addition, they also employed Markov blanket to perform causal inference. All predictive results validated the effectiveness for pulse diagnosis of the proposed system.

For the other purpose of classifying diseases from healthy persons or between the diseases, Yang et al. [79] utilized the independent component analysis to extract pulse feature for cholecystitis and gastritis diagnosis. Modeling with k-NN, the best classification recognition rate is obtained by the proposed feature extraction method competing with linear discriminant analysis and principle component analysis. Liu et al. [80] adopted a recent time series matching method and time warp edit distance, to diagnose four disease patients from healthy person with nearest neighbor classifier. Experimental results manifested that the introduced method is superior to other time series matching approaches. A mobile healthcare system was developed in [81] for cirrhosis diagnosis including signal denoising and baseline wander removal for wrist-pulse preprocessing; the proposed feature extraction algorithm is called binning method and k nearest neighbor classifier. Sun et al. [82] focused on the feature extraction for pulse analysis using kernel PCA and five diseases classification using k-NN.

Apart from k-NN for disease classification, a large amount of works prefers to adopt SVM to model their disease diagnosis system. Jiang et al. [83] investigated six classifiers to distinguish patients with gastritis and cholecystitis from the healthy persons. All classifiers include Fisher Linear Discriminant (FLD), Quadric-Programming Fisher linear Discriminant (FLD-QP), Batch-Mode Perceptron (Perc), Kozinec's perceptron (Kozi), k-NN, and L2-soft SVM. In three classification tasks, the performances of L2-soft SVM were better than others. Wang et al. [84] extracted lots of different features including shape, width, energy, frequency, wavelet coefficient, and PCA. The k-NN and RBF-SVM are employed to separate the health persons from diabetics. Final classification accuracy exhibited the fusion of all the above features and RBF-SVM achieved highest performance on this issue. Similarly, Chen et al. [85] proposed a modified autoregressive model to extract pulse signal feature. By means of SVM, they were able to distinguish healthy persons from acute appendicitis patients with over 82% accuracy and even higher accuracy for the other diseases. Jia et al. [86] fused three types of features on the decision level for disease versus health classification issue, referred to as spatial features, wavelet energy, and similarity features. The Bayes sum rule with SVM achieved best performance compared to other fusing rules in their experiments. Jiang [87] attempted to extract other features called five clinical Doppler parameters (DP), Wavelet Energies (WE), Wavelet Packet Energies (WPE), and Piecewise Axially Integrated Bispectra (PAIB). They input all features into L2-SVM for Doppler blood flow signal analysis. Actually, other works also focus on the feature extraction approaches in order to represent the pulse signals as accurately as possible, such as Hilbert-Huang transform (HHT) [88], Auto Regressive Prediction Error (ARPE) [89], and Wavelet (packet) Transforms (WT) [90] for Doppler ultrasound blood flow signal, multiscale sample entropy [91], and HTT combined with spatial features [92] for wrist pulse blood flow signal. Zhang et al. [93] have designed and implemented a Chinese wrist-pulse retrieval system using pressure sensors, called EasiCPRS. They demonstrated the system architecture and evaluated the pulse diagnosis performance with linear SVM to classify six categories: healthy, subhealthy, hypertension, coronary heart disease, pregnancy, and liver cirrhosis.

In addition, as for the other machine learning algorithms, Chen et al. [94] utilized an unsupervised learning method, fuzzy C-means, to directly aggregate all pulse data into three classes: health, pancreatitis, and duodenal bulb ulcer. By using the modified Gaussian model to feature extraction, their approaches provided a better classification performance than the wavelet transform and the autoregressive methods. Liu et al. [95] introduced Multiple Kernel Learning (MKL) algorithm to combine multiple features to perform pulse symptom classification and disease classification. Through different experimental results, the MKL framework achieved the best overall results competing with SVM and k-NN. More recently, Deep Convolutional Neural Networks (DCNN) were introduced into wrist pulse signals analysis [96], which is a type of representative learning in machine learning field. Based on this method, accuracy could achieve 72.31% on distinguishing health versus subhealth issue, and 96.33% on arteriosclerosis versus nonarteriosclerosis issue.

In summarization, objective palpation diagnosis has been studied extensively on the sign classification and disease classification. However, the research on the syndrome differentiation issue is seldom retrieved according to our current work. Besides, we also found that most works are concerned with the feature representation of pulse signals and rarely emphasized on the learning model construction on the basis of specific characteristics of pulse data.

4.4. Machine Learning Approaches for Interrogation and Medical Records. In this section, we will review the recent advances on interrogation and medical records analysis. Interrogation diagnosis (or called inquiry diagnosis) is to directly ask questions on various physiological and psychological feelings of patients. TCM experts who collect all these information could understand the medical history and present the disease, so as to provide evidences for syndrome differentiation. Medical records rely on the gathering of clinical information through four diagnostic methods.

Table 4: Overview of machine learning algorithms for patient classification using interrogation or medical records (SD_Int-MRs: syndrome differentiation based on interrogation or medical records; AA_Int-MRs: association analysis among symptoms, syndromes, and diseases based on interrogation or medical records).

Algorithms	Applications	
	SD_Int-MRs	AA_Int-MRs
K-nearest neighbor	[98, 99]	
Naïve Bayes	[107, 108, 121]	
Decision tree	[108, 115]	
Support vector machine	[98, 103–108]	[122]
Neural network	[104, 108, 116]	
Graphical models	[108, 112–114]	[123, 124]
Multilabel learning	[100, 101, 109–111]	
Miscellaneous	[102, 104, 108, 117–121]	[98, 125–128]

Both symptoms and signs of a patient would be examined with computational methods and recorded in the clinical database.

Sincerely, interrogation data are always one part of the medical records and known as one of the important diagnostic method in TCM diagnostics. But based on the retrieval of related literatures, we notice that few works are reported and investigated objective interrogation analysis for the issues of syndrome differentiation or disease classification purely. In most cases, the interrogation data are always combined with other diagnostic data to study these issues. Hence, we put interrogation and medical records reviews together. But certainly, a few of researches on the interrogation analysis regardless of other diagnostic data would be separately reviewed in the following.

Besides, we also notice that a majority of medical records data analysis are carried out for syndrome differentiation issue, which is essential purpose studied in objective TCM research. Meanwhile, sparse researches are reported to study some relationships based on medical records without conducting syndrome differentiation in TCM: symptom and symptom, symptom and syndrome, and syndrome and disease relationships. These works are also significant and we will present them separately. In general, we will summarize the retrieved articles to formulate a reference with respect to algorithms and their applications, as shown in Table 4. This table is slightly different from the previous table we made due to the distinct applications of medical records.

For the objective interrogation diagnosis, the data collection is generally carried out by inquiry diagnosis scale or questionnaire designed by TCM experts [97]. Li et al. [98] investigated the symptom-syndrome interactions for inquiry diagnosis of coronary heart disease (CHD). On the one side, they first built a large symptom-symptom interaction (SSI) network which reveals their potential connections. Then, on the other hand, the relationship among syndromes was also calculated by means of relative associated density (RAD). RAD was also utilized to show the connections between syndromes and symptom. Based on the above quantitative analysis, in the final stage, RAD was used for symptom selection and both SVM and k-NN were employed to predict syndrome from symptoms. Liu et al. [99] proposed a novel feature selection approach combined association analysis and information gain (IG) to perform relevant symptom selection for syndrome differentiation of CHD. Based on k-NN classifier, the proposed method achieved the best performance compared to document frequency (DF), IG, and mutual information (MI) feature selection methods.

For CHD syndrome differentiation, considering the multiple syndromes for each patient, Liu et al. [100] introduced multilabel learning algorithms to address this issue. Several multilabel learning algorithms are implemented in CHD dataset including multilabel learning k-Nearest Neighbor (ML-kNN), Support Vector Machine for Ranking (RankSVM), and backpropagation multilabel learning (BPMLL). Experimental results showed that multilabel learning is superior than single-label learning, and ML-kNN achieved better performances than RankSVM and BPMLL. Shao et al. [101] also used multilabel learning algorithms for CHD but focused on the symptom selection algorithms research. They proposed a multilabel feature selection algorithm called hybrid optimization based multilabel feature selection (HOML). A more advanced technique has been introduced for syndrome diagnosis of chronic gastritis [102], which is popular recently in machine learning area. The deep learning model Deep Belief Network (DBN) was combined with binary relevance method, a multilabel learning algorithm, to recognize six common syndromes. Overall performances on various multilabel criteria testified the powerful learning ability of the proposed method for inquiry diagnosis.

As for the medical records data analysis, most works design their systems and approaches to address syndrome differentiation problem. Yang et al. [103] developed the information management system of TCM syndrome which incorporated prior knowledge of TCM syndrome information to SVM and built a P-SVM model to classify TCM literatures as different syndromes. The accuracy rate is 95% on the sample set of 2000 records. Xia et al. [104] compared SVM with stepwise regression and neural network; experimental results indicated RBF kernel function with SVM was the best classifier to identify ten syndromes. Some other works [105, 106] studied the dimensionality reduction algorithms with SVM to improve the syndrome differentiation performance. Wang et al. [107] considered analyzing the raw free-text clinical records, which was very different from lots of well-structured datasets that were manually collected, structured, and normalized by TCM experts. Direct usage of existing diagnostic frameworks was impossible to clinical records. Therefore, they developed a novel automatic diagnosis framework to deal with this unstructured dataset. The architecture of diagnostic system is composed of four components: the TCM symptom names recognition, normalization of symptom names, feature selection, and training/diagnosing modules. First two modules transformed the raw data into well-structured data and latter two were utilized to build an effective syndrome differentiation model. Two classifiers (NB

and SVM) are employed to evaluate the effectiveness and feasibility of the proposed system. Wang et al. [108] compared several classifiers to predict syndrome for liver cirrhosis from three perspectives: TCM, WM, and their combined views. The classifiers are logistic regression (LR), BNs, NB, RBF-NN, C4.5, and SVM. Final classification accuracy indicated that the combined features of TCM and WM can achieve the highest performance.

In recent years, several multilabel learning algorithms are used for syndrome differentiation for medical records analysis. Li et al. [109] realized the multisource data of medical records of TCM including data sources from facial and tongue diagnosis, palpation diagnosis, inquiry diagnosis, and other information. Hence, feature level information fusion scheme was proposed based on multilabel learning algorithms. Experimental results validated that it was critical to process different source data separately for ZHENG classification. The multilabel algorithm relevant feature for each label (REAL) was introduced to study the syndrome classification and identification for cardiovascular disease [110]. Wang et al. [111] used a different multilabel learning algorithm to diagnose chronic fatigue via Conformal Predictor with Random Forest (CP-RF). Extensive experiments validated the CP-RF outperformed ML-kNN and other CP models with NB and k-NN.

Similarly, H. Wang and J. Wang [112] proposed a novel symptom selection algorithm for patients records syndrome differentiation and key element prediction. They utilized GBPS* algorithms to learn BNs and built a key element-blood stasis Markov blanket. The predictive accuracy rate validated the effectiveness of the proposed quantitative method. A self-learning diagnosis system was developed in [113], which was characterized by data-driven nature and learning knowledge. Improved hybrid BNs were proposed and combined with some knowledge discovery methods to identify syndromes of five representative patient cases. Based on the data-driven nature and knowledge discovery property, their system performed well in TCM diagnosis compared with other existing TCM rule-based systems. The BNs was combined with classic feature selection algorithm in [114], which was applied to three syndromes identification on Chronis Hepatitis B in TCM.

Expect for the above machine learning algorithms, Wang et al. [115] introduced decision tree to liver and kidney yin deficiency syndrome, damp heat smoldering syndrome, and stasis and heat smoldering syndrome. Shi and Zhou [116] proposed a modified BP neural network to syndrome differentiation, but only simulation experiment was reported. An attribute hierarchy model was employed to build the hierarchical diagnosis model for posthepatic cirrhosis data with three levels: patient level, symptom level, and diagnosis level [117]. An interval-valued cloud model, considered as an improvement of fuzzy theory, was adopted to diagnose eight subhealth syndromes in [118]. And the experimental results showed that this model achieved higher performances competing with their previous model trained by BP neural network. Wang et al. [119] designed a hierarchical model of syndrome differentiation with hypergraph in cluster and attributes combination in association procedure. Zhang et al. [120] used latent tree model for analysis of kidney deficiency data. Manifold ranking was proposed to explore the syndrome differentiation for viral hepatitis and compared with PCA, NB, association rules, and k-means [121].

Syndrome differentiation may be the core purpose for medical records in TCM. However, some works were also reported without syndrome identification experiment. Their objectives are to mainly explore the relationships between symptoms and symptoms, symptoms and syndromes, or syndrome and disease. Wang et al. [122] built two relationships for coronary heart disease by using SVM: relation between symptoms and syndromes and relation between syndromes and signs from tongue and pulse data. Works in [123, 124] both constructed Bayesian networks to study the associations between symptoms and symptoms, one for kidney disease and another for apoplexy and Chinese medicinal herbs. Cluster analysis was used to study the symptoms related to syndromes for unstable angina [125]. Zhang et al. [126] utilized latent tree models to validate the TCM theory by constructing symptoms and syndromes latent structure. Rough set theory was introduced in [127] to obtain the relationships between syndromes and syndrome elements. Wu et al. [128] used bootstrapping and term cooccurrence to produce the associations between genes and kidney Yang Xu symptom complex.

According to the above reviews and reference listed in Table 4 on interrogation and medical records, it is apparent that syndrome differentiation is what those data usually are used to study. The machine learning techniques have been extensively explored to address this issue in TCM. Even some sophisticated and progressive model learning approaches are investigated for syndrome differentiation, such as multilabel learning and deep learning. Wherein, associations among symptoms, syndromes, and diseases are also analyzed to facilitate the syndrome classification of symptoms and signs collected from different diseases. Furthermore, some TCM experts have proceeded to discover the syndromes which may be related to some genes and proteins in WM perspective.

4.5. Machine Learning Approaches for Miscellaneous Applications. Apart from the four diagnostic data and medical records data used for patient classification, some other works are indirectly related to TCM diagnosis. Some literatures explored the relationships between syndromes and herbs or formulas (prescriptions), others expected to discover useful and latent knowledge from text, clinical data, or TCM experts. Considering the significance of these researches in TCM, we will review several works in this section briefly.

Zhang et al. [129] applied a hierarchical symptom-herb topic (HSHT) model to analyze clinical diabetic data. They constructed a hierarchical symptom-herb topic model to describe the latent structures with both symptoms and their corresponding herbs. As a result, this model could provide a computer-aided patient treatment system by recommending some herbs for TCM practitioners. Liang et al. [130] introduced a decision tree with kernel mapping method to discover the underlying relationship between clinical outcomes and symptom types on acupuncture for neck pain.

Three questionnaires were applied as measured outcomes for evaluating the acupuncture effect, and nondominated sort algorithm is adopted to keep consistent ranking for the effect with these measurements. According to the experimental results for the classification task of therapy records, we found that this model provided an effective way for outcomes of acupuncture prediction. A knowledge discovery system named KISTCM [131] attempted to discover several relationships for TCM treatment. A novel algorithm called Medicine Dependency Relationship Evaluation (MDRE) was proposed to mine the dependency associations among medicines. Meanwhile, another algorithm GEP which combines genetic algorithms (GA) and genetic programming (GP), was introduced to explore formula-syndrome relationships for TCM treatment. Some major experiments have proved that the KISTCM system was useful and promising for the development of TCM knowledge discovery. Zhang et al. [132] proposed a symptom-herb-diagnosis topic (SHDT) model to automatically construct the potential associations among symptoms, herbs, and diagnosis based on a large-scale clinical diabetes data. Wang et al. [133] carried out a preliminary research on symptom name recognition by using conditional random fields. Final experimental recognition F-measure was approaching 63% with recognition rate 93.403%.

Regardless of symptoms and syndromes, some persons focus other aspects for patient treatment research. Fang et al. [134] developed a highly complicated database called TCM-GeneDIT to discover the relationships among medicines, genes, diseases, TCM effects, and TCM ingredients from a large amount of biomedical literatures. A herb-herb network was built in [135] to find the core effective formula by using genetic algorithm from a lung cancer dataset. All the results manifested the proposed network that is effective and agreed with the TCM theory. Besides, Tang et al. [136] expected to mine TCM masters knowledge for understanding the TCM diagnosis and treatment. In order to achieve this purpose, they proposed a preliminary framework of TCM master miner which integrated with correspondence analysis, graph theory, and complex networks analysis. Building a comprehensive TCM expert systems is strongly necessary and has been investigated for a long time, but lots of systems are not overall and intelligent as we expected. Huang and Chen [137] proposed a relatively unifying framework for intelligent disease diagnosis system named CMDS (Chinese Medical Diagnostic System for digestive system). This system has integrated various aspects of TCM such as symptoms, identification, treatments, prevention methods, and prescription. They also tested cases to compare the proposed system with diagnosticians. Experimental results indicated that they obtained almost identical answers from CMDS and the diagnosticians.

5. Discussions

In order to achieve effective TCM treatment for patient, patient classification is critical issue which has been studied for recent decades. Three subissues (sign classification, syndrome differentiation, and disease classification) are extensively researched according to different TCM source data. We consider the four main diagnostic methods and their fusion medical records data. After the survey from a machine learning perspective, we find out several situations and issues of current objective researches on patient classification for TCM, which are summarized as follows:

(1) For the four diagnostic methods, a large amount of works focuses on the inspection and palpation by using various machine learning algorithms. In order to make sign classification, syndromes differentiation based on specific disease and disease classification, inspection concerns the tongue, and face and lip diagnosis, palpation considers using the positions of Cun, Guan, and Chi of radial artery pulse, respectively or entirely. On the contrary, researches on auscultation and olfaction and interrogation are sparse. There are two possible reasons in our perspective. One reason may be the diverse chemical compositions of exhaled breath containing thousands of volatile organic compounds (VOCs) for olfaction, massive noises, or similar acoustical signals for auscultation and the difficulty of standardized inquiry scale for interrogation. Another reason we consider may be the limited disease entities related to auscultation and olfaction. Hence, it may be more apparent and more easier to study objective inspection and palpation in TCM.

(2) For medical records analysis, the application for syndrome differentiation is the main purpose in TCM. Moreover, exploring the associations among symptoms, syndromes, and diseases has been also studied for discovering the potential knowledge of medical records. Meanwhile, some recent works also manifest the genes and proteins in WM perspective that are related to syndromes in TCM. This would help us with deeper understandings of the TCM theory.

(3) For the other applications, their works are not directly related to patient classification problem. But based on the medical records and other clinical data, they always build some association models among syndromes, herbs, formulas, medicines, genes, diseases, TCM effects, TCM ingredients, and the like. All these researches are critical for TCM diagnosis and treatment after patient classification, so we also should refer to these works for facilitating the unifying system development of patient classification and treatment.

(4) From the machine learning perspective, a variety of learning algorithms are introduced to process those TCM data. Some works also proposed appropriate algorithms according to the special characteristics of TCM data. More recently, several advanced machine learning techniques are applied to solve TCM patient classification, such as multilabel learning and deep learning.

(5) According to the reviewed works, most of them do not study the machine learning for model construction. For instance, objective inspection and palpation analysis researches put more emphasis on feature representation. Medical records data analysis cares for how to select the optimal symptom subset for syndrome differentiation. But for the structure and distribution characteristics analysis of TCM data, minor works have engaged in these issues. Whereas the more detailed and deeper the researches on structure learning are, the more prominent the diagnosis system would be developed.

(6) Based on the current researches, there are no published TCM database reported to provide a benchmark for different diagnosis system evaluations. All works are carried out on their own database built by their respective data acquisition system. This is not beneficial to establish patient classification gold standards which is urgent to be studied.

(7) In addition, even a large amount of TCM diagnosis system is developed by computational methods. Meanwhile, most of them claimed that their methods or systems could analyze TCM data from a quantitative perspective. Actually, none of them could quantize their diagnostic data with meaningful implications corresponding to TCM theory, as the clinical indicators from a western medicine perspective. If this situation could not be improved, the establishment of diagnosis standards for TCM may be very difficult. Moreover, it may also hinder the development of objective TCM diagnosis research.

6. Conclusions

In this paper, we survey various works related to patient classification issue in traditional Chinese medicine from a machine learning perspective. We first elaborate the basic diagnosis methods and concepts between traditional Chinese medicine and western medicine. Then we illustrate the hierarchical relationships and corresponding clinical significance of TCM diagnostics for better understandings for TCM diagnosis. Afterwards, several common and advanced machine learning techniques are briefly introduced for understandings of their preliminary knowledge. Then, we discuss that the patient classification issue could be divided into three main aspects: sign classification, syndrome differentiation, and disease classification. According to these subissues, we review related works on five different TCM diagnostic data directly related to patient classification from machine learning perspective: inspection, auscultation and olfaction, palpation, interrogation and medical records, and some miscellaneous applications which are indirectly to patient classification.

Finally, based on the above overviews, some current research highlights and existing issues are discussed for further improvement of TCM diagnosis. Actually, due to a large amount of works on patient classification, the current survey in this paper may been not completed and need to be improved further. Nevertheless, it is enough to reflect the current advances in patient classification for TCM. For the comprehensive analysis of current TCM diagnosis for patient classification, we would complement our reviews and complete the current overview tables in the future work.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Analysis and Recognition of Traditional Chinese Medicine Pulse Based on the Hilbert-Huang Transform and Random Forest in Patients with Coronary Heart Disease

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Objective. This research provides objective and quantitative parameters of the traditional Chinese medicine (TCM) pulse conditions for distinguishing between patients with the coronary heart disease (CHD) and normal people by using the proposed classification approach based on Hilbert-Huang transform (HHT) and random forest. *Methods*. The energy and the sample entropy features were extracted by applying the HHT to TCM pulse by treating these pulse signals as time series. By using the random forest classifier, the extracted two types of features and their combination were, respectively, used as input data to establish classification model. *Results*. Statistical results showed that there were significant differences in the pulse energy and sample entropy between the CHD group and the normal group. Moreover, the energy features, sample entropy features, and their combination were inputted as pulse feature vectors; the corresponding average recognition rates were 84%, 76.35%, and 90.21%, respectively. *Conclusion*. The proposed approach could be appropriately used to analyze pulses of patients with CHD, which can lay a foundation for research on objective and quantitative criteria on disease diagnosis or Zheng differentiation.

1. Introduction

Traditional Chinese medicine (TCM) is an ancient medical practice system which emphasizes regulating the integrity of the human body and its interrelationship with natural environments [1]. Zheng (meaning syndrome or pattern) is a unique TCM concept. It is the overall physiological and/or pathological pattern of the human body in response to a given internal and external condition, which usually is an abstraction of internal disharmony defined by a comprehensive analysis of the clinical symptoms and signs gathered by a practitioner using inspection, auscultation, olfaction, interrogation, and palpation of the pulses [2]. Chinese practitioners diagnose diseases through "Zheng differentiation." The Zheng differentiation of TCM considers the etiology, location, nature, and condition of a disease during a specific stage of the disease process based on clinical symptoms and signs. Pulse taking is one of the key methods to gather the signs and symptoms of patients by a practitioner. During pulse taking, TCM practitioners place their fingers on the radial artery, from which various physiological and pathological conditions can be detected. Traditional pulse taking has important clinical value on the diagnosis and prognosis of the diseases, especially angiocardiopathy. Accurate pulse taking can only be done by TCM practitioners with years of experience. Therefore, objective and quantitative pulse diagnosis is highly desirable, which is of help to establish the objective and quantitative criteria on disease diagnosis or Zheng differentiation.

Coronary heart disease (CHD) is considered a primary cause of death in developed countries and is predicted to be one of the most common causes of death worldwide by 2020 [3]. Early diagnosis and prevention of CHD are essential and have critical public health implications. Identifying, vascular lesions in early stages to reverse and prevent CHD, stroke, sudden death, and other malignant vascular events are crucial [4]. Previous studies have been conducted to clarify and identify subclinical vascular disease. Thus, a noninvasive, convenient, and efficient method should be developed to detect vascular lesions. In TCM, visceral pathological changes and other information can be obtained by detecting pulses. For instance, pathological changes in CHD are clearly reflected in pulse diagnosis information. Therefore, CHD could be considered a breakthrough point for providing a theoretical basis for investigation the TCM pulse.

Modern medical research has shown that the arterial pulse is caused by heart contraction. The left ventricle ejects blood into the aorta through the aortic valve, causing the velocity, pressure, and diameter in the arterial tree to pulsate [5]. The signal acquired from the radial artery is the comprehensive reflection of the wave form (shape), velocity (fast or slow), period (rhythm), and swing (intensity) of pulse waves in the radial artery [6]. Pulse waves contain human physiological and pathological information. Pulse diagnosis is conducted to investigate this information. Thus, pressure pulse charts, which show pulses in TCM, can be used noninvasively and conveniently to provide insight into visceral diseases, particularly cardiovascular diseases such as CHD. Subjective judgments and description of pulse in TCM rely on the experience of doctors. However, clinical application and development of this technique are restricted. Thus, further study should be conducted using various modern information-processing methods, including time domain analysis [7]; frequency domain analysis, such as the Fourier transform [8]; and combined time-frequency analysis, such as wavelet decomposition [9]. Many quantifiable parameters can be obtained; moreover, fuzzy clustering, the Bayes classifier, support vector machine, artificial neural networks, and other methods can be used to classify and recognize pulse [10–13]. For feature extraction of pulse, although the Fourier transform provides the average distribution of signal energy, this technique fails to characterize time-varying information of signal frequency and cannot describe the time domain local features of signals. For characterizing the nonstationary signals of pulse waves, an extra high-frequency harmonic signal is necessary. However, a correct and reasonable interpretation of the signal cannot be provided because the high-frequency harmonic signal is noninherent [14]. Although wavelet transform is essentially a Fourier transform with an adjustable window, the signal in a wavelet window must be stable and cannot eliminate the limitations of Fourier analysis.

Hilbert-Huang transform (HHT) is a new self-adapting time-frequency analytic method. This method can be used to conduct self-adapting time-frequency decomposition according to local time-varying characteristics and can overcome the defects of insignificant harmonic component showing nonstationary and nonlinear signal in traditional methods. Moreover, this method enables obtaining high time-frequency resolution and sufficient time-frequency aggregation; hence, this technique is suitable for nonstationary and nonlinear signal analysis [15]. HHT is composed of empirical mode decomposition (EMD) and the Hilbert transform. The core of this technique is EMD, which is performed on the basis of the time-scale feature of data. Therefore, EMD is more suitable for nonstationary and nonlinear data processing than the Fourier and wavelet methods depending on the transcendental function based on the decomposition method. We used the random forest algorithm as the classifier. The training and prediction speeds of this algorithm are high, and an internal unbiased estimation of a generalization error can be generated. The interaction between features and their degree of importance can be detected, and the over fitting does not occur. For an unbalanced classified data set, this algorithm can balance the error and can be easily parallelized. Therefore, we analyzed and determined the pulse condition of patients with CHD in this study by using EMD time series analysis method and the random forest recognition algorithm.

2. Clinical Material

TCM pulse refers to the pulse sensed by doctors as they palpating the examinee's radial artery with their fingers. Imitating TCM doctors, measurement equipment (cooperatively developed by our research team and Shanghai Asia-Pacific Computer Co. Ltd) was employed to acquire pulse recordings, which provided the basis for objective pulse analysis.

Pulse recordings used in this study were acquired from 342 volunteers for 60 sec with a sampling rate of 720 Hz. Two groups without respiratory system and nervous system disorders were studied. Each subject was instructed to relax for more than 5 min before pulse was recorded.

Group 1 included 225 inpatients with CHD aged 64.8 ± 10.57 years from Longhua Hospital and Shuguang Hospital, which are affiliated to Shanghai University of Traditional Chinese Medicine.

Group 2 included 117 normal subjects, who are selected as control subjects aged 52.17 ± 11.00 years. The subjects were players in the "2010 Zhangjiang ball game competition for the elderly" and staff from Shanghai University of Traditional Chinese Medicine. These subjects have no documented history of cardiovascular disorders.

3. Method

3.1. HHT. Huang et al. proposed the HHT method [16]. The proposed technique is based on the intrinsic mode function (IMF) and EMD. EMD involves decomposing a given signal from a small scale to a large scale to obtain the component signal IMF according to local characteristic time scale. The IMF obtained through decomposition must satisfy two conditions: (1) for the entire signal length, the numbers of extreme points and zero crossing of an IMF component must be equal to or differ by 1 at most.; (2) at any time, the average

value of an upper envelope point defined by the maximum and a lower envelope defined by the minimum is 0.

EMD was performed as follows.

(1) Three sample interpolation fittings were used for obtaining the upper envelope curves and lower envelope curves of the signal to calculate the average value of the upper and lower envelope curves at each point and, thus, obtain the average curve $m_1(t)$.

(2) The average curve minus $m_1(t)$ was subtracted from the original signal $s(t)$. The first component $h_1(t)$ was subsequently obtained.

If $h_1(t)$ satisfied two conditions of the IMF, then $h_1(t)$ was the IMF component in the first order. Otherwise, the difference value between $h_1(t)$ and the other envelope median value was calculated again. The IMF component $c_1(t)$ in the first stage can only be obtained if the difference value sequence satisfies the two conditions of the IMF.

(3) The component $c_1(t)$ was subtracted from the original signal to obtain the residual signal of the original signal $r_1(t)$. The signal $r_1(t)$ was redefined as the original signal. Steps (1) to (3) were repeated and n IMF components were obtained until $r_n(t)$ was converted into monotone function or reached a constant value.

By performing EMD, n IMF components and a residual signal $r_n(t)$ can be obtained. Thus, the original signal can be represented using the following equation:

$$s(t) = \sum_{i=1}^{n} c_i + c_n(t). \tag{1}$$

Each IMF component $c(t)$ and its Hilbert transform were used to construct an analytic signal as shown in the following equation:

$$z_i(t) = c_i(t) + j\widetilde{c_1}(t) = a_i(t)\, e^{j\emptyset_i(t)}, \tag{2}$$

where $a_i(t)$ is the amplitude function, which shows the instantaneous amplitude energy of the signal at each sampling point and $\emptyset_i(t)$ is the phase function, which shows the instantaneous phase of a signal at each sampling point; instantaneous frequency $w(t)$ can be obtained by calculating its derivative. Thus, the amplitude and frequency of the signal are functions of time and are plotted on the time-frequency plane to obtain the Hilbert spectra $H(w,t)$. Hilbert showed the global transformation rule for a signal amplitude with time and frequency conversions; this corresponds to the distribution of signal energy in various characteristic scales (time or frequency) to a certain extent.

3.2. Energy Feature of a Pulse Signal Based on EMD. IMF component was obtained after a signal was decomposed through EMD. The energy of each IMF component was calculated according to the following equation:

$$E_i = \int_{-\infty}^{\infty} \left|c_i(t)\right|^2 dt, \quad i = 1, 2, \ldots, n. \tag{3}$$

For subsequent statistical analysis, normalized energy can be obtained according to the following:

$$E = \sum_{i}^{n} E_i, \qquad E_i' = \frac{E_i}{E}. \tag{4}$$

3.3. Sample Entropy of Pulse Signals Based on EMD. Richman and Moorman [17] developed a new and related complexity measure, sample entropy (SampEn), based on the research of Grassberger, and so forth. The sample entropy calculation of each IMF component is introduced as follows.

(1) For a time series (pulse signal) of N points $u(j)$, $j = 1, \ldots, N$. The time series $u(j)$ forms a set of m-dimensional vectors $Xm(i)$, $i = 1, \ldots, N-m+1$, where $Xm(i) = \{u(i+k) \mid k = 0, \ldots, m-1\}$ is the vector of m data points from $u(i)$ to $u(i+m-1)$.

(2) The distance between two such vectors is defined as the maximum difference in their corresponding scalar components:

$$d\left[Xm(i), Xm(j)\right] = \max\left\{\left|u(i+k) - u(j+k)\right|\right\}, \tag{5}$$

where $k = 0, 1, \ldots, m-1$.

(3) Given r of $Xm(i)$, for every value from 1 to $N-m$, the number of $d[Xm(i), Xm(j) < r]$ is calculated, and $j \neq i$ to exclude self-matches. The ratio of the number to $(N-m-1)$ is defined as follows:

$$B_i^m(r) = \frac{1}{N-m-1}\left\{\mathrm{Num}_{d[X_m(i), X_m(j)]<r}\right\}, \tag{6}$$

where $1 \leq j \leq N-m$. The average value of $B_i^m(r)$ is defined as follows:

$$B^m(r) = \frac{1}{N-m}\sum_{i=1}^{N-m} B_i^m(r). \tag{7}$$

(4) Given r of $X_{m+1}(i)$, set

$$A_i^m(r) = \frac{1}{N-m-1}\left\{\mathrm{Num}_{d[X_{m+1}, X_{m+1}(i)]<r}\right\}, \tag{8}$$

where $1 \leq j \leq N-m$, and $j \neq i$. The average value of $A_i^m(r)$ is then obtained using the following equation:

$$A^m(r) = \frac{1}{N-m}\sum_{i=1}^{N-m} A_i^m(r). \tag{9}$$

(5) $B^m(r)$ is the probability that two sequences match at m points, whereas $A^m(r)$ is the probability that two sequences match for $m+1$ points. The parameter $\mathrm{SampEn}(m,r)$ is defined as follows:

$$\lim_{N\to\infty}\left\{-\ln\left(\frac{A^m(r)}{B^m(r)}\right)\right\}. \tag{10}$$

The sample entropy of pulse signal with finite length N is estimated using the following statistic:

$$\mathrm{SampEn}(m,r,N) = -\ln\left(\frac{A^m(r)}{B^m(r)}\right). \tag{11}$$

The parameters m and r are used to estimate SampEn [18]. Pincus suggested that $m = 2$, $r = 0.1$ to 0.25δ, and δ is the standard deviation of the original signal $u(i)$, $i = 1, \ldots, N$. SampEn$(m = 2, r, N)$ reflects the rate of information production as m increases from 2 to 3. The higher the SampEn value is, the higher the rate of the information production, indicating that the signal is more complex.

3.4. Random Forest Recognition Method. A random forest [19] is composed of numerous decision trees, which are formed using a stochastic method. Thus, it is also called a random decision tree. Trees in a random forest do not correlate. After test data are used as input in a random forest to classify each decision tree, the category with the highest classification results in all decision trees is selected as the final result. Therefore, a random forest is a classifier that contains multiple-decision trees, and its output category relies on the mode of output categories of individual trees.

A random forest resampling technique uses the bootstrap method, which entails repeatedly and randomly selecting k samples from the original training sample set N to generate new training sample sets. Subsequently, K classification trees are generated according to the bootstrap sample set to construct random forests. The classification results of the new data rely on the score formed by the vote of the classification tree. The algorithm is presented as follows.

(1) The original training set is N, and the bootstrap method is used to randomly select K new self-help sample sets and to construct K classification trees. Samples not drawn at each time constitute K data outside the bag.

(2) In total, m_{all} variables are set, and m_{try} variables ($m_{\text{try}} \ll m_{\text{all}}$) are randomly selected at each node of each tree. The variable with the greatest classification ability is selected. The variable classification threshold is determined by examining each classification point.

(3) Each tree grows to the maximum size, with on pruning.

(4) The generated multiple classification trees constitute random forests. New data are obtained and classified according to the random forest classifier. The classification results depend on the number of votes provided by the tree classifiers.

Random forests are an improvement of the decision tree algorithm, in which multiple decision trees are merged. Each tree is established on the basis of an independently extracted sample. All of the trees in the forest are uniformly distributed. Classification error depends on the classification ability of each tree and the correlation among these trees. Feature selection is performed to divide each node by using a stochastic method. The errors generated in various circumstances are then compared. Internal estimation error, or the classification and correlation ability, is detected to determine the number of selected features. The classification capability of a single tree may be low. The most likely classification of a test sample is selected after a high number of decision trees are randomly generated and after statistical analysis is performed according to the classification result of each tree.

The number of decision trees in a random forest in this study was 500, and m_{try} took the mean square root of m_{all}.

4. Results

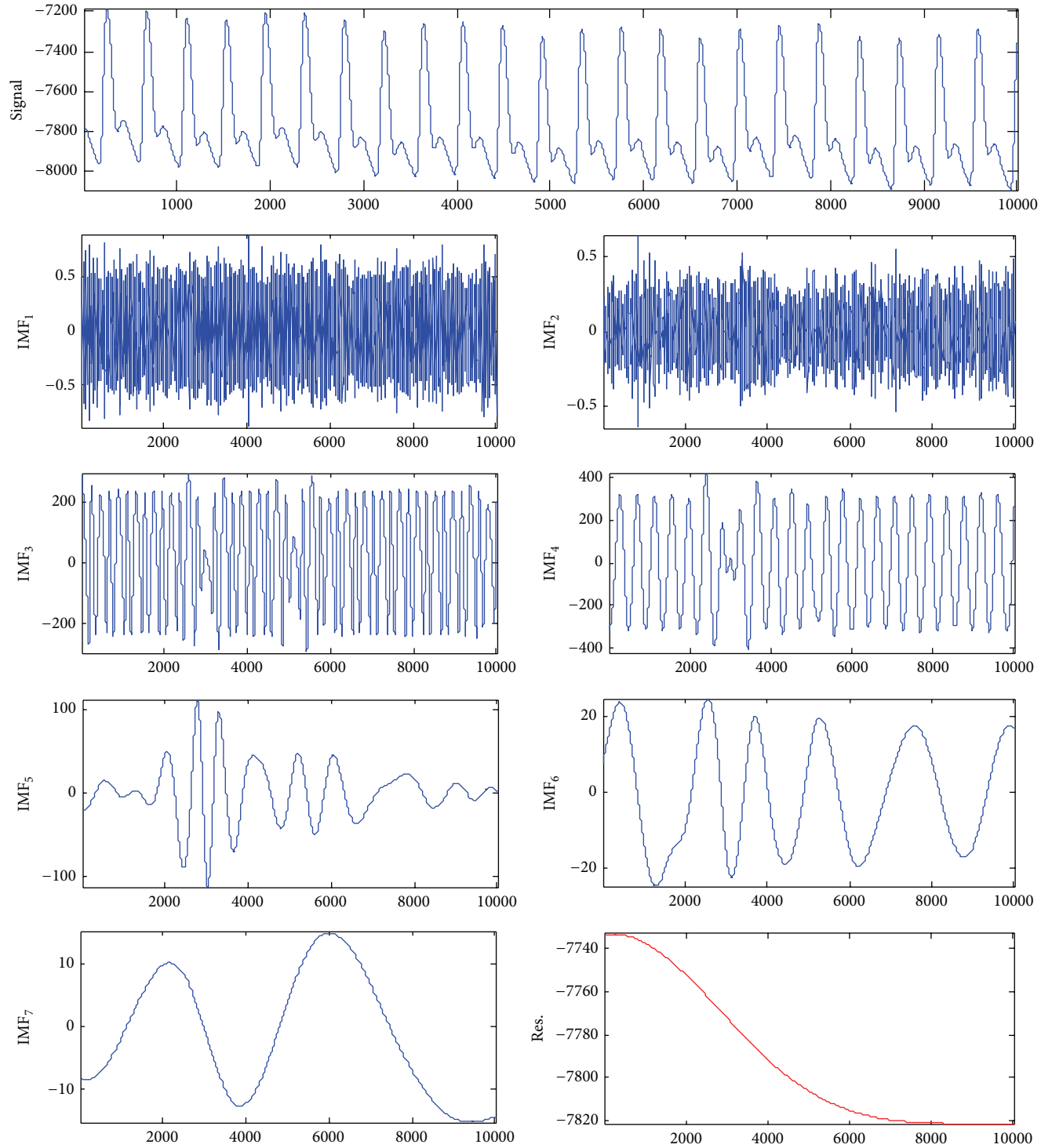
4.1. Statistical Analysis of Energy and Sample Entropy of Pulse Signal Based on EMD. EMD involves adaptively decomposing a signal frequency into a series of IMFs from a high level to a low level. IMF at each level adaptively showed signal characteristics with various resolutions. The amplitude of the IMF at each level at each time differed. The amplitude showed the strength change in the signal at a modal. Most pulse signals can be decomposed to level 7 or higher through EMD (IMF_1–IMF_i, $i \geq 7$), and only two pulse signals of patients with CHD could be decomposed to level 6 ($\text{IMF}_i = 0$, $i \geq 7$). In EMD, the modal energy at high levels was low; their effects on the entire system were weak. Therefore, we analyzed the IMF_1–IMF_7 in front of all modals further. The IMF at each level of a patient with CHD and one normal pulse signal after EMD are shown in Figure 1.

Figure 1 shows that the components, including IMF_1–IMF_7 and the residual parameters res., were obtained after EMD of the pulse signal. The frequencies of IMF_1–IMF_7 decreased successively, and the amplitudes of IMF_1–IMF_7 increased progressively. The differences of IMFs between Figures 1(a) and 1(b) can be observed. For example, Figure 1(b) shows that components of IMF_1–IMF_7 had higher morphological variation than those in Figure 1(a), reflecting the irregularity of a normal pulse signal, and had more high-frequency parts especially in IMF_3–IMF_7 than those in Figure 1(a). In order to quantitatively describe the differences between the CHD patients and the healthy subjects, we extracted the IMF energy and the IMF sample entropy of the pulse signals to make an analysis.

We observed that the variances were nonhomogeneous in the distribution of the IMF energy and the IMF sample entropy of the pulse signals in the CHD and normal groups by using IBM SPSS20.0 statistical software. Thus, we used a nonparametric test for statistical analysis. For the nonparametric test of independent samples of the two groups, we used the rank sum test method to calculate the statistical difference between the two groups. Table 1 shows the statistical difference in the average rank of IMF energy between the two groups. The average rank with IMF normalized energy in the normal group was significantly greater than that in the CHD group. Table 2 shows the statistical difference in the average rank of the IMF sample entropy between the two groups. Owing to the high-frequency modes IMF_1 and IMF_2 were caused by interference, the modes IMF_1 and IMF_2 were discarded without the following analysis. The intermediate-frequency modes, such as IMF_3, IMF_4, IMF_5, and IMF_6 in the CHD group were significantly lower than those in the normal group. No statistically significant difference was observed in IMF_7 between the two groups.

4.2. Pulse Recognition Based on the Random Forest Classifier. We classified and recognized the energy and sample entropy characteristics of the IMFs of the two groups of pulses by using random forest classifier, and the recognition results are shown in Table 3.

Table 3 shows that the average recognition rate was 76.35%, when we used only the sample entropy of IMFs as



(a) Signal with CHD and IMFs

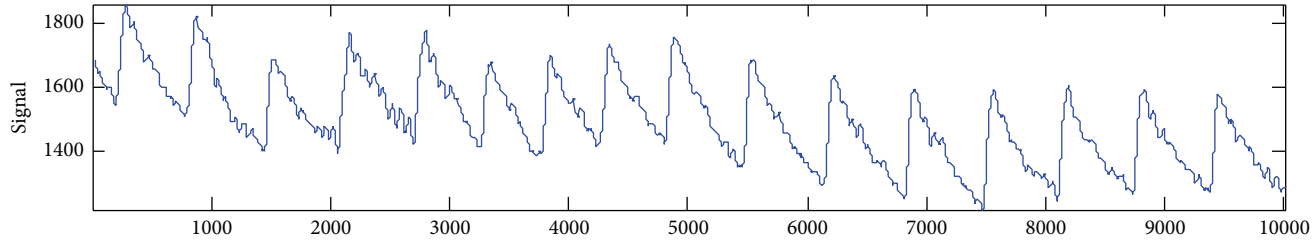
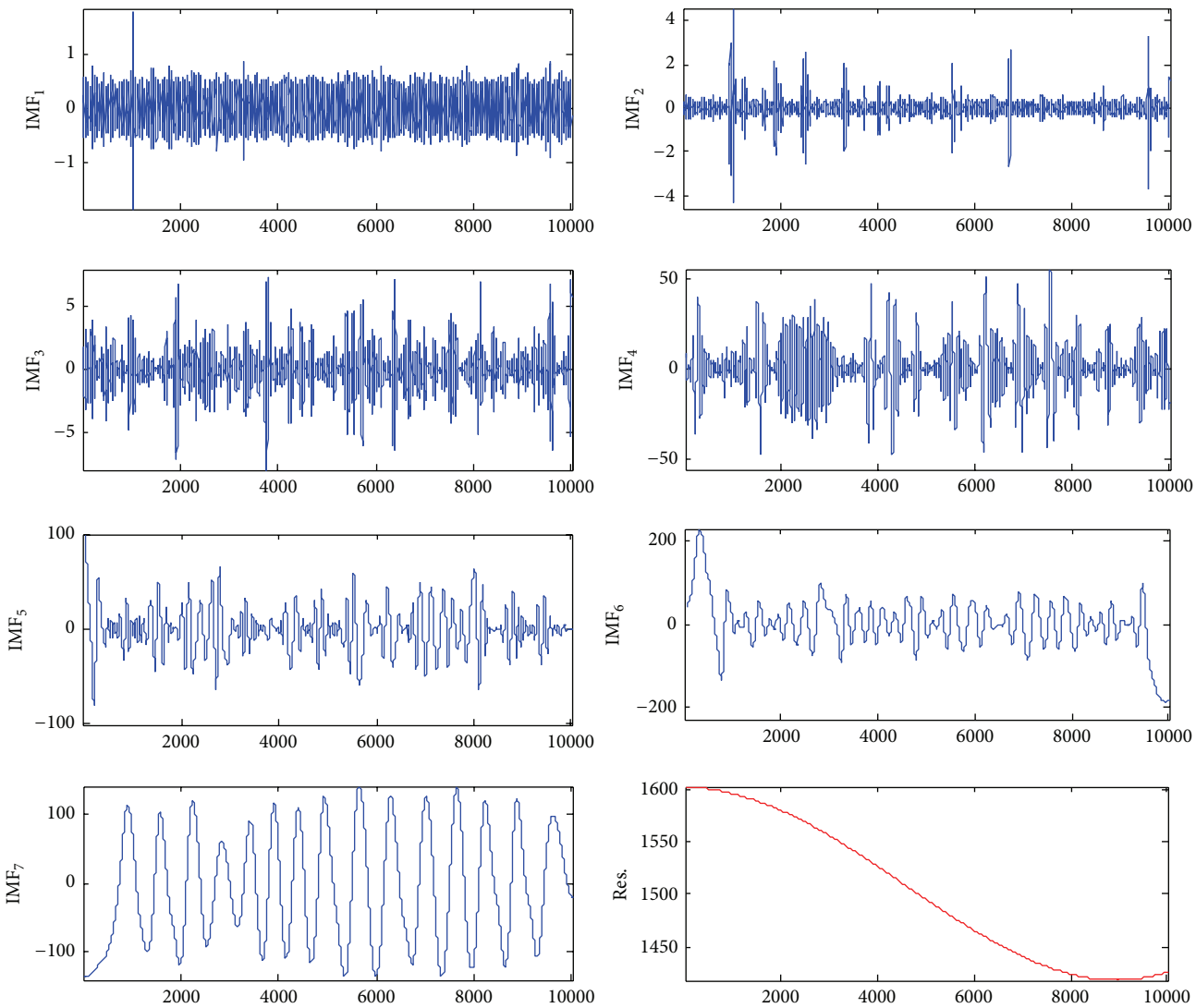


Figure 1: Continued.



(b) Normal signal and IMFs

Figure 1: IMFs of a pulse graph for a normal subject and a patient with CHD after EMD.

Table 1: Rank sum test of IMF energy in two groups.

	(Mean rank)						
Group	IMF_1	IMF_2	IMF_3	IMF_4	IMF_5	IMF_6	IMF_7
The CHD	172.10	132.50	148.68	153.93	152.81	146.98	142.89
The normal subjects	250.65*	240.32*	209.35*	199.29*	201.45*	212.59*	220.43*

* $P < 0.001$, *versus* normal group.

Table 2: Rank sum test of IMF sample entropy in two groups.

	(Mean rank)						
Group	IMF_1	IMF_2	IMF_3	IMF_4	IMF_5	IMF_6	IMF_7
The CHD	180.28	188.17	156.74	143.86	150.93	158.98	164.09
The normal subjects	148.86*	133.77*	193.91*	218.56*	205.04*	189.64*	179.84

* $P < 0.001$, *versus* normal group.

Table 3: Average recognition rate of different pulse characteristics obtained using random forest (%).

Group	Feature		
	IMF sample entropy	IMF entropy	Combination of IMF sample entropy and IMF sample entropy
The CHD group	88.32 ± 3.89	89.20 ± 6.76	95.49 ± 2.78
The normal group	53.48 ± 10.15	73.99 ± 15.47	80.07 ± 9.13
The two groups	76.35 ± 4.77	84.00 ± 5.04	90.21 ± 4.09

the feature vector to recognize pulses in the two groups. Furthermore, the average recognition rate was 84%, when we used only the IMF energy as the feature vector to recognize the pulses in the two groups. If the IMF energy and IMF sample entropy were jointly used as the feature vector to recognize pulses in the two groups, the average recognition rate could reach 90.21%.

5. Discussion

Adaptive HHT exhibits a high time-frequency resolution and local orthogonal self-adaption; moreover, this technique is superior to the wavelet transform and other signal analysis methods. Adaptive HHT can be used to examine instantaneous frequency and energy at multiple scales and is a powerful tool for analyzing biomedical signals [20]. The IMF sequence of pulse signals obtained using EMD is directly separated from the original time series data. The number of decompositions need not be determined in advance without being affected by human factors. Thus, the IMF sequence can effectively reflect the inherent physical characteristics of original data. Its decomposition is objective, inherent, and adaptive. The IMF at each level represents band information with a specific meaning. Table 1 shows that the IMF energy at each level in the CHD group was significantly lower than that in the normal group, which indicates that the energy of the cardiovascular system in patients with CHD was likely lower than that in the normal subjects. Human biological waves such as the pulse wave can directly reflect physical function and health status. Human biological wave energy can be produced through the metabolism of water, air, sunlight, food, and other substances, which are absorbed by molecules and cells of the human body and can be naturally supplied with nutrients and oxygen. High pulse wave energy in the healthy people may result when qi of the viscera and meridians moves harmoniously. As Table 2 shows, the sample entropy of pulse signals in patients with CHD in modes IMF_3–IMF_6, which showed statistically significant differences, was lower than that in the normal subjects. Entropy is the rate at which new information is generated; the entropy value reflects the complexity of a system. A higher entropy value shows that the signal generated by the system is possibly random and irregular and that the system adaptability is stronger. A lower entropy value shows that the signal generated by the system is simpler and regular, and that the system adaptability is lower. The result of Table 2 indicated that the adaptive ability of the cardiovascular system of patients with CHD was likely lower than that of the normal subjects. This finding is consistent with a relatively weaker physiological complexity of the human body in the pathological state and, thus, corresponds to regular pathological states. The energy and sample entropy of IMFs are valuable features for characterizing the pathological state of pulse in patients with CHD. The HHT method can be used to analyze pulse signals of nonstationary dynamic change. This method can sensitively capture the primary features of various pulse signal components with the dynamic changes in time and frequency. The energy and sample entropy of IMF provides a new basis for the feature extraction and pattern recognition of various pulses.

Random forest is a classifier that produces highly accurate with high training and prediction speeds. This classifier can generate an internal unbiased estimation of a generalization error during classification. Furthermore, overfitting never occurs. Random forest can also balance the errors in unbalanced data sets. In this study, we classified and determined the IMF energy and IMF sample entropy of pulse signals by using random forest classifier. The energy of IMFs, sample entropy of IMFs, and their combination were inputted as pulse feature vectors; the corresponding average recognition rates were 84%, 76.35%, and 90.21%, respectively. Compared with the separate use of IMF energy or IMF sample entropy as a feature vector, the combined use of IMF energy and IMF sample entropy as a feature vector improved the classified accuracy for the CHD group and the normal group. Although the sample size in the CHD group was differed from that in the normal group, the unbalanced sample capacity of random forest was superior. Nevertheless, we achieved satisfactory classification results.

6. Conclusion

Pulse diagnosis is a characteristic diagnostic method in TCM. Pulse detection is a noninvasive technique with the simple and easy operation and the stable performance, which does not require expensive equipment. A pressure pulse signal that corresponds to the pulse condition in TCM can be detected noninvasively and conveniently to obtain the pathological and physiological status of the cardiovascular system. We extracted the energy and sample entropy of IMFs of pulse signals as pulse features and used random forests as the classifier of pulse signals. The results illustrate that the proposed methods or pulse-signal processing and classification is effective and efficient. This study offers a new method for developing and promoting a noninvasive pulse diagnostic technique. Furthermore, this research provides

objective and quantitative parameters of TCM pulse and lays a foundation for research on objective and quantitative criteria on disease diagnosis or Zheng differentiation.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

A Novel Classification Method for Syndrome Differentiation of Patients with AIDS

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We consider the analysis of an AIDS dataset where each patient is characterized by a list of symptoms and is labeled with one or more TCM syndromes. The task is to build a classifier that maps symptoms to TCM syndromes. We use the minimum reference set-based multiple instance learning (MRS-MIL) method. The method identifies a list of representative symptoms for each syndrome and builds a Gaussian mixture model based on them. The models for all syndromes are then used for classification via Bayes rule. By relying on a subset of key symptoms for classification, MRS-MIL can produce reliable and high quality classification rules even on datasets with small sample size. On the AIDS dataset, it achieves average precision and recall 0.7736 and 0.7111, respectively. Those are superior to results achieved by alternative methods.

1. Introduction

Acquired immune deficiency syndrome (AIDS) is common and extremely harmful to humans. Recently, more and more patients have died of AIDS. AIDS is classified as a plague in traditional Chinese medicine (TCM). Though AIDS is not mentioned in the ancient literatures [1], TCM has been able to clarify the initial basic pathogenesis and evolution of AIDS over 30 years of research [2]. Significant clinical practice [3–14] proved that TCM is better at improving clinical symptoms and quality of life in patients with human immunodeficiency virus (HIV) infection/AIDS clinical symptoms. Moreover, TCM is better at reducing pain and some adverse antiviral reactions for patients with AIDS [3]. TCM plays an important role in the treatment of AIDS. In TCM, treatment based on syndrome differentiation is the basis of clinical assessment and clinical study. However, since TCM usually describes diseases with qualitative and fuzzy quantitative words, there is no clear functional relationship between the symptoms and syndromes [15]. Particularly for AIDS, there are few systematic studies of quantitative syndrome differentiation because of the disease complexity and novelty [4]. Moreover, TCM syndrome differentiation (i.e., patient classification) is a challenging problem as there are no reliable gold standards in TCM research [15]. Therefore, exploring the objective and inherent relationships between the symptoms and syndromes, followed by constructing classification models of syndromes, is a fast developing field.

Currently, some innovative classification techniques are appealable in quantitative syndrome analysis, for example, naïve Bayes, support vector machine (SVM), k nearest neighbor (kNN), and latent structure models [16–23]. Better results have been obtained for several important diseases, for example, coronary heart disease, viral hepatitis, and diabetes. These methods are divided into discriminative [24–28] and generative models [29–33]. Generative models can be developed from discriminative models and are more suitable for missing data, which is a common problem in clinical

research. As an integrative method of both discriminative and generative models, multiple instance learning (MIL) obtains the feature representations of homogeneous data using the differences of heterogeneous data. Moreover, since MIL treats the instances in bags as the training samples, MIL is able to describe the feature distribution of classes with small positive labeled classes and the big negative labeled classes. MIL is able to resolve the problem of TCM syndrome differentiation because of two main considerations. On the one hand, the standardization and objectification of TCM syndrome differentiation not only need to identify the syndrome classes of patients, but also give the symptoms representation of each syndrome class. On the other hand, since each patient with AIDS is diagnosed with more than one TCM syndrome, the sample of an AIDS syndrome is smaller than that of all other AIDS syndromes. That is, the positive samples are small and the negative samples are big when a patient is taken as a bag and his symptoms are taken as the instances in the bag. Therefore, MIL is suitable to resolve the problem of TCM syndrome differentiation.

MIL was proposed by Dietterich et al. [34, 35] for the prediction of drug molecule activity. MIL has become widely used in many applications [36–42]. One kind of existing MIL methods embeds each bag into an instance space based on a representative instance set selected from the training bags and then to learn a classifier in the instance space. This kind of method mainly uses the representative instances and similar function to map bags into an instance space, which includes multiple instance learning via embedded instance selection (MILES) [36], diverse density based support vector machine (DD-SVM) [37], key instance detection (KID) [38], multiple instance learning with instance selection (MILIS) [39], multiple instance learning via disambiguation (MILD_B) [40], multiple instance learning via dominant sets (MILDS) [41], and multiple instance learning via constructive covering algorithm (MilCa) [42]. However, it is inappropriate to use these novel MIL methods to resolve the problem of AIDS syndrome differentiation. That is, since the patients with AIDS often experience complications, such as dermatosis, hepatitis, TCM symptoms of intraclass syndromes will be relevant to each other. Some similar symptoms overlap for different AIDS syndromes. In fact, the samples of syndrome differentiation need to be larger if the symptoms of patients with AIDS overlap more. Thus, the symptoms overlap causes the small sample problem for AIDS syndrome differentiation. However, these MIL methods with instance selection ignore the problem of small samples. That is, the learning performance is degraded greatly when less labeled training bags are provided for most existing MIL methods with instance selection. To address the problem of small samples, minimum reference set (MRS) is a prospective method applied to many studies [43]. Therefore, inspired by the above analysis, we attempt to touch on the small sample problem and propose a novel AIDS syndrome differentiation method based on MRS-MIL. With only a small set of labeled patients with AIDS for a syndrome class, the motivation of MRS-MIL is to efficiently select a collection of representative instances (i.e., symptoms) embedded in the positive bags (i.e., patients). Then, the selected representative instances are used to build the feature models of AIDS syndromes. Compared to existing syndrome differentiation methods, the performance of syndrome differentiation based on MRS-MIL is significantly improved even with small samples.

2. Materials and Methods

2.1. Dataset of AIDS in TCM. The AIDS data comes from the TCM pilot project for treating AIDS, which began in August 2004 in 17 provinces. The ethics committees of Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, granted exempt status for this study and also waived the need for informed consent. Until May 2013, 12,080 patients participated in the project and were treated with Chinese herbs. The treatment is classified into two groups, that is, Chinese herbs and Chinese herbs integrated with Western medicine. The longest treatment of patients with AIDS was continuous 92 months. From the entire AIDS dataset, we selected 3,500 cases based on the inclusion criteria. Inclusion criteria of the patients were (1) age more than 18; (2) TCM syndrome diagnosis record completed; (3) explicit symptoms; (4) patients presenting with at least two symptoms; (5) patients providing informed consent. Of the 3,500 patients, 2,197 patients are male (62.76% with mean age of 38.79 ± 8.02), and 1,303 patients are female (37.24% and 35.67 ± 6.36). The symptoms collected for the case report form (CRF) included a total of 88 symptoms under nine dimensions: skin, chest and abdomen, head, fever, sweating, appetite, arthritis, tongue, and pulse. According to the AIDS syndrome diagnostic standard [44], there are seven syndromes for these 3,500 patients with AIDS. They are (C1) phlegm-heat obstructing the lung and accumulation of heat toxin syndrome; (C2) deficiency of both qi and yin and deficiency of lung and kidney syndrome; (C3) stasis blood and qi deficiency and toxin stasis syndrome; (C4) hot liver and accumulated dampness toxicity syndrome; (C5) stagnation of qi and phlegm and stasis blood syndrome; (C6) deficiency of spleen and stomach and dampness retention syndrome; and (C7) qi deficiency and kidney yin deficiency syndrome.

2.2. Methods. There are three main aspects in AIDS syndrome differentiation based on MRS-MIL. The framework of the proposed method is shown in Figure 1.

First, the representative instances (i.e., symptoms) are selected from the labeled bags (i.e., patients) by MRS-MIL algorithm. Here, a patient is taken as a bag and symptoms are taken as the instances in the bag. A bag is labeled positive as long as one of its instances is positive and a bag is labeled negative only if its instances are all negative. The purpose of MRS-MIL is to find a point with a high density of positive instances and a low density of negative instances. This is identical to finding some symptoms related to a given AIDS syndrome but unrelated to all other AIDS syndromes. Thus, in the process of MIL, these found symptoms are named as the representative instances of the given AIDS syndrome. During the learning process of MRS-MIL in Figure 1, each current representative instance set is associated with its MRS obtained by the algorithm of generating MRS. The size of MRS is a nice measurement for evaluating the significance

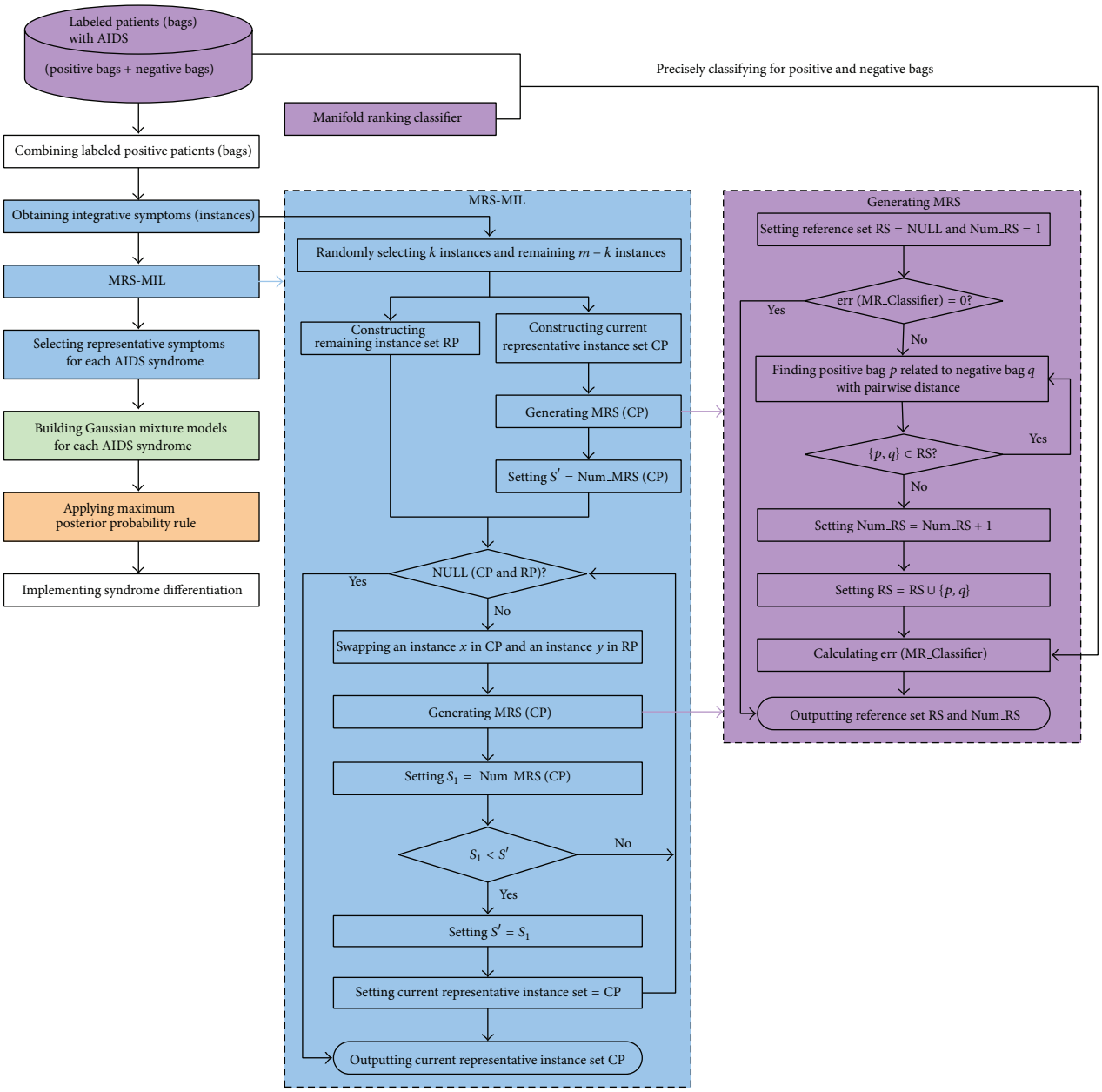

Figure 1: Framework of AIDS syndrome differentiation based on MRS-MIL.

of representative instance set chosen. Smaller MRS size indicates that fewer labeled bags are selected to build the classifier. That is, the fewer selected labeled bags have better generalization ability to classify the other bags. Thus, the representative instance set appears to be an optimal choice if its size of MRS is the smallest. During the process of generating MRS in Figure 1, MRS denotes the smallest subset of labeled bags that can correctly classify all labeled bags. Starting with an empty set, the reference set is updated by adding the closest bags between two classes until all labeled bags are correctly classified by the algorithm of the manifold ranking (MR) classifier. The generalization of reference set is irrelevant to the number of the labeled training bags. Thus, MRS is especially suitable for the situation of limited labeled training bags. The detailed algorithm is referred to Zhao et al. [45].

Second, based on the selected representative instances, Gaussian mixture model (GMM) is used to characterize the features of the given AIDS syndrome. Here, the parameters of GMM are determined by expectation maximization (EM) and minimum description length (MDL) [46].

Third, AIDS syndrome differentiation is implemented by the rule of maximum posterior probability. The top three AIDS syndromes are selected for the test bag.

Table 1: Selected representative symptoms for seven AIDS syndromes.

AIDS syndrome	Selected representative symptoms	Precision
C1	White fur; string-like pulse; fever; rash or herpes; red tongue; dizziness; chest pain; insomnia; cough	0.9026
C2	Loose stool; fatigue; night sweats; pale complexion; red tongue; sticky sputum; low fever; rapid pulse; blood clots; yellow urine; skin ulcer	0.9233
C3	Dry mouth; dyspnea on exertion; stationary pain; local fever of body; loose stool; dark and gloomy complexion; small blister; fever in the afternoon and at night; white fur; alopecia; deep pulse; dark purple tongue	0.8512
C4	Skin ulcer; irritability; herpes; skin itching; red tongue; brief yellow urine; loose stools; asthma; blister searing; slippery pulse	0.8079
C5	Cold sweat; pink tongue; thin fur; depression; string-like pulse; skin itching; lack of appetite; scrofula bump; difficult stool; weight loss	0.8145
C6	Prolapse; loose stools; blister searing; diarrhea; nausea; deep pulse; tired soreness; greasy fur; abdominal pain; slippery pulse; anal burning; diarrhea; pharyngeal	0.8324
C7	Fatigue; diarrhea; dry mouth; fever; chills; grey fur; difficult stool; tired soreness; blister searing; weak pulse	0.8658

3. Results

3.1. Experimental Method and Evaluation Indicators. In the AIDS dataset, 80 percent of the samples are randomized as the training set and the other 20 percent are chosen as the testing set. The performance of syndrome differentiation based on MRS-MIL is calculated after retesting the models 10 times and taking the mean value. The following criteria are used to evaluate the performance of AIDS syndrome differentiation based on MRS-MIL.

Precision evaluates the fraction of syndrome labels ranked above a particular label, which actually is in the label set as Precison $= B/A$. The performance is perfect when it is 1; the larger the average precision value, the better the classifier performance.

Recall evaluates how difficult it is for the labeled syndrome, on average, to review the list of syndrome labels in order to select all the proper labels of the instance as Recall $= B/C$; the performance is perfect when it is 1; the better the recall value, the better the performance.

Here, A is the number of patients automatically differentiated with the given AIDS syndrome in the top three of the returned syndrome list; B is the number of patients correctly differentiated with that AIDS syndrome in the top three returned syndrome list; and C is the number of patients having that syndrome in ground truth syndrome list.

Selected precision evaluates the performance of selected representative instances. Referring to the syndrome diagnosis criteria in [44], the selected precision is evaluated as the percentage of compliance between the representative symptoms and the standard symptoms.

Parameter setting is as follows. In MRS-MIL, the classification error, which is the end condition of the iteration process of generating MRS, is set to be 0 in order to obtain the best classification result by MR classifier. The parameters (i.e., mean, variance, and weight) of GMM are learnt determined by EM algorithm and the parameter k is decided by MDL [46]. The estimation of parameters is an adaptive process.

3.2. Selected Representative Symptoms for Each AIDS Syndrome. Syndrome differentiation based on MRS-MIL selects the representative symptoms to characterize the features of each AIDS syndrome. Table 1 illustrates the selected representative symptoms for seven AIDS syndromes.

3.3. Comparison with Other MIL Methods with Representative Instances. To evaluate the performance of MRS-MIL selecting representative instances, we compare it with other relevant MIL methods with representative instances, that is, MILD_B, MILIS, KID, and MilCa. Table 2 illustrates the compared quality of selected representative instances.

3.4. Comparison with Other Syndrome Differentiation Methods. Currently, the common data mining methods are directly used for TCM syndrome differentiation. This is the main reason for unsatisfied results of syndrome differentiation. In this paper, we propose a novel MRS-MIL classification method to specifically be used for TCM syndrome differentiation of patients with AIDS. To evaluate the performance of syndrome differentiation based on MRS-MIL, we compare it to existing syndrome differentiation methods: k-mean, naïve Bayes, and SVM. Table 3 illustrates the comparative results.

3.5. Sensitivity to the Number of Labeled Patients. To further investigate the advantages of MRS-MIL with smaller labeled bags, we show the precision of seven AIDS syndromes. By gradually increasing the number of labeled patients, Figure 2 illustrates the average precision curve for each AIDS syndrome. As given, there are 100, 200, 400, 600, 800, 1,000, 1,500, and 2,000 labeled patients with AIDS used to calculate the performance of syndrome differentiation based on MRS-MIL. Note that the labeled patients of each AIDS syndrome are randomly selected from the experimental dataset.

3.6. MR versus 1-NN for Generating MRS. According to the selection algorithm in Methods, the representative instances

Table 2: Precision of selected representative instances of various MIL methods.

AIDS syndromes	Precision of selected representative instances				
	MILD_B	MILIS	KID	MilCa	MRS-MIL
C1	0.6713	0.7361	0.7707	0.8541	0.9026
C2	0.7026	0.7699	**0.8216**	**0.8832**	**0.9233**
C3	0.6436	0.67921	0.7931	0.8046	0.8512
C4	0.6513	0.6613	0.7156	0.7681	0.8079
C5	0.5925	0.6984	0.7654	0.7934	0.8145
C6	**0.7135**	0.7518	0.7116	0.7769	0.8324
C7	0.6981	**0.7735**	0.8011	0.8234	0.8658
Avg.	**0.6676**	**0.7243**	**0.7684**	**0.8148**	**0.8568**

Table 3: Comparative results of existing syndrome differentiation methods.

AIDS syndromes	Syndrome differentiation methods							
	k-means		Naïve Bayes		SVM		MRS-MIL	
	Precision	Recall	Precision	Recall	Precision	Recall	Precision	Recall
C1	**0.5133**	0.4435	**0.6236**	**0.5600**	**0.6255**	**0.5529**	0.8327	0.7782
C2	0.5089	0.4512	0.5592	0.5029	0.5913	0.4639	**0.8526**	**0.8098**
C3	0.5001	0.4359	0.5208	0.4756	0.5347	0.4378	0.7771	0.7013
C4	0.4642	0.3815	0.4714	0.4011	0.4923	0.3874	0.6303	0.5620
C5	0.4912	0.4209	0.5108	0.4398	0.5488	0.4711	0.7371	0.6927
C6	0.5024	**0.4711**	0.5988	0.5219	0.5835	0.4826	0.8012	0.7384
C7	0.4920	0.4456	0.5678	0.5333	0.6011	0.4465	0.7843	0.6952
Avg.	**0.4960**	**0.4357**	**0.5503**	**0.4907**	**0.5682**	**0.4632**	**0.7736**	**0.7111**

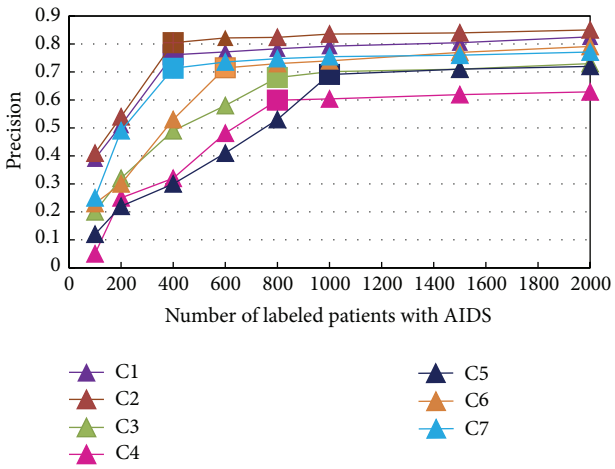

Figure 2: Influence of various numbers of labeled patients with AIDS.

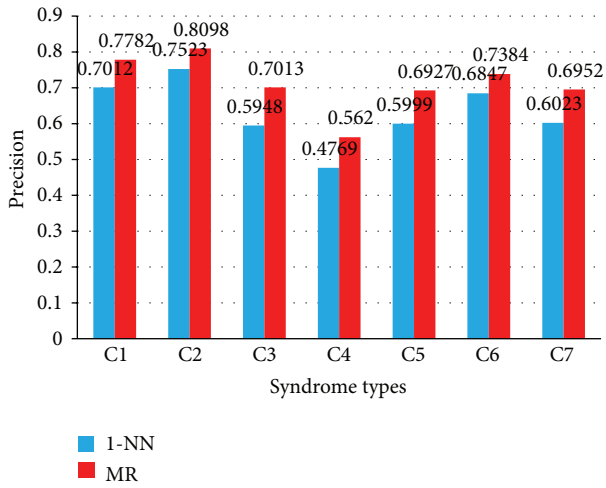

Figure 3: Recall of seven syndromes.

embedded in the positive bags are more precise if the generated MRS is more accurate. Thus, it is significant for generating better MRS. Instead of applying the 1-NN classifier, MRS is generated via the MR classifier in this paper. The MR classifier can benefit from the intrinsic global structure revealed by the labeled and unlabeled bags. That is, the intrinsic global structure is not relevant to the number of labeled training bags. To show the advantages of MRS generated by the MR classifier, Figure 3 demonstrates the recall of seven AIDS syndromes with 3,500 samples.

4. Discussion

4.1. Visual Symptoms Representation of AIDS Syndromes. According to Table 1, MRS-MIL selects the representative symptoms to characterize the feature of each AIDS syndrome well. In detail, the C1 syndrome and C2 syndrome obtain

more than 90% selected precision. In particular, the selected precision of the C2 syndrome is best, reaching 0.9233. Moreover, even for the worst performance (C4 syndrome), the selection precision is achieved at 0.8079. In addition, for the seven AIDS syndromes, the average selected precision of representative symptoms is more than 80% by the AIDS clinical experts' evaluation. The results show the high common viewpoint for the clinical experts. By the selected representative symptoms of each syndrome, patients with AIDS can also be automatically diagnosed and the experience of famous experts can also be subsumed in TCM clinical practice. We can conclude that some representative symptoms characterize the feature of each AIDS syndrome by MRS-MIL well.

4.2. Selected Representative Instances Performance. From the results in Table 2, the average selected precision of MRS-MIL is the best. In detail, the average selected precision of the seven AIDS syndromes is 0.6676, 0.7243, 0.7684, 0.8148, and 0.8568 for MILD_B, MILIS, KID, MilCa, and MRS-MIL, respectively. Compared to the other MIL methods with representative instances, MRS-MIL gains 18.93%, 13.25%, 8.84%, and 4.20% improvement, respectively. The best selected precision of MILD_B and MILIS is achieved for C6 syndrome and C7 syndrome, respectively. The best precision of KID, MilCa, and MRS-MIL is all achieved at C2 syndrome. We can conclude that the performance of MRS-MIL selecting representative instances is better than state-of-the-art MIL with representative instances.

4.3. Syndrome Differentiation Performance. As shown in Table 3, the results of syndrome differentiation based on MRS-MIL obtain better performance than k-means, naïve Bayes, and SVM. The SVM results are better than the Bayesian. The k-means method has the worst performance. In detail, the average precision of syndrome differentiation based on MRS-MIL is 0.7736 and the average recall is 0.7111. Compared to k-means, Bayesian, and SVM, MRS-MIL gains 21.08%, 22.33%, and 27.76% improvement, respectively, for the average precision of seven AIDS syndromes. The best precision of k-means, Bayesian, and SVM is achieved at C1 syndrome. The best precision of MRS-MIL is achieved at C2 syndrome. Similarly, compared to k-means, naïve Bayes, and SVM, MRS-MIL is able to gain 24.79%, 22.04%, and 27.54%, respectively, for the average recall of seven AIDS syndromes. The best recall of k-means is achieved at C6 syndrome. The best recall of Bayesian and SVM is achieved at C1 syndrome. The best recall of MRS-MIL is achieved at C2 syndrome. We conclude that the MRS-MIL performance of syndrome differentiation is better than existing syndrome differentiation methods.

4.4. Influence of Small Samples. From the trend of cures in Figure 2, the precision of syndrome differentiation is insensitive to the small samples of seven AIDS syndromes. The precision of syndrome differentiation based on MRS-MIL maintains a steady status when the samples reach a specific number of samples. Obviously, there is a steady status for all the AIDS syndromes. In Figure 2, the bigger square in each cure denotes the steady point. The final precision of syndrome differentiation is reached at 0.8504, 0.8256, 0.7300, 0.6289, 0.7200, 0.7911, and 0.7712 for the seven AIDS syndromes, respectively. However, the precision of syndrome differentiation improves slightly when the samples of seven AIDS syndromes arrive at 400, 400, 800, 800, 1,000, 600, and 400, respectively. In detail, C1, C2, C3, C4, C5, C6, and C7 syndromes will be steady at (400, 0.8047), (400, 0.7614), (800, 0.6801), (800, 0.5993), (1,000, 0.6911), (600, 0.7147), and (400, 0.7132), respectively. That is, for seven AIDS syndromes, the precision of syndrome differentiation only improves slightly (4.57%, 6.42%, 4.99%, 2.97%, 2.89%, 7.64%, and 5.8%) with a significant increase in number of labeled patients (1,600, 1,600, 1,600, 1,200, 1,200, 1,000, 1,400, 1,400, and 1,600). We conclude that the performance of syndrome differentiation based on MRS-MIL is still good even with small samples.

4.5. MR versus 1-NN for Generating MRS. As shown in Figure 3, it is obvious that MR based performance is better than 1-NN, since the precision is improved from 75.23% to 80.98% for C2 syndrome and the precision is boosted by 5.37% even for C6 syndrome. In particular, the average precision is promoted by 8.08% for total seven AIDS syndromes. In detail, the recall based on MR classifier gains the most improvement (10.65%) against 1-NN classifier for C3 syndrome and the least improvement (5.37%) for C6 syndrome. For C1, C2, C4, C5, and C7 syndromes, the recall based on MR classifier gains 7.70%, 5.75%, 8.51%, 9.28%, and 9.29% improvement, respectively, against the 1-NN classifier. We conclude that the performance based on MR classifier is better than that based on 1-NN classifier.

5. Conclusions

MRS-MIL-based classification methods facilitated the building of syndrome differentiation models for patients with AIDS. Syndrome differentiation based on MRS-MIL can not only select the representative instances for each AIDS syndrome, but also provide a practical solution to the small sample problem. Compared to other classification methods, this method improves the average syndrome differentiation precision of seven AIDS syndromes as well as the average syndrome differentiation recall. MRS-MIL also improves average selected precision of representative instances compared to the state-of-the-art MIL methods with representative instances.

There are three advantages of syndrome differentiation based on MRS-MIL. First, compared to the discriminant syndrome differentiation methods, syndrome differentiation based on MRS-MIL can accurately select the representative symptoms to explicitly characterize the features of AIDS syndromes. This will provide reliable evidence for the standardization and objectification of TCM syndrome differentiation. Moreover, since TCM development is a method of empirical medicine, the method of explicit representative symptoms for TCM syndrome is a feasible way to propagate the experience of famous TCM experts. Second, syndrome differentiation based on MRS-MIL can gain good performance even using

small samples for patients with AIDS. On the one hand, each patient usually has several AIDS syndromes because of disease complexity. There are some similar symptoms for different AIDS syndromes. The samples labeled with a special syndrome will become relatively small. On the other hand, methods based on small samples are frequently met in clinical research since collecting clinical cases is difficult and costly. Therefore, compared to the state-of-the-art MIL methods with representative instances, syndrome differentiation based on MRS-MIL has better performance even with small samples and hence is more suitable for TCM clinical study. Third, the intrinsic global structure of AIDS symptoms can be revealed by the MR classifier well. Hence, the performance of syndrome differentiation based on MRS-MIL is improved as per the experimental results.

The disadvantage of MRS-MIL is that the selected symptoms have the same representative degree for each AIDS syndrome. In the future, MRS-MIL will address the representative degree of selected symptoms to AIDS syndromes.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Cerebral Activity Changes in Different Traditional Chinese Medicine Patterns of Psychogenic Erectile Dysfunction Patients

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Background. Pattern differentiation is the foundation of traditional Chinese medicine (TCM) treatment for erectile dysfunction (ED). This study aims to investigate the differences in cerebral activity in ED patients with different TCM patterns. *Methods.* 27 psychogenic ED patients and 27 healthy subjects (HS) were enrolled in this study. Each participant underwent an fMRI scan in resting state. The fractional amplitude of low-frequency fluctuation (fALFF) was used to detect the brain activity changes in ED patients with different patterns. *Results.* Compared to HS, ED patients showed an increased cerebral activity in bilateral cerebellum, insula, globus pallidus, parahippocampal gyrus, orbitofrontal cortex (OFC), and middle cingulate cortex (MCC). Compared to the patients with liver-qi stagnation and spleen deficiency pattern (LSSDP), the patients with kidney-yang deficiency pattern (KDP) showed an increased activity in bilateral brainstem, cerebellum, hippocampus, and the right insula, thalamus, MCC, and a decreased activity in bilateral putamen, medial frontal gyrus, temporal pole, and the right caudate nucleus, OFC, anterior cingulate cortex, and posterior cingulate cortex ($P < 0.005$). *Conclusions.* The ED patients with different TCM patterns showed different brain activities. The differences in cerebral activity between LSSDP and KDP were mainly in the emotion-related regions, including prefrontal cortex and cingulated cortex.

1. Introduction

Erectile dysfunction (ED), defined as the consistent inability to attain or maintain penile erection sufficient for satisfactory sexual performance [1], has become a global health issue with a high prevalence [2, 3] and considerable impact on the quality of life (QoL) of sufferers and their partners [4, 5]. In addition, ED may share a common pathologic mechanism with cardiovascular diseases [6–8], metabolic syndromes [9], and other endocrine disorders [10, 11]. ED

is generally categorized as organic, psychogenic, or mixed. Psychogenic ED is diagnosed when physical factors are excluded. Patient has risk factors and history for psychogenic ED and has normal androgen status and normal findings on penile duplex Doppler ultrasonography (DUS) [12, 13]. Although organic factors were responsible for the most of the ED cases, psychological factors contribute to and worsen the situation afterwards in almost every organically caused ED case [14].

Despite the advances in clinical and basic researches which have led to several new options, the ideal treatment of ED has not been identified [15]. TCM has been used to treat sexual dysfunction such as ED in China for more than 2000 years. A number of studies showed that TCM treatment could significantly improve the quality of erection and sexual activity of ED patients [16–20] and that correct pattern differentiation ("Bian Zheng") was the prerequisite for achieving the hoped-for efficacy of TCM for treating ED. Pattern differentiation is one of the essential characters of TCM. It means analyzing and judging the data obtained from the four diagnostic methods (inspection, auscultation and olfaction, inquiry, and pulse-taking and palpation) so as to differentiate the nature, location, and cause of disease. So pattern differentiation is the premise and foundation of treatment. However, the pattern differentiation of TCM is mainly based on subjective symptoms and signs, such as tongue condition and pulse condition, and the collection and analysis of those symptoms and signs nearly depend on the clinical experience of doctors. This phenomenon significantly affects the veracity of pattern differentiation and the curative effect of TCM further. So seeking more objective and intelligible evidence for pattern differentiation becomes an urgent task in TCM research and attracts increasing attention.

Normal erectile function is an integrated response under the control of the central nervous system (CNS) and involves the supraspinal centers, the spinal cord, and peripheral nerves. In the last decade, using functional neuroimaging techniques, people found that many brain regions are involved in the supraspinal control of penile erection including the cingulate cortex (CC), insula, orbitofrontal cortex, caudate nucleus, putamen, thalamus, and hypothalamus [21–25]. Furthermore, recent studies [26] indicated that, compared to HS, ED patients showed significant and extended activation in multiple brain regions including the CC, frontal mesial, and frontal basal cortex. Our previous study [27] showed increased fractional anisotropy (FA) values, reduced mean diffusivity (MD) values, and reduced axial diffusivity (AD) values in multiple white matter tracts including the corpus callosum (genu, body, and splenium), corticospinal tract, internal capsule, corona radiata, external capsule, and superior longitudinal fasciculus. Whether there are significant differences in cerebral activities among ED patients with different TCM patterns and whether the brain function changes can be used as potential evidences for pattern differentiation remain uncovered and are worthy of investigation.

By functional magnetic resonance imaging (fMRI), this study aims to (a) investigate the brain activity changes of psychogenic ED patients by comparing with those of HS and (b) explore the differences in cerebral activity between two TCM patterns of psychogenic ED.

2. Materials and Methods

2.1. Participant

2.1.1. Psychogenic ED Patient. ED patients were recruited from the Outpatient Department in The 1st and 2nd Teaching Hospital of Chengdu University of Traditional Chinese Medicine from May 2012 to December 2012. Twenty-seven ED patients were enrolled in this study after undergoing (1) a detailed history taking, including psychosocial history (including the patient's assessment of his own sexual performance and his general attitude and knowledge about sex), medical history, relevant drug history (including alcohol, tobacco, or illicit drug use), and surgical disorder; (2) a careful physical examination, especially the urology and andrology examination; (3) a basic laboratory test which included a penile duplex Doppler ultrasonography (DUS), a nocturnal penile tumescence (NPT) test, as well as routine blood examinations, thyroid-stimulating hormone level, prostate-specific antigen, and the serum sexual hormone status (free/total testosterone, sexual hormone binding globulin, follicle-stimulating hormone, luteinizing hormone, estrogen, and prolactin); and (4) a psychophysical status evaluation by 2 separate psychologists.

Inclusion criteria were (1) 18–45 of age, (2) being right-handed, (3) having been in impotence for more than six months according to National Institutes of Health criteria [1], (4) being diagnosed as psychological ED, and (5) being in a stable heterosexual relationship for at least one year.

Exclusion criteria were (1) being diagnosed as organic ED or (2) having a history of urological surgery or head trauma with loss of consciousness or (3) having been using medication affecting sexual function for over two weeks before enrollment or (4) having suffered from serious psychiatric, neurological, cardiovascular, respiratory, gastrointestinal, or renal illnesses or (5) being drug or alcohol users and smokers.

2.1.2. Healthy Subject. Twenty-seven right-handed and age-matched healthy subjects (HS) without urosexual symptoms or signs, psychiatric or neurologic disorders were enrolled in this study by advertisement. The same examinations including history taking and physical and laboratory tests were performed on all HS by andrology physician and psychologist.

2.2. Ethics Statement. This study was performed according to the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Chengdu University of Traditional Chinese Medicine. Written consent was obtained from all participants.

2.3. Symptom Assessment. The symptom severity was assessed by the International Index of Erectile Function (IIEF-5) [28], Quality of Erection Questionnaire (QEQ) [29, 30], the Erection Hardness Score (EHS) [31], and the self-esteem and

relationship (SEAR) [32, 33]. Also, the Self-Rating Depression Scale (SDS) [34] and the Self-Rating Anxiety Scale (SAS) [35] were used to evaluate the emotional state of the participants.

2.4. TCM Pattern Differentiation. The pattern differentiation of ED patients was employed according to the *Guiding Principle of Clinical Study on New Traditional Chinese Medicine*. Details were in the supplementary material [36].

After careful pattern differentiation, 10 of the 27 ED patients were differentiated from liver-qi stagnation and spleen deficiency pattern (LSSDP) and 10 patients from kidney-yang deficiency pattern (KDP) and 3 patients from dampness-heat accumulation pattern and 2 patients from kidney-yin deficiency pattern and 2 patients from heart-spleen deficiency pattern.

2.5. fMRI Data Acquisition. Resting state fMRI scan was acquired by a 3.0T Siemens scanner (Allegra, Siemens Medical System, Erlangen, Germany) at the Huaxi MR Research Center, West China Hospital of Sichuan University, Chengdu, China. To minimize the head motion to diminish scanner noise, a standard birdcage head coil was used along with a restraining foam pad. The axial three-dimensional T1-weighted image was obtained with a spoiled gradient recall sequence (TR = 1900 ms; TE = 2.26 ms; flip angle: 9°; in-plane matrix resolution: 256 × 256; slices: 176; field of view: 256 mm; voxel size: $1 \times 1 \times 1\,\text{mm}^3$). Functional images were acquired by using a gradient-echo echo planar imaging sequence (TR = 2000 ms; TE = 30 ms; flip angle: 9°; in-plane matrix resolution: 64 × 64; slices: 30; voxel size: $3.75 \times 3.75 \times 5\,\text{mm}^3$). During scanning, they were asked to remain relaxed, to keep their eyes closed, and to remain still.

2.6. fMRI Data Preprocessing. The fMRI images were preprocessed with the SPM8 (http://www.fil.ion.ucl.ac.uk/spm). All of the subject's head movements were less than 1 mm maximum displacement in any direction of x, y, and z and less than 1° in any angular dimension. The preprocessing steps were as follows: to discard the first ten volumes, correct slice timing and head motion, normalize the corrected images to Montreal Neurological Institute space with a resampling resolution of $3 \times 3 \times 3\,\text{mm}^3$, remove linear trend, and smooth with a Gaussian kernel of 6 mm full width at half maximum.

2.7. Data Analysis

2.7.1. Clinical Variables. All the physiologic and psychological measures were analyzed with SPSS 17.0 software (SPSS Inc., Chicago, IL). All data are given as mean ± standard deviation (SD). Independent-samples t-test was used on numerical variables and two-sided test was applied on all available data. P value < 0.05 was considered statistically significant.

2.7.2. Fractional Amplitude of Low-Frequency Fluctuation (fALFF) Analysis. After the above preprocessing, the fractional amplitude of low-frequency fluctuation (fALFF) analysis was carried out using the Analysis of Functional Neuroimaging (AFNI) software [37]. The procedure of the analysis was as follows: (1) transforming the time series for each voxel to a frequency domain without band-pass filtering; (2) calculating the square root at each frequency of the power spectrum; (3) acquiring the sum of amplitude across 0.01–0.08 Hz and dividing the sum by that across 0–0.25 Hz (entire frequency range). The fractional value was taken as fALFF [38]. Therefore, fALFF represents a ratio of the power of each frequency at the low-frequency range (0.01–0.08 Hz) to that of the entire frequency range (0–0.25 Hz).

The individual fALFF map was transformed to Z score by subtracting the global mean value and being divided by the standard deviation. Spatial smoothing was conducted on the Z maps with an isotropic Gaussian kernel (6 mm). The Z maps were transformed into the Talairach and Tournoux coordinates [39]. The further processing of group comparisons was performed on the Z maps to evaluate fALFF differences. The threshold for statistical significance was $P < 0.005$, using threshold-free cluster enhancement (TFCE) method [40, 41].

3. Results

3.1. Differences between Psychogenic ED Patients and HS

3.1.1. Clinical Variables. Compared to HS, the ED patients showed significant decrease in the IIEF-5 score, EHS score, SEAR score, and QEQ score ($P < 0.01$) (Table 1).

3.1.2. Brain Activity. Compared to HS, the ED patients showed an increased cerebral activity in bilateral cerebellum, insula (BA47\48), globus pallidus, parahippocampal gyrus (BA20), OFC (BA11) and middle cingulate cortex (MCC) (BA23), and the right putamen, superior temporal gyrus (BA21), and the left supplementary motor area (BA32, BA6) and rectus gyrus (BA11) and a decreased cerebral activity in bilateral brainstem and precuneus (BA7) and the right MCC (BA23), superior parietal lobule (BA5) and superior temporal gyrus (BA48), and the left precentral gyrus (BA6) ($P < 0.005$, a minimal cluster size of 50 voxels) (Table 2, Figure 1(a)).

3.2. Differences between Psychogenic ED Patients with Different TCM Pattern

3.2.1. Clinical Variables. There were no significant differences in demographics (including age, height, and weight), IIEF-5 score, EHS score, SEAR score, and QEQ score between ED patients with LSSDP and patients with KDP ($P > 0.05$). There were significant differences in SDS score (30.75 ± 1.46 versus 39.99 ± 7.61) and SAS score (30.38 ± 1.77 versus 38.00 ± 6.41) between these two patterns ($P < 0.05$) (Table 3).

3.2.2. Brain Activity. Compared to the patients with LSSDP, ones with KDP showed an increased cerebral activity in bilateral brainstem, cerebellum, hippocampus (left BA37, right BA27), and the right insula (BA48), thalamus, paracentral lobule (BA4), MCC (BA23), superior temporal gyrus (BA22), inferior temporal gyrus (BA20), and the left middle temporal gyrus (BA39) and a decreased cerebral activity in bilateral putamen, medial frontal gyrus (left BA10 and BA8, right

Table 1: Comparison between psychogenic ED patients and healthy subjects: clinical variables.

Characteristic	ED patients $N = 27$	Healthy subjects $N = 27$	P value
Age (y), mean ± SD	33.22 ± 5.92	31.41 ± 5.82	0.261
Weight (Kg), mean ± SD	65.11 ± 6.66	66.52 ± 9.47	0.530
Height (cm), mean ± SD	171.67 ± 3.98	171.41 ± 4.37	0.821
IIEF-5 (0–25), mean ± SD	13.56 ± 3.61	22.26 ± 0.95	0.000
EHS (1–4), mean ± SD	2.70 ± 0.54	3.93 ± 0.27	0.000
SEAR (0–80), mean ± SD	32.38 ± 11.14	68.36 ± 4.96	0.000
QEQ (0–100), mean ± SD	33.63 ± 15.44	80.04 ± 7.20	0.000

Table 2: Comparison between psychogenic ED patients and healthy subjects: resting brain activity.

Regions	Sign	Side	Talairach			t value	BA
			X	Y	Z		
Cerebellum	↑	R	11	−64	−50	3.40	—
	↑	L	−26	−37	−35	3.13	—
Insula	↑	R	32	23	−2	3.48	BA47
	↑	L	−32	22	−3	4.06	BA48
Globus pallidus	↑	R	20	2	8	2.66	—
	↑	L	−10	1	−1	2.75	—
Parahippocampal gyrus	↑	R	33	−25	−17	3.29	BA20
	↑	L	−25	−24	−16	3.03	BA20
OFC	↑	R	8	30	−13	3.13	BA11
	↑	L	−7	29	−12	2.68	BA11
MCC	↑	R	11	23	38	2.79	BA32
	↑	L	−7	20	36	2.81	BA32
Putamen	↑	R	23	0	8	2.56	—
Superior temporal gyrus	↑	R	44	−42	7	4.01	BA21
Rectus gyrus	↑	L	−7	30	−17	2.99	BA11
Supplementary motor area	↑	L	−10	0	67	2.72	BA6
	↑	L	−8	16	48	3.98	BA32
Brainstem	↓	R	3	−35	−30	−3.13	—
	↓	L	−1	−34	−29	−2.88	—
Precentral gyrus	↓	L	−44	2	42	−3.23	BA6
MCC	↓	R	2	−28	34	−3.40	BA23
Superior parietal lobule	↓	R	16	−44	66	−2.83	BA5
Superiortemporalgyrus	↓	R	60	−10	11	−4	BA48
Precuneus	↓	R	10	−65	37	−2.80	BA7
	↓	L	−10	−65	35	−3.05	BA7

"Sign" indicates whether the structure showed a signal increase or decrease. "↑/↓": increase/decrease. R: right; L: left; BA: Brodmann area; OFC: orbitofrontal cortex; MCC: middle cingulate cortex; $P < 0.005$, a minimal cluster size of 50 voxels.

BA32) and precuneus (BA7), and the right OFC (BA47), anterior cingulate cortex (ACC) (BA23), posterior cingulate cortex (PCC) (BA30), middle temporal gyrus (BA21), and the left middle frontal gyrus (BA10) and supplementary motor area (BA32) ($P < 0.005$, a minimal cluster size of 50 voxels) (Table 4, Figure 1(b)).

4. Discussion

This was the first neuroimaging study that focused on the differences in cerebral activity of psychogenic ED patient with different TCM patterns. The results confirmed the brain dysfunction of psychogenic ED patient compared with that of HS and preliminarily indicated that patients with different TCM patterns had relatively different cerebral activity changes.

4.1. Differences in Resting Brain Activity between Psychogenic ED Patients and HS. In present study, psychogenic ED patients showed abnormal cerebral activity in brainstem, cerebellum, basal ganglia, multiple limbic regions including insula, MCC, prefrontal cortex (PFC), parahippocampal gyrus, and parietal, temporal lobes ($P < 0.005$, Figure 1(a)).

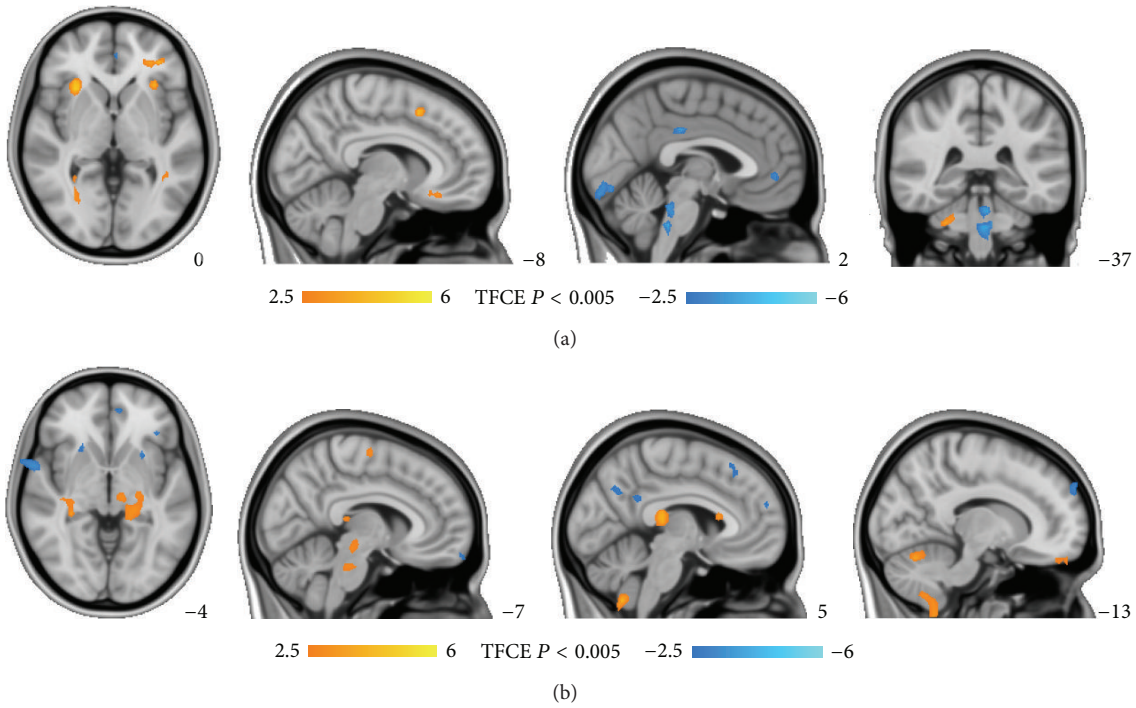

Figure 1: The differences in cerebral activities between psychogenic ED patients with different TCM patterns. (a) The differences in cerebral activities between psychogenic ED patients and HS. Compared to HS, psychogenic ED patients showed abnormal cerebral activity in brainstem, cerebellum, basal ganglia, and multiple limbic regions including insula, MCC, PFC, parahippocampal gyrus, and parietal, temporal lobes. ($P < 0.005$, a minimal cluster size of 50 voxels). (b) The differences in cerebral activities between ED patients with different TCM patterns. The brain regions associated with emotion modulation such as cerebellum, OFC, ACC, and MCC are the main different brain areas between psychogenic ED patients with kidney-yang deficiency pattern and liver-qi stagnation and spleen deficiency pattern ($P < 0.005$, a minimal cluster size of 50 voxels).

Table 3: Comparison between psychogenic ED patients with liver-qi stagnation and spleen deficiency pattern and kidney-yang deficiency pattern: clinical variables.

	Kidney-yang deficiency pattern $N = 10$	Liver-qi stagnation and spleen deficiency pattern $N = 10$	P value
Age (y), mean ± SD	32.90 ± 5.89	32.10 ± 3.17	0.71
Weight (Kg), mean ± SD	65.30 ± 11.10	66.90 ± 6.36	0.70
Height (cm), mean ± SD	172.00 ± 5.14	173.60 ± 4.09	0.45
IIEF-5 (0–25), mean ± SD	14.20 ± 3.85	15.00 ± 2.16	0.58
EHS (1–4), mean ± SD	2.90 ± 0.32	2.90 ± 0.32	1.00
SEAR (0–80), mean ± SD	31.41 ± 10.14	33.14 ± 7.32	0.67
QEQ (0–100), mean ± SD	33.36 ± 16.79	31.28 ± 5.29	0.71
SDS (0–100), mean ± SD	30.75 ± 1.46	39.99 ± 7.61	0.003
SAS (0–100), mean ± SD	30.38 ± 1.77	38.00 ± 6.41	0.002

The results were similar to the findings in other studies on sexual dysfunction [42–45].

The limbic system is involved in emotion, reward, cognition, and human sexual activity. A number of experimental studies suggested that the limbic system play an important role in the regulation of penile erection [46, 47] and some limbic regions which expressed plentiful sex hormone receptors were essential in arousing and regulation of sex behavior [47–49]. Moreover, neuroimaging studies on human being also demonstrated the limbic regions such as amygdala, hypothalamus, and insula involved in sexual arousal [21, 38, 50, 51]. In fact, the unusual activation in PFC, CC, insula, and hippocampus can be found in nearly all reported functional brain imaging studies related to sexual psychology and sexual activity, regardless of study paradigm and analysis method [42].

In this study, we found that multiple limbic regions, including insula, MCC, PFC, and parahippocampal gyrus in psychogenic ED patients, showed significant cerebral functional changes in resting state. Other neuroimaging studies

Table 4: Comparison between psychogenic ED patients with liver-qi stagnation and spleen deficiency pattern and kidney-yang deficiency pattern: resting brain activity.

Regions	Sign	Side	Talairach			t value	BA
			X	Y	Z		
Brainstem	↑	R	8	−19	7	3.21	—
	↑	L	−7	−23	−10	3.13	—
Cerebellum	↑	R	14	−51	−31	3.54	—
	↑	L	−14	−66	−22	4.82	—
Hippocampus	↑	R	22	−30	−4	3.48	BA27
	↑	L	−31	−35	4	3.59	BA37
Insula	↑	R	39	−7	17	3.16	BA48
Thalamus	↑	R	10	−21	1	3.07	—
Paracentral lobule	↑	R	8	−33	53	3.13	BA4
MCC	↑	R	2	−15	48	2.88	BA23
Superior temporal gyrus	↑	R	57	−33	11	3.16	BA22
Inferior temporal gyrus	↑	R	59	−42	−15	4	BA20
Middle temporal gyrus	↑	L	−43	−50	20	3.4	BA39
Putamen	↓	R	24	13	−2	−2.94	—
	↓	L	−22	18	3	−3.61	—
Medial frontal gyrus	↓	R	13	57	25	−2.58	BA10
	↓	R	8	29	54	−3.48	BA8
	↓	L	−1	41	30	−2.64	BA32
Middle frontal gyrus	↓	L	−35	49	11	−4.47	BA10
Supplementary motor area	↓	L	−4	17	46	−3.59	BA6
OFC	↓	R	8	51	−4	−3.02	BA10
ACC	↓	R	11	24	29	−2.59	BA23
PCC	↓	R	4	−49	26	−2.72	BA30
Middle temporal gyrus	↓	R	51	−39	2	−3.46	BA21
Precuneus	↓	R	8	−64	33	−3.95	—
	↓	L	−3	−68	37	−2.99	BA7

"Sign" indicates whether the structure showed a signal increase or decrease. "↑/↓": increase/decrease. R: right; L: left; BA: Brodmann area; OFC: orbitofrontal cortex; ACC: anterior cingulate cortex; MCC: middle cingulate cortex; PCC: posterior cingulate cortex.
$P < 0.005$, a minimal cluster size of 50 voxels.

[43–45] also proved the dysfunction of limbic system in ED patients. For example, Hagemann and his coinvestigators [43] found the abnormal cerebral activities in ACC and PFC in ED patients in visual sexual stimuli task state. Cera et al. [45] found that ED patients showed decreased connectivity values in the inferior parietal lobes, medial PFC, and the right insula and increased connectivity values in the ACC. Furthermore, our previous diffusion tensor imaging (DTI) study [27] demonstrated that multiple white matter regions which associated with limbic system such as corpus callosum (genu, body, and splenium), internal capsule (anterior limb and posterior limb), and corona radiata had significantly microstructural alternations. All these studies proved that functional and structural abnormalities in limbic system might be an important character of the central pathogenesis of ED.

In this study, decreased activities in brainstem were observed in psychogenic ED patients compared with HS. Some researchers found that transition zones between the midbrain and pons, dorsal pons, and cerebral peduncles were strongly activated during sexual arousal with visual sexual stimulation, and the regional cerebral blood flow (rCBF) of midbrain was significantly increased [52]. These findings consistently suggested brainstem involved in the regulation of sex activity. Meanwhile, we found that activities in the bilateral cerebellum significantly decreased in the psychogenic ED patients compared to HS. Redouté et al. reported the positive correlation between markers of sexual arousal (perceived sexual arousal, penile tumescence) and rCBF in the vermis and the left part of the cerebellum, respectively [51]. Similarly, a cerebellar activation was found in response to excerpts of erotic films [53, 54]. In addition, meta-analysis indicated cerebellum activation consistently reported across functional imaging studies of sexual arousal [42]. Along with the previous studies, our results also suggested that cerebellum is involved in human sexual arousal and that cerebellum function abnormality is a potential central pathological character in psychogenic ED patient.

4.2. Differences in Resting Brain Activity between Different Patterns of Psychogenic ED Patient. In current study, our findings indicated that the cerebral activity differences between

patients with KDP and LSSDP mainly are in brainstem, cerebellum, insula, CC (including ACC, MCC, and PCC), and OFC. These regions not only are involved in the central regulation of human sexual behavior, but also play important role in cognition as well as emotion modulation.

Among these regions, the brainstem, the important pathways for cerebrum, cerebellum, and spinal cord interconnection, contains the vital centers controlling the basic life activities. The cerebellum provides a significant role in both human sexual arousal [55] and emotion regulation [56, 57]. For example, Siuda et al. [58] reported that cerebellum participated in detection, integration, and filtration of emotional information and in regulation of autonomic responses. The insula, an important part of limbic system, serves as a primary "interoceptive cortex" for the integration of viscera and emotion. Several studies indicated that insula activation was specifically correlated with penile erection [24, 59] and that insula processing of feeling showed cultural effects [60]. CC, an important part of limbic system, is involved in emotion, learning, and memory. In CC, ACC and MCC are considered closely related to sexual psychology and sexual activity and have important interconnection with insula, PFC, and other subcortical structures. The OFC is seen as a central node in the emotional circuits of the brain. Profoundly altered emotion regulation is a hallmark of damage or dysfunction within OFC [61, 62]. So the current results indicated that the brain regions associated with emotion modulation were the main different brain areas between the psychogenic ED patients with KDP and the psychogenic ED patients with LSSDP.

Furthermore, this study found that the SAS score and the SDS score of the patients with LSSDP were significantly higher than those of patients with KDP. This result indicated the emotional symptoms were the main difference between LSSDP patients and KDP patients. The theory of TCM holds that the emotional disorders such as anxiety and depression are the main characteristics of liver-qi stagnation pattern [63]. Although the sample size of each pattern was relatively smaller, the results were also consisted with the theory of TCM.

So, in this study, the scores of SAS and SDS were the main different clinical variables between the psychogenic ED patients with LSSDP and the patients with KDP, and the brain regions involved in affect regulation were the main different brain areas between the two patterns. This neuroimaging result might be an objective reference for distinguishing LSSDP from KDP in pattern differentiation of TCM.

5. Conclusion

This study investigated the cerebral activity changes in psychogenic ED patient and explored the differences in brain function between ED patients with different patterns. The results confirmed that psychogenic ED patient had cerebral dysfunction in resting state and firstly demonstrated that the brain activity of ED patients with KDP differed from those with LSSDP.

In clinic practice, the scales for pattern differentiation are faster and more convenient than neuroimaging scan, but the results of questionnaires are subjective and are easily affected by experience of doctors. So although the sample size in our study was relatively smaller and the P value of clinical variables was not corrected for multiple comparisons, this study provided potentially objective evidence for pattern differentiation of ED and a new approach to further study the mechanism of TCM pattern.

Conflict of Interests

The authors declared that no conflict of interests exists.

Authors' Contribution

(i) Study protocol and design are done by Degui Chang, Peihai Zhang, Qi Liu, J. Junjie Pan, Zhengjie Li, Jixin Liu, Guangsen Li, Wei Qin, Yaodong You, Xujun Yu, Jinbo Sun, Minghao Dong, Qiyong Gong, and Jun Guo. (ii) Acquisition of data is done by Peihai Zhang, Qi Liu, J. Junjie Pan, Zhengjie Li, Guangsen Li, Yaodong You, Xujun Yu, Jun Guo, Qiyong Gong, and Degui Chang. (iii) Analysis and interpretation of data are done by Jixin Liu, Jinbo Sun, Minghao Dong, and Wei Qin. (iv) Drafting of the paper is done by Qi Liu, Peihai Zhang, Junjie Pan, Zhengjie Li, and Guangsen Li. (v) Revision of the paper is done by Degui Chang, Yaodong You, Xujun Yu, Jixin Liu, Wei Qin, Jinbo Sun, Minghao Dong, Qiyong Gong, and Jun Guo. Qi Liu and Peihai Zhang contributed equally to this work.

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Review Article

Correlations between Phlegm Syndrome of Chinese Medicine and Coronary Angiography: A Systematic Review and Meta-Analysis

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Phlegm is one of the most common patterns of coronary artery disease (CAD) in Chinese medicine. Our research was aimed at investigating the association between phlegm syndrome of CAD and coronary angiography (CAG) by meta-analysis. According to inclusion criteria, a total of 30 studies involving 5,055 CAD patients were included. The meta-analysis showed that phlegm syndrome patients were prone to multivessel disease (28 studies, OR = 1.53, 95% CI, 1.24 to 1.88, $P < 0.01$) and higher Gensini score (2 studies, OR = 5.90, 95% CI, 1.86 to 9.94, $P = 0.004$), but not obviously relevant to severe stenosis (≥75%) of coronary arteries (13 studies, OR = 1.20, 95% CI, 0.63 to 2.27, $P = 0.57$). We concluded that the coronary arteries lesions of CAD patients with phlegm syndrome were more severe than those with nonphlegm syndromes. Phlegm syndrome should, therefore, be regarded as a dangerous pattern of CAD with worse prognosis.

1. Introduction

Coronary artery disease (CAD) is a prevalent disease against human health, dedicated to one of the leading causes of death [1]. Traditional Chinese medicine (TCM) has fought against CAD (belonging to the categories of Xiong-bi and cardialgia in TCM) for thousands of years, establishing unique theories for etiology and systems of diagnosis and treatment. The syndrome (also called pattern [2]) and syndrome differentiation are the comprehensive analysis of clinical information and can be deemed to be the TCM theoretical interpretation of the symptom profiles [3]. Syndrome differentiation can be used for further stratification of the patients' conditions with certain disease, identified by orthodox medical diagnosis. It guides the choice of treatment either by acupuncture or by TCM herbal formulae and helps in the improvement of efficacy of the selected intervention [4].

Phlegm and blood-stasis are regarded as the most common patterns of CAD patients [5]. They are significantly related to hyperlipidemia [6] and atherosclerosis and platelet activating system [7], which determines the prognosis and stratification of CAD. Phlegm is defined as a viscous, turbid pathological product that can accumulate in the body, causing a variety of diseases [2]. TCM has two general categories of phlegm: broadly defined phlegm and narrowly defined phlegm (visible phlegm such as nasal discharge or sputum from respiratory passages). If the former, invisible phlegm accumulated in the chest and blocked the channels and vessels of heart, it would lead to the so-called phlegm syndrome of Xiong-bi characterized as choking or crushing chest discomfort, shortness of breath, heavy feeling in the limbs, gastric stuffiness, sticky slimy sensation in the mouth, slimy and thick tongue coating, and slippery pulse [8], which was similar to manifestations of typical angina.

Lots of studies about the correlations between TCM syndromes and coronary angiography (CAG) were published recently, providing new objective information for syndrome differentiation of CAD [9]. Our previous pooled analysis showed a strong relation between blood-stasis syndrome and CAG [10], but the relevance of phlegm syndrome to presentations of CAG was not explored. This study was to investigate whether the phlegm syndrome was related to CAG through a systematic review and meta-analysis.

2. Methods

2.1. Search Strategy. MOOSE (Meta-Analysis of Observational Studies in Epidemiology) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statements were carefully consulted [41, 42]. To identify all relevant studies, we performed a literature search (Chinese and English languages) in China Academic Journal Network Publishing Database (CAJD), Chinese Biomedical Literature Database (CBM), China Doctor Dissertation Full-Text Database (CDFD), Chinese Selected Master's Theses Full-Text Databases (CMFD), and Medline and Embase (January 1990 through June 2014) under strict-making search strategy using Medical Subject Heading (MeSH) term (list of tables, Table 1). We also hand-searched the reference lists of all primary studies and reviews identified by the initial search.

2.2. Study Selection. All diagnostic cross-sectional studies, cohort studies, case-control studies, and randomized studies were retrieved to investigate association between TCM syndromes and presentations of CAG. We included a study if (1) obstructive CAD, with ≥50% diameter stenosis, was selected as the standard for significant CAD, using catheter-based X-ray angiography as the compared standard; (2) reported cases are in absolute numbers that can distinguish between phlegm syndrome and the others; (3) CAG results included at least one of the following parameters: the number of diseased arteries (defined *multivessel disease* [43] as cases with more than one stenotic (≥50%) diameter coronary artery), degree of coronary artery stenosis (defined *severe artery stenosis* as ≥75% by CAG), and Gensini score [44] (a common score system for evaluating the culprit coronary vessels). Studies were excluded if (1) animals; (2) review and case report; (3) study focused on specific CAD population, for example, female CAD patients, acute myocardial infarction, CAD with diabetes, and so on (4) duplicate reports.

2.3. Data Extraction and Quality Assessment. Two independent reviewers (Liang and Sun) extracted the following data from the selected studies. Inconsistencies were settled by discussion and consensus. We extracted year of publication, study design, clinical setting, methods of syndrome differentiation, and angiographic parameters. Methodological quality of included primary studies was assessed by two authors (Zhou and Gong) using a modified QUADAS-2 tool that included eight items [45]: *patient selection*: (1) consecutive or randomized patients; (2) avoiding inappropriate exclusions; (3) inclusion criteria of patients described; *syndrome differentiation*: (4) syndrome differentiation results interpreted without knowledge of the results of CAG; (5) syndrome differentiation by more than two independent doctors; *reference standard*: (6) CAG results interpreted without knowledge of the results of the syndrome differentiation; *flow and timing*: (7) an appropriate interval between syndrome differentiation and CAG; (8) perspective design. They are answered as "yes," "no," or "unclear" and are phrased such that "yes" indicates low risk of bias. Tabular and graphic displays served in summarizing quality assessments.

2.4. Statistical Analysis and Data Synthesis. To identify potential correlations between phlegm syndrome and CAG, we calculated an overall OR with a fixed or random effects model meta-analysis for the indices, which assumes the underlying effect varies according to studies. We performed tests of heterogeneity between studies using a standard chi-square test and I^2 statistic [46]. To examine sources of heterogeneity, subgroups of studies identified by selected covariates were meta-analyzed separately. Egger's test and Begg's funnel plot were applied for detecting publication bias in the meta-analysis. One-way sensitivity analysis was performed to assess the stability of the results; namely, a single study in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled OR [47]. Statistical significance was set at $P < 0.05$ and all statistical analyses were performed using RevMan 5.2.2 (The Cochrane Collaboration).

3. Results

3.1. Description of Included Studies. The literature process was outlined in Figure 1, and 88 potentially relevant studies were retrieved for detailed evaluation. 58 were excluded because (1) they had overlapping data; (2) it was not possible to calculate absolute numbers from the presented data; (3) or data was inconsistent in the context of the article. Finally, 30 included studies met the inclusion criteria, 29 Chinese articles, and 1 English article. All of the studies were from hospitals of China. Study and population characteristics of the included studies are summarized in Table 2, involving a total of 5,029 patients, reporting age ranging from 37 to 87 years. Analysis of the syndromes showed that there were 1,674 (33.3%) phlegm syndrome patients compared with 3,355 (66.7%) of the others. Most studies reported elective assessment for CAD, with study groups including those with suspected and known CAD. Eight studies were theses from medical universities of China. Methods for syndrome differentiation of CAD were divided into syndrome-element differentiation (SED) and other methods called conventional syndrome differentiation (CSD). CSD contains the classical syndrome differentiation methods, such as viscera syndrome differentiation and eight-principal syndrome differentiation [2].

3.2. Quality Assessment of Included Studies. Table 3 and Figure 2 summarized the quality assessment for the 30 full-text studies. Quality assessment of most studies was not satisfactory, especially the blinding method. None of the studies for those interpreting syndrome differentiation data

Table 1: Search strategy.

Number	Search terms	Detailed strategy in CAJD and Medline	
		CAJD (Chinese)	Medline (English)
#1	Coronary heart disease (冠心病) or coronary artery disease	(SU = (“冠心病” + “冠状动脉粥样硬化性心脏病”) or TI = (“冠心病” + “冠状动脉粥样硬化性心脏病”) or KY = (“冠心病” + “冠状动脉粥样硬化性心脏病”)) and (SU = (“中医” + “证型” + “辨证”) or TI = (“中医” + “证型” + “辨证”) or KY = (“中医” + “证型” + “辨证”)) and (SU = (“冠脉造影” + “冠状动脉造影”) or TI = (“冠脉造影” + “冠状动脉造影”) or KY = (“冠脉造影” + “冠状动脉造影”))	(Chinese medicine [Title/Abstract]) AND (Coronary angiography [Title/Abstract]) AND (syndrome [Title/Abstract] OR pattern [Title/Abstract])
#2	Xiong-bi (胸痹) or chest pain (心痛)		
#3	Chinese medicine (中医) or syndrome (证) or pattern		
#4	Coronary angiography (冠状动脉造影) or CAG (冠脉造影)		
#5	Search #1 or #2		
#6	Search (#1 or #2) and #3		
#7	Search (#1 or #2) and #3 and #4	Number of papers: 245	Number of papers: 12

Table 2: Study and population characteristics of the included studies.

Number	Author, year	Age	n	Male/female	Thesis	Clinical setting	Method of syndrome differentiation	Syndrome overlap	Indexes of CAG
1	Wang et al., 2003 [11]	59.2 ± 7.8	158	98/60	No	Cross-sectional	CSD	No	CVN, DAS (70% as the classification)
2	Su, 2004 [12]	69.1 (unknown SD)	31	Unknown	Yes	Case-control	CSD	No	CVN
3	Zhang et al., 2004 [13]	58.5 ± 10.2	269	Unknown	No	Case-control	SED	Yes	CVN
4	Liuand Jiang, 2005 [14]	63.8 ± 9.6	259	209/50	No	Cross-sectional	CSD	No	CVN, Gensini score
5	Wang, 2005 [15]	64.6 ± 11.5	81	52/29	Yes	Cross-sectional	SED	Yes	CVN
6	Li et al., 2006 [16]	59.6 ± 10.1	96	77/19	No	Cross-sectional	CSD	No	CVN, DAS, Gensini score
7	Liu et al., 2006 [17]	65.4 ± 10.8	69	52/61	No	Cross-sectional	SED	Yes	CVN
8	Xue, 2006 [18]	Unknown	68	37/31	Yes	Cross-sectional	CSD	No	CVN, DAS, Gensini score
9	Zhang et al., 2006 [19]	57.6 (unknown SD)	279	—	No	Case-control	CSD	No	CVN
10	Guo, 2007 [20]	Unknown	147	104/43	Yes	Cross-sectional	CSD	No	CVN, DAS
11	Wang et al., 2007 [21]	Unknown	81	Unknown	No	Case-control	SED	Yes	CVN
12	Zhangand Xu, 2007 [22]	59.8 ± 12.3	126	99/27	No	Cross-sectional	CSD	No	CVN, DAS
13	Pan et al., 2008 [23]	68.0 ± 10.7	61	40/21	No	Cross-sectional	SED	Yes	CVN
14	Wang et al., 2008 [24]	58.2 ± 10.58	324	250/74	No	Cross-sectional	SED	Yes	CVN
15	Liao, 2009 [25]	Unknown	143	68/75	Yes	Cross-sectional	CSD	No	CVN, DAS
16	Wang, 2009 [26]	Unknown	100	57/43	Yes	Cross-sectional	CSD	No	CVN, Gensini score
17	Wang et al., 2009 [27]	Unknown	252	192/60	No	Cross-sectional	CSD	No	CVN, DAS
18	Wang et al., 2009 [28]	63.4 ± 11.7	229	128/101	No	Cross-sectional	SED	Yes	CVN, Gensini score
19	Zhu et al., 2009 [29]	Unknown	100	85/15	No	Cross-sectional	CSD	No	CVN, DAS
20	Du, 2010 [30]	59.6 ± 11.2	369	291/78	Yes	Cross-sectional	SED	Yes	Gensini score
21	Hou, 2010 [31]	Unknown	87	48/39	No	Cross-sectional	CSD	No	CVN, DAS, Gensini score
22	Ren et al., 2010 [32]	58.3 ± 10.7	405	307/98	No	Cross-sectional	SED	Yes	CVN, Gensini score
23	Tong, 2010 [33]	62.8 ± 9.3	97	57/40	Yes	Cross-sectional	CSD	No	CVN, DAS
24	Zhang et al., 2010 [34]	59.8 ± 12.3	368	252/116	No	Cross-sectional	CSD	No	CVN, DAS (70% as the classification), Gensini score
25	Bi et al., 2011 [35]	67.2 ± 8.3	67	Unknown	No	Cross-sectional	SED	Yes	DAS
26	Xu et al., 2011 [36]	59. 6 ± 10.1	250	200/50	No	Cross-sectional	CSD	No	CVN, Gensini score
27	Yan et al., 2011 [37]	69.0 ± 10.5	189	103/86	No	Cross-sectional	SED	Yes	CVN, DAS
28	Zhou et al., 2011 [38]	Unknown	95	73/22	No	Cross-sectional	CSD	No	CVN, DAS, Gensini score
29	Tanand Leng, 2012 [39]	Unknown	70	38/32	No	Cross-sectional	CSD	No	CVN
30	Wang et al., 2013 [40]	Unknown	150	68/82	No	Cross-sectional	CSD	No	CVN
		Total	5055						

Note: CSD = conventional syndrome differentiation, CVN = culprit-vessel number, DAS = degree of artery stenosis, and SED = syndrome-element differentiation.

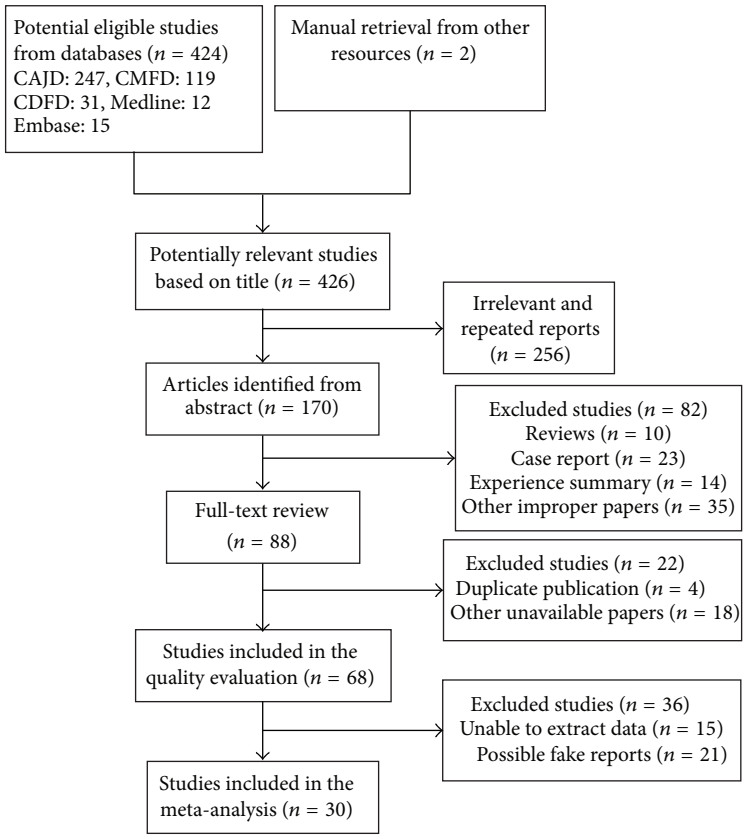

Figure 1: Flow diagram of studies considered for the review.

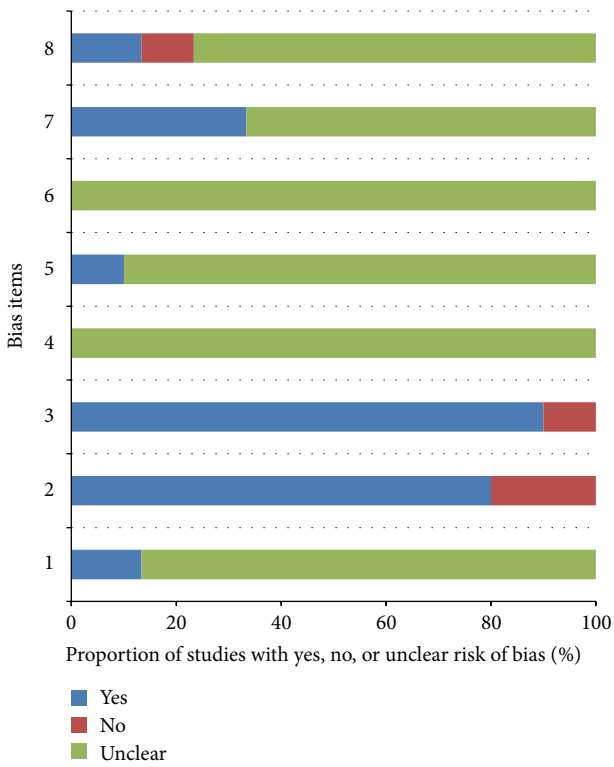

Figure 2: Graphic display of quality assessment. Note: (1) consecutive or randomized patients; (2) avoiding inappropriate exclusions; (3) inclusion criteria of patients described; (4) syndrome differentiation results interpreted without knowledge of the results of CAG; (5) syndrome differentiation by more than two independent doctors; (6) CAG results interpreted without knowledge of the results of the syndrome differentiation; (7) an appropriate interval between syndrome differentiation and CAG; (8) perspective design.

Table 3: Tabular display of quality assessment.

Number	Study, year	Patient selection			Syndrome differentiation		Reference standard	Flow and timing	
		(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
1	Wang et al., 2003 [11]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear
2	Su, 2004 [12]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear
3	Zhang et al., 2004 [13]	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes
4	Liu and Jiang, 2005 [14]	Unclear	No	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
5	Wang, 2005 [15]	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
6	Li et al., 2006 [16]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
7	Liu et al., 2006 [17]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear
8	Xue, 2006 [18]	Unclear	Yes	Yes	Unclear	Yes	Unclear	Unclear	Unclear
9	Zhang et al., 2006 [19]	Unclear	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes
10	Guo, 2007 [20]	Unclear	No	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
11	Wang et al., 2007 [21]	Unclear	No	Yes	Unclear	Unclear	Unclear	Yes	Yes
12	Zhang and Xu, 2007 [22]	Unclear	No	No	Unclear	Unclear	Unclear	Unclear	Unclear
13	Pan et al., 2008 [23]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear
14	Wang et al., 2008 [24]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear
15	Liao, 2009 [25]	Yes	No	Yes	Unclear	Unclear	Unclear	Yes	No
16	Wang, 2009 [26]	Unclear	Yes	Yes	Unclear	Yes	Unclear	Unclear	Unclear
17	Wang et al., 2009 [27]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Yes
18	Wang et al., 2009 [28]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
19	Zhu et al., 2009 [29]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
20	Du, 2010 [30]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No
21	Hou, 2010 [31]	Unclear	Yes	No	Unclear	Unclear	Unclear	Unclear	Unclear
22	Ren et al., 2010 [32]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
23	Tong, 2010 [33]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	No
24	Zhang et al., 2010 [34]	Unclear	No	No	Unclear	Unclear	Unclear	Unclear	Unclear
25	Bi et al., 2011 [35]	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
26	Xu et al., 2011 [36]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
27	Yan et al., 2011 [37]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
28	Zhou et al., 2011 [38]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
29	Tan and Leng, 2012 [39]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
30	Wang et al., 2013 [40]	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear

Note: (1) consecutive or randomized patients; (2) avoiding inappropriate exclusions; (3) inclusion criteria of patients described; syndrome differentiation: (4) syndrome differentiation results interpreted without knowledge of the results of CAG; (5) syndrome differentiation by more than two independent doctors; (6) CAG results interpreted without knowledge of the results of the syndrome differentiation; (7) an appropriate interval between syndrome differentiation and CAG; (8) perspective design.

were blinded to the results of the reference standard test (test review bias avoided) and vice versa (diagnostic review bias avoided).

3.3. Results of Meta-Analysis. After the 30 eligible studies involving 5,055 CAD patients were pooled, there was a significant association between phlegm syndrome and CAG in some parameters. Overall, the multivessel disease OR associated with phlegm syndrome was 1.53 (95% CI, 1.24 to 1.88, $P < 0.01$; $I^2 = 47\%$, Figure 3), while severe artery stenosis was 1.20 (95% CI, 0.63 to 2.27, $P = 0.57$; $I^2 = 84\%$, Figure 4) and Gensini score was 5.90 (95% CI, 1.86 to 9.94, $P = 0.004$; $I^2 = 0\%$, Figure 5). Although the heterogeneity among the analyzed studies was high, most of the studies referred to a positive association for multivessel disease. As the studies were divided into two subgroups by SED or CSD, the OR of multivessel disease in SED group was 1.34 (95% CI, 1.08 to 1.67, $P = 0.008$; $I^2 = 10\%$, Figure 3), showing that the heterogeneity between the studies decreased substantially compared with the main analysis (Figure 3). For the association between phlegm syndrome and degree of artery stenosis, though the result was negative, the heterogeneity between the analyzed studies of thesis subset

Study or subgroup	Phlegm syndrome Events	Phlegm syndrome Total	Nonphlegm syndrome Events	Nonphlegm syndrome Total	Weight	Odds ratio M-H, Random, 95% CI	Year
1.1.1 Nonelement							
Wang et al. 2003	18	47	59	111	4.4%	0.55 [0.27, 1.10]	2003
Su 2004	13	20	2	11	1.2%	8.36 [1.40, 49.88]	2004
Liu and Jiang 2005	88	124	72	135	5.6%	2.14 [1.28, 3.58]	2005
Li et al. 2006	20	26	42	70	2.8%	2.22 [0.79, 6.22]	2006
Xue 2006	9	11	38	47	1.3%	1.07 [0.20, 5.81]	2006
Zhang et al. 2006	27	45	98	279	4.7%	2.77 [1.45, 5.28]	2006
Guo 2007	43	61	59	86	4.3%	1.09 [0.54, 2.23]	2007
Zhang and Xu 2007	18	27	59	99	3.3%	1.36 [0.55, 3.32]	2007
Wang et al. 2009	10	15	61	85	2.3%	0.79 [0.24, 2.54]	2009
Wang et al. 2009	47	59	142	193	4.3%	1.41 [0.69, 2.86]	2009
Zhu et al. 2009	29	33	35	67	2.4%	6.63 [2.10, 20.94]	2009
Liao 2009	30	45	66	98	4.1%	0.97 [0.46, 2.05]	2009
Hou 2010	18	23	38	64	2.5%	2.46 [0.81, 7.47]	2010
Tong 2010	8	24	28	73	3.0%	0.80 [0.30, 2.12]	2010
Zhang et al. 2010	36	54	122	198	4.8%	1.25 [0.66, 2.35]	2010
Zhou et al. 2011	15	22	38	73	2.9%	1.97 [0.72, 5.41]	2011
Xu et al. 2011	58	68	67	108	3.9%	3.55 [1.63, 7.71]	2011
Tan and Leng 2012	25	27	24	43	1.5%	9.90 [2.08, 47.14]	2012
Wang et al. 2013	22	31	64	119	3.5%	2.10 [0.89, 4.94]	2013
Subtotal (95% CI)		**762**		**1959**	**62.8%**	**1.73 [1.28, 2.35]**	
Total events	534		1114				
Heterogeneity: $\tau^2 = 0.23$; $\chi^2 = 40.28$, df = 18 ($P = 0.002$); $I^2 = 55\%$							
Test for overall effect: $Z = 3.56$ ($P = 0.0004$)							
1.1.2 Syndrome-element							
Zhang et al. 2004	89	125	98	144	5.6%	1.16 [0.69, 1.96]	2004
Wang 2005	19	24	49	57	2.2%	0.62 [0.18, 2.14]	2005
Liu et al. 2006	24	32	21	37	2.8%	2.29 [0.82, 6.41]	2006
Wang et al. 2007	19	30	116	215	3.9%	1.47 [0.67, 3.25]	2007
Pan et al. 2008	27	35	22	26	1.9%	0.61 [0.16, 2.31]	2008
Wang et al. 2008	99	127	146	197	5.5%	1.24 [0.73, 2.09]	2008
Wang 2009	66	89	84	140	5.1%	1.91 [1.07, 3.43]	2009
Ren et al. 2010	131	177	148	228	6.2%	1.54 [1.00, 2.37]	2010
Yan et al. 2011	73	90	84	99	4.0%	0.77 [0.36, 1.64]	2011
Subtotal (95% CI)		**729**		**1143**	**37.2%**	**1.32 [1.06, 1.65]**	
Total events	547		768				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 8.17$, df = 8 ($P = 0.42$); $I^2 = 2\%$							
Test for overall effect: $Z = 2.46$ ($P = 0.01$)							
Total (95% CI)		**1491**		**3102**	**100.0%**	**1.53 [1.24, 1.88]**	
Total events	1081		1882				
Heterogeneity: $\tau^2 = 0.14$; $\chi^2 = 50.81$, df = 27 ($P = 0.004$); $I^2 = 47\%$							
Test for overall effect: $Z = 3.95$ ($P < 0.0001$)							
Test for subgroup differences: $\chi^2 = 2.03$, df = 1 ($P = 0.15$); $I^2 = 50.7\%$							

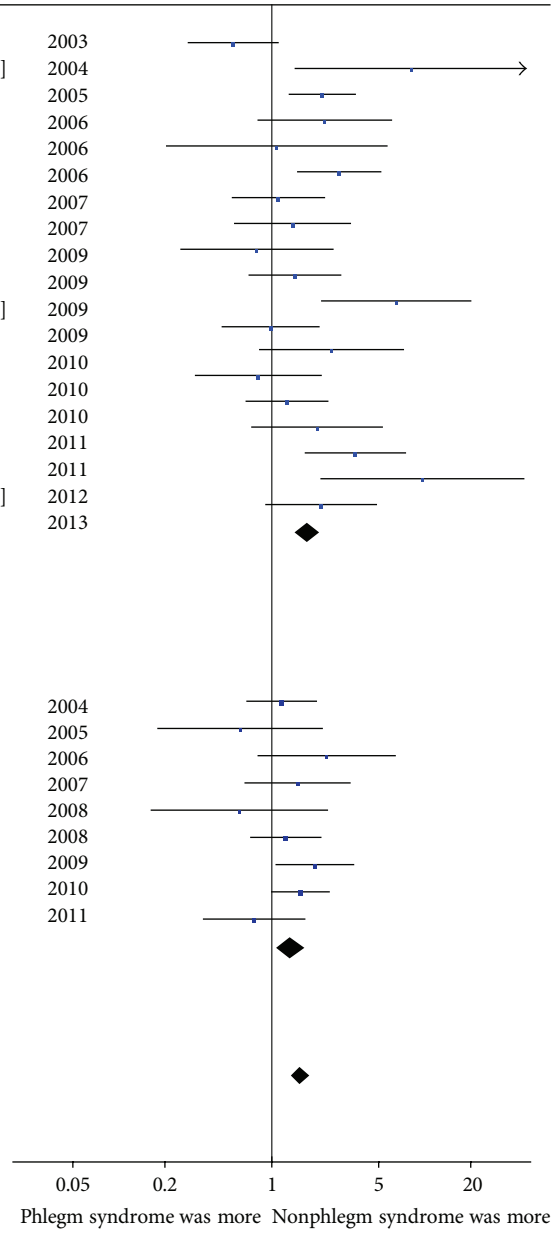

Figure 3: Meta-analysis of association between phlegm syndrome and multivessel disease.

sharply reduced ($I^2 = 0$) compared with the main analysis (Figure 4).

3.4. Results of Sensitivity Analysis and Publication Bias. No individual studies influencing the summary OR found by one-way sensitivity analysis, indicating that the pooled data was stable. There was no evidence of publication bias, because the funnel plot according to meta-analysis of association between phlegm syndrome and multivessel disease did not show obvious asymmetry by visual inspection (Figure 6), which was also confirmed by Egger's test ($P = 0.527$). However, some studies located out of the border, which may affect the result of the meta-analysis.

4. Discussion

This was the first meta-analysis to address the relationship between phlegm syndrome and CAG. The parameters of culprit vessel, stenosis degree, and Gensini score under CAG were important indicators for CAD patients, and we discovered that serious coronary artery lesions are associated with the presence of phlegm syndrome. The phlegm syndrome

Study or subgroup	Phlegm syndrome Events	Phlegm syndrome Total	Nonphlegm syndrome Events	Nonphlegm syndrome Total	Weight	Odds ratio M-H, random, 95% CI	Year
1.3.1 Thesis							
Xue 2006	5	11	44	57	6.9%	0.25 [0.06, 0.94]	2006
Guo 2007	26	61	55	86	8.9%	0.42 [0.21, 0.82]	2007
Tong 2010	14	24	32	41	7.6%	0.39 [0.13, 1.18]	2010
Subtotal (95% CI)		**96**		**184**	**23.4%**	**0.38 [0.22, 0.64]**	
Total events	45		131				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.49$, df = 2 ($P = 0.78$); $I^2 = 0\%$							
Test for overall effect: $Z = 3.60$ ($P = 0.0003$)							
1.3.2 Non-thesis							
Wang et al. 2003	23	47	80	111	8.8%	0.37 [0.18, 0.75]	2003
Zhang et al. 2004	134	151	171	224	9.1%	2.44 [1.35, 4.41]	2004
Li et al. 2006	22	26	50	70	7.4%	2.20 [0.67, 7.19]	2006
Zhu et al. 2009	33	33	64	67	3.1%	3.64 [0.18, 72.47]	2009
Wang et al. 2009	48	59	141	193	8.7%	1.61 [0.78, 3.33]	2009
Hou 2010	19	23	44	64	7.3%	2.16 [0.65, 7.17]	2010
Yan et al. 2011	63	90	87	99	8.7%	0.32 [0.15, 0.68]	2011
Bi et al. 2011	34	40	14	27	7.5%	5.26 [1.67, 16.62]	2011
Xu et al. 2011	68	72	108	178	7.8%	11.02 [3.85, 31.56]	2011
Wang et al. 2013	22	31	74	115	8.3%	1.35 [0.57, 3.21]	2013
Subtotal (95% CI)		**572**		**1148**	**76.6%**	**1.74 [0.85, 3.57]**	
Total events	466		833				
Heterogeneity: $\tau^2 = 1.03$; $\chi^2 = 53.58$, df = 9 ($P < 0.00001$); $I^2 = 83\%$							
Test for overall effect: $Z = 1.52$ ($P = 0.13$)							
Total (95% CI)		**668**		**1332**	**100.0%**	**1.20 [0.63, 2.27]**	
Total events	511		964				
Heterogeneity: $\tau^2 = 1.07$; $\chi^2 = 73.34$, df = 12 ($P < 0.00001$); $I^2 = 84\%$							
Test for overall effect: $Z = 0.56$ ($P = 0.57$)							
Test for subgroup differences: $\chi^2 = 11.26$, df = 1 ($P = 0.0008$); $I^2 = 91.1\%$							

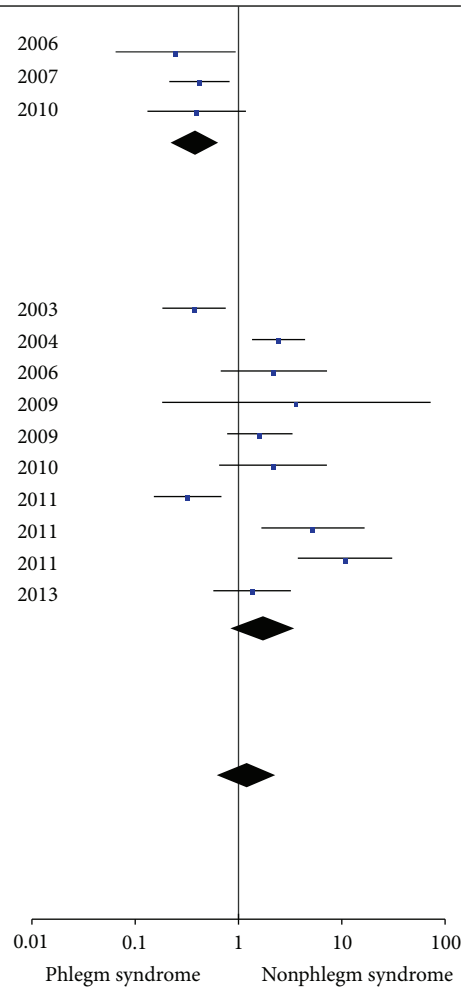

Figure 4: Meta-analysis of association between phlegm syndrome and severe artery stenosis.

Study or subgroup	Phlegm syndrome Mean	Phlegm syndrome SD	Phlegm syndrome Total	Nonphlegm syndrome Mean	Nonphlegm syndrome SD	Nonphlegm syndrome Total	Weight	Mean difference IV, fixed, 95% CI	Year
Du 2010	32.72	29.13	143	25.24	24.28	226	49.8%	7.48 [1.75, 13.21]	2010
Ren et al. 2010	36.82	29.55	177	32.49	28.38	228	50.2%	4.33 [−1.37, 10.03]	2010
Total (95% CI)			**320**			**454**	**100.0%**	**5.90 [1.86, 9.94]**	
Heterogeneity: $\chi^2 = 0.58$, df = 1 ($P = 0.44$); $I^2 = 0\%$									
Test for overall effect: $Z = 2.86$ ($P = 0.004$)									

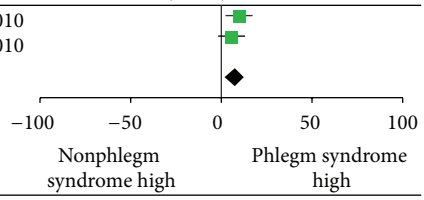

Figure 5: Meta-analysis of association between phlegm syndrome and Gensini score.

patients were inclined to suffer from multivessel disease and higher Gensini score, but no obvious correlation with the severe artery stenosis was found, which was different from our previous study of meta-analysis for the blood-stasis syndrome [10]. The difference can partly explain the essence of phlegm and blood-stasis syndrome. Blood-stasis and phlegm are both pathological products of abnormal metabolism of body fluid and blood in Chinese medicine. Phlegm formed in the spleen can easily expand and accumulate not only in the lungs but also in almost all other parts of the body, including five viscera, six bowels, joints, and surface tissue, through Meridians or Triple Energizers [48, 49]. Multivessel disease could be considered as diffuse changes of coronary arteries representing the pathological features of phlegm.

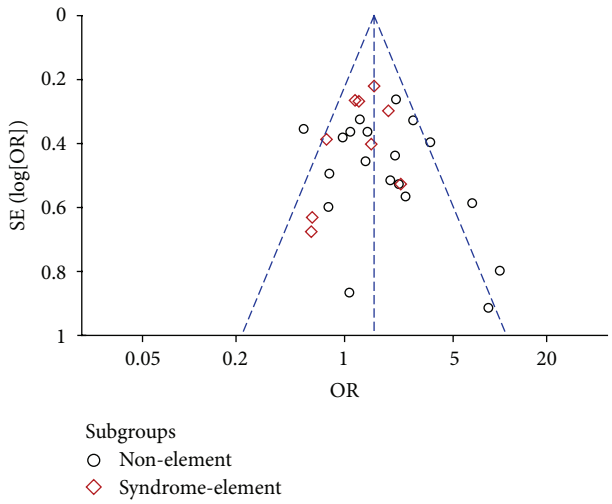

Figure 6: Funnel plot for publication bias by association between phlegm syndrome and multivessel disease.

The blood-stasis focused on the "stasis," which means block, retardance, and fixation, so patients of blood-stasis pattern were significantly related to >75% degree of artery stenosis [10]. Unfortunately, we were unable to judge which syndrome was worst (phlegm or blood-stasis) for difficulty in extracting the independent data.

Considered as the base of modernization and scientification of TCM, the syndrome diagnostic criteria began to be researched from the 1980s. They were drawn up by different organizations and departments nonrecognized by one another, including Tentative Standard approved by National Academic Seminar on TCM Syndrome Differentiation Based Treatment of CAD in 1980 and Standards for Diagnosis and Curative Effect of TCM Diseases and Syndromes by State Administration of Traditional Chinese Medicine in 1994. Even the process of syndrome differentiation was judged by symptoms and signs with accepted criterion. Plus, the results could be affected by the doctor's learning, medical experience, academic origins, methods, and other factors. Therefore, the judgment made by doctors on cause, location, nature, and trend of disease is individual and variable, and no wonder that 10 TCM doctors may give 10 different diagnoses when facing the same patient [50]. It is crucial, however, to find the source of heterogeneity, usually an obstacle to the meta-analysis. Based on our subgroup analysis, it is strongly supported that different diagnostic methods were the source of heterogeneity and restriction for syndrome differentiation. The heterogeneity of syndrome differentiation based on SED studies decreased to 2% (Figure 3), while the CSD group increased a little. SED method, now widely used in clinical and basic research, was created by Professor Zhu et al. [51], who proposed the theory of syndrome-element and divided those "elements" into categories of location and nature. The differentiation system was established by clarifying that "syndrome" was composed of the key elements of the location and the nature of disease. Thus, a complete syndrome name was combined by elements of location and nature diagnosed from symptoms and signs. Unlike inflexible CSD, the syndrome could be free combination of possible syndrome-elements, allowing any forms of elements summation. For instance, phlegm is its high affinity with other pathogenic factors such as heat, cold, wind, dampness, and dryness and, because of this, phlegm is often combined with other pathogenic factors to form more complex patterns such as heat-phlegm, cold-phlegm, or wind-phlegm [52]. Moreover, our subanalysis proved that SED method led to homogeneity between studies, which would be more promising than CSD. The heterogeneity was also affected by the factor of thesis or not. For postgraduates lack of clinical experience, their diagnosis of syndrome differentiation may be different from older doctors, causing a discrepancy of studies. In a word, the thinking characteristics of syndrome are more similar to physical image thinking rather than image thinking [50]; thus, methods may play an important role during implementation based on the syndrome differentiation criteria.

Any process that yields information used to inform patient management can be regarded as a clinical test [53]. The basic aim of test accuracy studies is to assess how well a test can distinguish between people with and without the disease/syndrome/condition of interest [54]. Nevertheless, unlike index test compared with a reference standard in western medicine, the diagnostic test accuracy (DTA), such as specificity or sensitivity, was still tough for syndrome differentiation just by a profile of symptom combination, or clinical phenotypes. Above all, the design of syndrome differentiation research is similar to diagnostic tests, which means cross-sectional and descriptive in nature [55], and RCT [56, 57] case-control and two-gate designs could be feasible [55]. Using QUADAS-2 tool for quality assessment was an innovation of our research. Avoiding subjective impact on researchers, double blind, for instance, is the key to quality of diagnostic study. In the summary of tabular and graphic results, items of (4), (5), and (6) concerning improving objective diagnosis for syndromes were not optimistic (Table 3, Figure 2). It tells us that most of TCM researchers did not take diagnostic design seriously. Lack of blinding can lead to overestimation of test accuracy, especially when the interpretation of test results is subjective [58].

Evaluation score systems of CAG, such as Gensini score [44] and SYNTAX score [59], are more comprehensive and better than just number or degree of stenosis for vessel lesions to estimate conditions of diseased coronary arteries. Due to difficulty of extracting available data, only two studies containing Gensini score were included in the meta-analysis. Moreover, CAD patients could be subdivided into acute coronary syndrome (ACS) and non-ACS, and ACS attacks suddenly often with worse outcomes than non-ACS. The clinical manifestations and CAG of the two types of patients are quite different [60]. Once mixed up, it would produce more difficulties and confusion for the study. We hope patient spectrum of next researches is aimed at ACS or non-ACS individually. Last but not least, there were no standards or statements specific for publishing meta-analysis of diagnostic tests, so as the TCM syndrome diagnosis. The researchers have to only reference other standards, such as MOOSE [61]

to finish the review, to some degree limiting the diagnostic research on meta-analysis.

5. Conclusions

From the meta-analysis, we found there were correlations between phlegm syndrome of CAD patients and image of CAG: the coronary arteries lesions of CAD patients with phlegm syndrome were more severe than those with other syndromes. Syndrome differentiation was not only important for diagnosis and treatment, but also useful for the prognosis. Phlegm syndrome could be considered as risk syndrome of CAD patients, whom doctors should pay closer attention to. However, from the quality assessment, we found that the design quality of TCM diagnostic test urgently needs to be addressed.

Conflict of Interests

There is no conflict of interests declared.

Authors' Contribution

Qiuyan Zhang proposed the idea and drafted the paper. Hao Liang carried out some writing of the paper, performed the meta-analysis by RevMan, and submitted the paper to journals. Houwu Gong participated in the methodological quality evaluation and drew the graphic display of quality assessment. Hui-yong Huang participated in the design of the study and extracted data. Xiaoqing Zhou conceived of the study and participated in quality assessment and helped to draft the paper. All the authors read and approved the final paper.

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Review Article

Prescription of Chinese Herbal Medicine in Pattern-Based Traditional Chinese Medicine Treatment for Depression: A Systematic Review

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Traditional Chinese medicine (TCM) treatments are often prescribed based on individuals' pattern diagnoses. A systematic review of randomized controlled trials in Chinese and English literatures on TCM pattern-based treatment for depression has therefore been conducted. A total of 61 studies, 2504 subjects, and 27 TCM patterns were included. Due to the large variation of TCM pattern among participants, we only analyzed the top four commonly studied TCM patterns: *liver qi depression, liver depression and spleen deficiency, dual deficiency of the heart, and spleen* and *liver depression and qi stagnation*. We found that Xiaoyao decoction was the most frequently used herbal formula for the treatment of *liver qi depression* and *liver depression with spleen deficiency*, while Chaihu Shugan decoction was often used for *liver depression and qi stagnation*. Bai Shao (*Paeonia lactiflora* Pall.) and Chai Hu (*Bupleurum chinense* DC.) were commonly used across different TCM patterns regardless of the prescribed Chinese herbal formulas. The rationale underlying herb selection was seldom provided. Due to the limited number of studies on TCM pattern-based treatment of depression and their low methodological quality, we are unable to draw any conclusion regarding which herbal formulas have higher efficacy and which TCM patterns respond better to CHM.

1. Introduction

According to the Global Burden of Disease Study 2010, major depressive disorder (MDD) was ranked the second leading cause of years lived with disability, accounting for 8.2% of all years lived with disability [1]. The World Mental Health Survey Initiative showed that the average lifetime prevalence for major depressive episode based on the Diagnostic and Statistical Manual, Fourth Edition [2], was 14.6% in 10 high-income countries and 11.1% in 8 low- to middle-income countries [3]. Pharmacotherapy is currently the most commonly used treatment for MDD because of its reported effectiveness; however, complaints such us nausea, headache, insomnia, agitation, weight gain, daytime somnolence, and sexual dysfunction are common during the course of treatment, leading to early termination in some patients. The use of psychotherapy as an alternative is no better because of its time-intensive nature, limited access to skilled providers, high cost, and requirement of patients' participation and motivation. Faced with the limitations of the currently available treatments, complementary and alternative medicine for depression is very common. A national representative survey in the United States found that 53.6% of people with depression reported using some forms of complementary and alternative therapies to treat depression during the past 12 months [4].

Chinese herbal medicine (CHM) is one of the oldest medical treatments in the world and it is a common form of complementary and alternative medicine therapy for MDD [5, 6]. Previous studies have been conducted to examine the efficacy of CHM for depression [7–14]; however, limited

information is available on pattern-based CHM treatment. According to the traditional Chinese medicine (TCM) theory, eight major parameters, *yin* and *yang*, *external* and *internal*, *hot* and *cold*, and *excess* and *deficiency*, are used to describe the patterns of bodily disharmony. Additional systems, such as *qi*, *blood*, and *body fluid* differentiation and *zang fu* (organ) differentiation are also used [15]. In terms of the TCM theory, the onset of depression is often due to "damages" by extreme emotions. *Liver qi* is first affected, followed by disharmony of the *qi* mechanism of the five viscera, particularly *liver*, *spleen*, and *heart*, resulting in a loss of regulation of the *qi* and *blood*. The *liver* depression may repress the *spleen* and lead to consumption and damage of the *heart qi*. If *heart* loses its nourishment and the restfulness to *heart shen* (spirit) occurs, it will lead to unstable and depressed mood. When *qi* depression is prolonged, it will accumulate and transform into fire [16, 17].

TCM pattern differentiation is a diagnostic conclusion of the pathological changes of a disease state based on an individual's symptoms, physical signs, pulse form, and tongue appearance. Although it is believed that pattern-based TCM treatment will provide better efficacy, previous studies regarding the additional benefits of TCM pattern differentiation are scarce. One randomized controlled trial (RCT) found that the therapeutic effect of Chinese herbal treatment according to TCM pattern was more sustainable than a standard formula in treating irritable bowel syndrome [18]. It has also been reported in rheumatoid arthritic patients that TCM pattern diagnoses can guide the use of Western medicine [19]. To the best of our knowledge, no systematic review has been conducted on pattern-based CHM treatment for depression. Given the high prevalence of depression and its frequent presentation to TCM practitioners, it is important to review the current application of pattern differentiation in CHM treatment for depression. The objectives of this paper were (1) to summarize the commonly diagnosed TCM patterns in patients with depression and (2) to find out the current practice of pattern-based CHM treatment for depression.

2. Materials and Methods

The present study was part of our systematic review on Chinese herbal medicine for depression [11, 20]. Two researchers (Ka-Yan Ng and Yee-Man Yu) independently searched nine Chinese language databases (China Journals Full-text Database, China Proceedings of Conference Full-text Database, Chinese Biomedical Literature Database, China Doctor Dissertations Full-text Database, China Master Theses Full-text Database, Chinese Science and Technology Documents Database, Chinese Dissertation Document Bibliography Database, Taiwan Electronic Periodical Services, and WanFang Database) and seven English language databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, Allied and Complementary Medicine, PsycINFO, and ProQuest Dissertations and Theses A&I) using the grouped terms "depression* or depressive* or dysthymia* or mood disorder* or "affective disorder*" or "affective symptoms" or MDD" and "Chinese herb* or herbal medicine* or traditional Chinese medicine* or TCM or Chai-Hu-Shu-Gan-San or ChaiHuShuGan* or Xiao-Yao-San or XiaoYao* or Ban-Xia-Hou-Pu-Tang or BanXiaHouPu* or Gan-Mai-Da-Zao-Tang or GanMaiDaZao* or Gui-Pi-Tang or GuiPi* or Wen-Dan-Tang or WenDan or Yue-Ju-Wan or Yue-Ju" and the equivalent Chinese terms. We imposed no language restriction. We also checked the reference lists of the included papers and previous systematic reviews [7–14] for relevant articles.

2.1. Selection Criteria. Studies included in this review were RCTs that described TCM patterns of depressed subjects who received CHM treatment for depression. In order to obtain a full coverage of the topic, we had not set any specification for outcome measure and study quality. In addition, to derive a general picture of TCM pattern utilization, studies were excluded if they (1) had less than 30 subjects; (2) examined male or female only; (3) focused on subjects aged below 18 or above 70 years; (4) focused on a particular life transition period or a specific TCM pattern; (5) had no statistical information regarding the frequency of individual TCM pattern; or (6) were duplicated publications.

2.2. Data Extraction Process. Any disagreement about the eligibility of a study was resolved by discussion between the two researchers who independently selected the relevant publications and by consultation with the senior authors (Wing-Fai Yeung and Ka-Fai Chung). One author extracted the data (Ka-Yan Ng) and the other (Yee-Man Yu) checked the extracted data. For each study, the following variables were extracted: study design, sample size, mode of recruitment, sampling and diagnostic procedure, inclusion and exclusion criteria, and participants' characteristics including age, gender, and duration of depression. TCM patterns, treatment principles, treatment regimen and outcome of TCM treatments were obtained. All Chinese to English translations were deduced primarily from the *World Health Organization (WHO) International Standard Terminologies on Traditional Medicine in the Western Pacific Region* [21] and additionally from *Traditional Chinese Internal Medicine* [22], a commonly used English-language TCM textbook in China.

2.3. Study Quality Assessment. We assessed the methodological quality using the Jadad scale [23]. Points are awarded if the study is described as randomized, 1 point; has appropriate randomization method, 1 point; is described as double-blind, 1 point; uses appropriate blinding method, 1 point; or has description of withdrawals and dropouts, 1 point. A Jadad scale score ≥3 represents better quality trials.

2.4. Statistical Analysis. SPSS version 20.0 was used for statistical analysis. Data were summarized using mean (SD) and 95% confidence intervals (CIs).

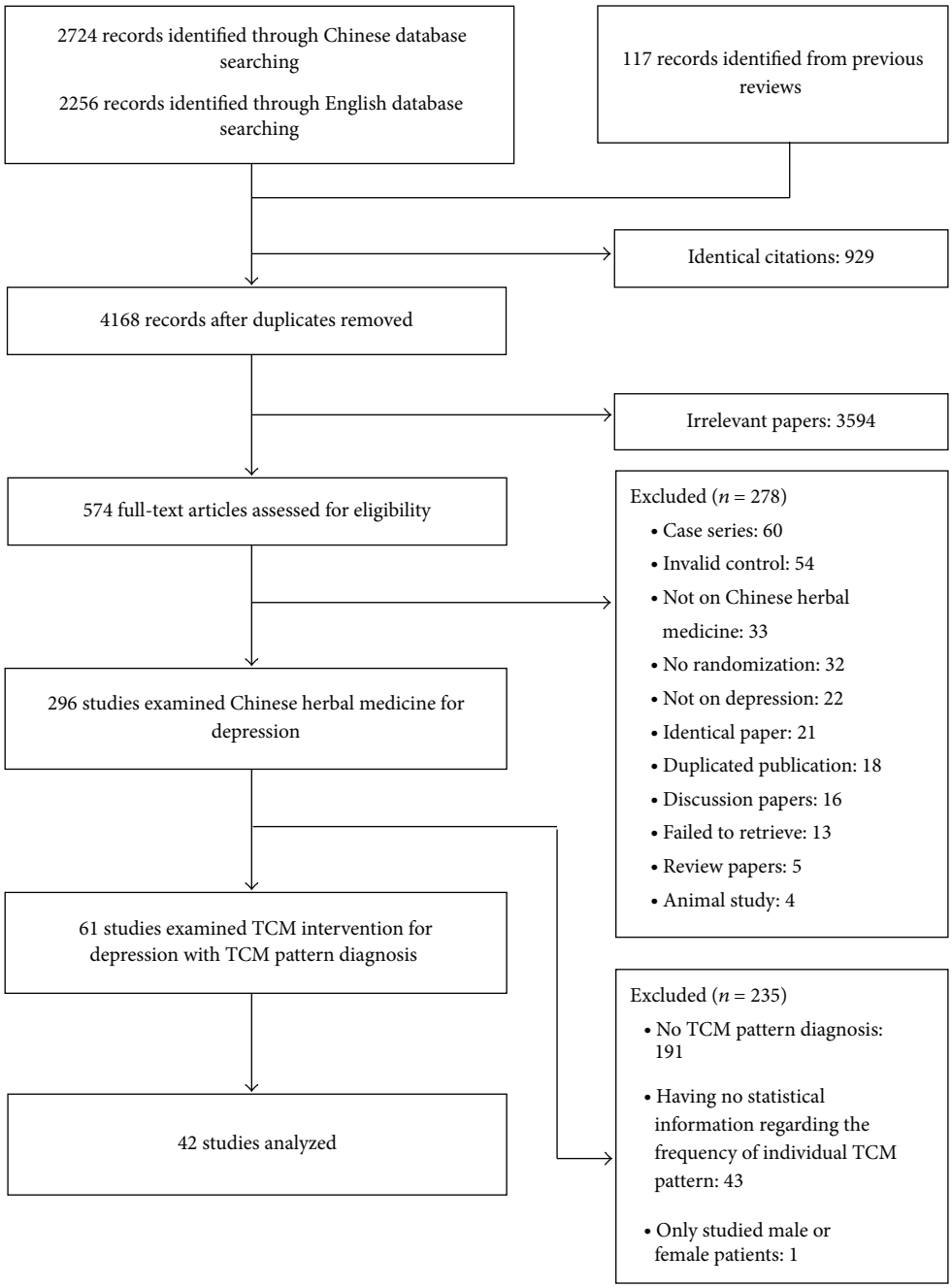

Figure 1: Study selection flowchart.

3. Results

The search yielded 5097 potential titles for review, of which 929 were duplicated records and 3594 were excluded for reasons of irrelevance. The full text of 574 was retrieved for detailed assessment, of which 278 were excluded for various reasons (Figure 1). Of the 296 studies on CHM for depression, 61 of them examined pattern-based treatment. A total of 27 different TCM patterns were identified in the 61 studies. We analyzed the most commonly studied TCM patterns: *liver qi depression, liver depression and spleen deficiency, dual deficiency of the heart and spleen, and liver depression and qi stagnation* and *liver-kidney yin deficiency*. These four commonly studied TCM patterns were described in 42 of the 61 studies (68.9%) and involved 1762 subjects accounting for 70.4% of the total 2504 subjects (Table 1). Eighteen of the 42 studies examined CHM alone and the other 24 studies examined CHM plus antidepressants [24–65]. The 1762 participants had a mean age of 40.7 years, of which 59.0% were female. The participants were suffering

Table 1: The most common TCM patterns diagnosed in people with depression.

TCM pattern	Chinese name	Number of subjects diagnosed with the TCM pattern (%) (total $N = 1762$)	Number of studies that examined the TCM pattern (%) (total $N = 42$)[a]
Liver qi depression	肝氣鬱結	797 (45.2%)	19 (45.2%)
Liver depression and spleen deficiency	肝鬱脾虛	425 (24.1%)	13 (31.0%)
Dual deficiency of the heart and spleen	心脾兩虛	315 (17.9%)	9 (21.4%)
Liver depression and qi stagnation	肝鬱氣滯	225 (12.8%)	8 (19.0%)

[a]Six studies examined more than one TCM pattern.

from depression unspecified in 33 of the 42 studies, six studies on poststroke depression and three on depression comorbid with diabetes. The diagnosis of depression was based on 17-item or 24-item Hamilton Depression Rating Scale ($HAMD_{17/24}$) in 36 studies, the Chinese Classification of Mental Disorder Second/Second-revised/Third Edition (CCMD-2/2-R/3) in 35 studies, Zung Self-rating Depression Scale (SDS) in seven studies, and one study each using DSM-IV, Clinical Global Impression Scale (CGI), and International Classification of Diseases Version 10 (ICD-10). The response to intervention was assessed by the HAMD17/24 in 34 studies and by effective rate in 33 studies.

The criteria used for TCM pattern diagnosis were reported in 27 of the 42 studies. The criteria were based on the TCM Syndrome Diagnostic Standard ($N = 7$), New Guidelines for TCM Clinical Research ($N = 3$), TCM Diagnostic Standard for Depression ($N = 2$), Chinese Professional Association of Integrative Medicine Diagnostic Criteria for Mental Disorders, Version 1991/2001 ($N = 3$), Chinese Classification and Diagnostic Criteria of Mental Disorders ($N = 1$), and TCM textbooks ($N = 13$). However, none of the studies described other details of the diagnostic procedure and the background of practitioners who made the pattern diagnosis.

3.1. Methodological Quality. Twenty-three (54.8%) of the 42 studies were described as randomized but the randomization method, blinding, and dropouts were not presented; hence, these 23 studies only had a Jadad scale score of one. Seventeen studies (40.5%) had a Jadad scale score of two, and only two studies (4.8%) obtained a Jadad scale score of four.

3.2. Pattern-Based CHM Treatment

3.2.1. Liver qi Depression. According to the TCM theory, *liver qi depression* is an impairment of the *liver* function, obstructing free movement of *qi* and resulting in stagnation of *qi* in *liver* [21]. Nineteen studies examined CHM treatment in patients with *liver qi depression*. Seven studies used CHM alone and 12 used CHM-antidepressant combination. Xiaoyao decoction was investigated in 13 (68.4%) of the 19 studies, while other CHM formulas were studied in only one to two studies. Seventeen studies reported the ingredients of the CHM formulas for the treatment of *liver qi depression*. Chai Hu (*Bupleurum chinense* DC.) was the most commonly used herb, followed by Bai Shao (*Paeonia lactiflora* Pall.), Dang Gui (*Angelica sinensis* (Oliv.) Diels), Fu Ling (*Poria Cocos* (Schw) Wolf.), and Bai Zhu (*Atractylodes macrocephala* Koidz.). These five herbs were chosen for treating *liver qi depression* in more than half of the 17 studies that had reported the CHM ingredients (Table 2). The mean effective rate of Xiaoyao decoction for the treatment of *liver qi depression* was 84.7% and the mean HAMD change score was 19.1 (Table 3); for Xiaoyao decoction-antidepressant combination for *liver qi depression*, it was 86.0% and 19.1, respectively (Table 4). Tables 3 and 4 present the overall efficacy of pattern-based CHM monotherapy and CHM-antidepressant combination for *liver qi depression*.

3.2.2. Liver Depression and Spleen Deficiency. According to the TCM theory, *liver depression and spleen deficiency* is a pathological change in which the transporting and transforming function of the *spleen* is affected by depressed *liver qi*, leading to *spleen* deficiency [21]. Of the 13 studies on *liver depression and spleen deficiency*, three studies examined CHM alone and 10 investigated CHM-antidepressant combination. The most frequently used CHM formula was also Xiaoyao decoction, which was used in 9 of the 13 studies. Nine of the 13 studies provided ingredients of the CHM formulas. The commonly used single herbs for the treatment of *liver depression and spleen deficiency* were Bai Shao (*Paeonia lactiflora* Pall.), Fu Ling (*Poria Cocos* (Schw) Wolf.), Chai Hu (*Bupleurum chinense* DC.), Zhi Ke (*Citrus* × *aurantium* L.), Dang Gui (*Angelica sinensis* (Oliv.) Diels), and Bai Zhu (*Atractylodes macrocephala* Koidz.) (Table 2). Only one study was conducted on Xiaoyao decoction monotherapy for *liver depression and spleen deficiency*, and the HAMD change score was 7.3 (Table 3). The mean effective rate of Xiaoyao decoction-antidepressant combination for *liver depression and spleen deficiency* was 86.0% and the mean HAMD change score was 20.1 (Table 4). Tables 3 and 4 show the overall efficacy of pattern-based CHM monotherapy and CHM-antidepressant combination for *liver depression and spleen deficiency*.

3.2.3. Dual Deficiency of the Heart and Spleen. *Dual deficiency of the heart and spleen* is a condition in which both *heart blood* and *spleen qi* are deficient, leading to disordered *heart* function and an impairment of the transporting and transforming function of *spleen* [21]. There was significant

Table 2: The commonly used Chinese herbal medicine for depression in subjects diagnosed with different TCM patterns.

	Liver qi depression	*Liver depression and spleen deficiency*	*Dual deficiency of the heart and spleen*	*Liver depression and qi stagnation*
Number of studies that examined the TCM pattern	$N = 19$	$N = 13$	$N = 9$	$N = 8$
Commonly used Chinese herbal formula (N, % of studies that examined the TCM pattern)	Xiaoyao decoction (13, 68.4%)	Xiaoyao decoction (9, 69.2%)	Guipi decoction (2, 22.2%); Ningcao Wangyou decoction (2, 22.2%)	Chaihu Shugan decoction (5, 62.5%)
Number of studies that provided the composition of herbal formula	$N = 17$	$N = 9$	$N = 8$	$N = 6$
Number of studies that provided TCM treatment principle	$N = 6$	$N = 4$	$N = 3$	$N = 4$
Composition of herbal formula (% of studies that provided the formula's composition)[a]				
Bai He [*Lilium brownii* F.E.Br. ex Miellez]	11.8%	/	/	/
Bai Shao [*Paeonia lactiflora* Pall.]	70.6%	100%	50.0%	100%
Ban Xia [*Pinellia ternata* (Thunb.) Makino]	17.6%	11.1%	37.5%	16.7%
Bai Zhu [*Atractylodes macrocephala* Koidz.]	52.9%	55.6%	25.0%	16.7%
Bei Mu [*Fritillaria cirrhosa* D.Don]	/	/	25.0%	/
Bing Pian [*Dryobalanops aromatica* Gaertn. f.]	/	/	12.5%	/
Bo He [*Mentha haplocalyx* Briq.]	29.4%	33.3%	/	/
Bo Zi Ren [*Platyclatus orientalis* (L.) Franco]	/	/	50.0%	/
Chan Su [*Bufo bufo gargarizans* Cantor]	/	/	12.5%	/
Chai Hu [*Bupleurum chinense* DC.]	94.1%	77.8%	50.0%	83.3%
Cao Bai Zhu [*Atractylodes macrocephala* Koidz.]	5.6%	22.2%	/	/
Chen Pi [*Citrus reticulata* Blanco]	17.6%	33.3%	25.0%	33.3%
Chuan Xiong [*Ligusticum striatum* DC.]	17.6%	22.2%	25.0%	83.3%
Chi Wu Jia Pi [*Acanthopanax gracilistylus* W.W.Sm.]	/	/	12.5%	/
Dang Gui [*Angelica sinensis* (Oliv.) Diels]	64.7%	55.6%	12.5%	16.7%
Dan Pi [*Paeonia* × *suffruticosa* Andrews]	29.4%	11.1%	/	16.7%
Dan Shen [*Salvia miltiorrhiza* Bunge.]	11.8%	11.1%	25.0%	/
Da Zao [*Ziziphus jujuba* Mill.]	11.8%	/	50.0%	/
Fu Ling [*Poria Cocos* (Schw) Wolf.]	58.8%	88.9%	50.0%	33.3%
Fo Shou [*Citrus medica* L.]	/	22.2%	37.5%	/
Gan Cao [*Glycyrrhiza uralensis* Fisch.]	29.4%	22.2%	62.5%	33.3%
Gan Cao (Honey-toasted) [*Glycyrrhiza uralensis* Fisch.]	35.3%	33.3%	25.0%	16.7%
Gui Yuan [*Dimocarpus longan* Lour.]	/	/	37.5%	/
Gui Zhi [*Cinnamomum cassia* (L.) J.Presl]	/	/	12.5%	/
He Huan Hua [*Albizia julibrissin* Durazz.]	5.9%	/	/	16.7%
He Huan Pi [*Albizia julibrissin* Durazz.]	29.4%	22.2%	37.5%	50.0%
Huang Lian [*Coptis chinensis* Franch.]	/	/	12.5%	/

Table 2: Continued.

	Liver qi depression	*Liver depression and spleen deficiency*	*Dual deficiency of the heart and spleen*	*Liver depression and qi stagnation*
Huang Qin [*Scutellaria baicalensis* Georgi]	5.9%	11.1%	12.5%	/
Huang Qi (Honey-toasted) [*Astragalus membranaceus* (Fisch.) Bunge]	/	/	12.5%	/
Jiang [*Zingiber officinale* Roscoe]	23.5%	/	25.0%	/
Mai Dong [*Ophiopogon japonicus* (Thunb.) Ker Gawl.]	5.9%	/	12.5%	/
Mu Xiang [*Aucklandia lappa* DC.]	/	22.2%	12.5%	/
Niu Huang [Bos taurus domesticus Gmelin.]	/	/	12.5%	/
Qing Pi [*Citrus reticulata* Blanco]	/	11.1%	25.0%	33.3%
Ren Shen [*Panax ginseng* C.A.Mey.]	/	/	12.5%	/
Rou Gui [*Cinnamomum cassia* (L.) J.Presl]	/	/	12.5%	/
She Xiang [*Moschus berezovskii* Flerov]	/	/	12.5%	/
Di Huang [*Rehmannia glutinosa* (Gaertn.) DC.]	/	11.1%	12.5%	/
Shi Chang Pu [*Acorus tatarinowii* Schott]	41.2%	11.1%	/	/
Su He Xiang [*Liquidambar orientalis* Mill.]	/	/	12.5%	/
Tai Zi Shen [*Pseudostellaria heterophylla* (Miq.) Pax ex Pax et Hoffm.]	/	11.1%	12.5%	/
Xiang Fu [*Cyperus rotundus* L.]	23.5%	44.4%	/	83.3%
Xiao Mai [*Triticum aestivum* L.]	5.9%	/	25.0%	/
Ye Jiao Teng [*Reynoutria multiflora* (Thunb.) Moldenke]	5.9%	/	/	16.7%
Yu Jin [*Curcuma wenyujin* Y.H.Chen & C.Lin]	41.2%	11.1%	50.0%	100%
Yuan Zhi [*Polygala tenuifolia* Willd.]	23.5%	/	37.5%	16.7%
Zao Ren [*Ziziphus jujuba* var. *spinosa* (Bunge) Hu ex H.F.Chow]	35.3%	11.1%	25.0%	16.7%
Zhi Ke [*Citrus* × *aurantium* L.]	35.3%	66.7%	/	83.3%
Zhi Zi [*Gardenia jasminoides* J.Ellis]	41.2%	11.1%	/	16.7%

[a] Individual herbs used in at least 10% of the studies on a particular TCM pattern were listed.

Table 3: Effective rate and Hamilton Depression Rating Scale (HAMD) score of pattern-based Chinese herbal medicine treatment for depression.

Chinese herbal formula	Type of cases	Mean effective rate in % (range, 95% CI)	Mean HAMD change score (range, 95% CI)
Liver qi depression			
Xiaoyao decoction/pill ($N = 4$)	Depression ($N = 4$)	84.7 (70.0–93.3, 80.8–84.7)	19.1 (12.8–26.0, 18.4–19.9)
Chaihu Shugan decoction ($N = 2$)	Depression ($N = 1$); poststroke depression ($N = 1$)	90.0 (86.7–93.3, 88.8–91.2)	15.0 (14.6–15.4, 14.9–15.1)
Jieyu Heji ($N = 1$)	Depression ($N = 1$)	51.0 (NA)	NR
Yushu pill ($N = 1$)	Depression ($N = 1$)	74.3 (NA)	NR
All ($N = 8$)		85.1 (51.0–93.3, 77.3–80.9)	17.7 (12.8–26.0, 17.2–18.63)
Liver depression and spleen deficiency			
Xiaoyao decoction/pill ($N = 1$)	Depression comorbid diabetes ($N = 1$)	NR	7.3 (NA)
Yiqiyangyin Shuganjieyu decoction ($N = 1$)	Depression comorbid diabetes ($N = 1$)	83.3 (NA)	12.1 (NA)
Chaihu Shugan decoction ($N = 1$)	Depression ($N = 1$)	92.1 (NA)	NR
All ($N = 3$)		87.7 (83.3–92.1, 86.2–89.2)	9.7 (7.3–12.1, 8.9–10.5)
Dual deficiency of the heart and spleen			
Guipi decoction ($N = 1$)	Depression ($N = 1$)	NR	NR
Xiaochaihu Tang ($N = 1$)	Depression ($N = 1$)	NR	NR
Anshen Jieyu Fang decoction ($N = 1$)	Depression comorbid diabetes ($N = 1$)	NR	10.7 (NA)
Jieyu Yi Hao ($N = 1$)	Depression ($N = 1$)	90.0 (NA)	11.4 (NA)
Shexiang Baoxin pill ($N = 1$)	Depression ($N = 1$)	92.2 (NA)	NR
All ($N = 5$)		91.5 (90.0–92.2, 91.3–91.6)	10.8 (10.7–11.4, 10.6–11.0)
Liver depression and qi stagnation			
Chaihu Shugan decoction ($N = 2$)	Depression ($N = 2$)	89.8 (86.7–93.0, 88.8–90.9)	17.3 (13.9–20.7, 16.2–18.4)
Shujiele Wutang pill ($N = 1$)	Depression ($N = 1$)	91.4 (NA)	18 (NA)
All ($N = 3$)		90.4 (86.7–93.0, 89.7–91.0)	17.5 (13.9–20.7, 16.9–18.2)
All studies ($N = 18$) [a]		85.0 (51.0–93.33, 84.1–85.9)	15.4 (7.3–26.0, 15.0–15.8)

[a] One study studied more than one TCM pattern; NA: not applicable; NR: not reported.

Table 4: Effective rate and Hamilton Depression Rating Scale (HAMD) score of combined pattern-based Chinese herbal medicine treatment and antidepressants for depression.

Chinese herbal formula	Type of cases	Mean effective rate in % (range, SD, 95% CI)	Mean HAMD change score (range, 95% CI)
Liver qi depression			
Xiaoyao decoction/pill ($N = 9$)	Depression ($N = 6$); poststroke depression ($N = 3$)	86.0 (70.0–94.3, 85.1–87.0)	19.1 (11.4–23.2, 18.4–19.9)
Banxia Houpu decoction ($N = 1$)	Depression ($N = 1$)	97.2 (NA)	16.0 (NA)
Kaiyu Quhuo decoction ($N = 1$)	Depression ($N = 1$)	100 (NA)	NR
All ($N = 11$)		88.3 (70.0–100.0, 87.4–89.2)	17.8 (11.4–23.2, 17.5–18.2)
Liver depression and spleen deficiency			
Xiaoyao decoction/pill ($N = 8$)	Depression ($N = 8$)	86.0 (66.7–95.1, 84.6–87.4)	21.5 (20.4–23.0, 21.3–21.7)
Self-invented formula ($N = 1$)	Depression ($N = 1$)	91.7 (NA)	NR
Kuaiwei Shugan pill ($N = 1$)	Depression ($N = 1$)	NR	12.2 (NA)
All ($N = 10$)		86.8 (66.7–95.1, 85.6–88.0)	20.1 (12.2–23.0, 19.6–20.5)
Dual deficiency of the heart and spleen			
Guipi decoction ($N = 1$)	Depression comorbid diabetes ($N = 1$)	92.1 (NA)	NR
Ningcao Wangyou decoction ($N = 2$)	Depression ($N = 2$)	53.8 (NA)[a]	16.8 (NA)[a]
Ganmai Dazao decoction plus Suanzaoren decoction ($N = 1$)	Poststroke depression ($N = 1$)	100.0 (NA)	6.0 (NA)
All ($N = 4$)		77.0 (53.8–100.0, 68.7–85.2)	11.4 (6.0–16.8, 9.5–13.3)
Liver depression and qi stagnation			
Chaihu Shugan decoction ($N = 3$)	Depression ($N = 2$); poststroke depression ($N = 1$)	80.0 (NA)[a]	15.0 (8.9–21.1, 12.8–17.1)
Xiaoyao decoction/pill ($N = 2$)	Depression ($N = 2$)	NR	NR
All ($N = 5$)		80.0 (NA)	15.0 (8.9–21.1, 12.8–17.1)
All studies ($N = 24$)[b]		86.3 (53.8–100.0, 85.5–87.2)	17.7 (6.0–22.6, 17.4–18.0)

[a]Only one study presented the data; [b]five studies studied more than one TCM pattern; NA: not applicable; NR: not reported.

variation in the TCM pattern-based CHM treatment for *dual deficiency of the heart and spleen*. Of the 10 relevant studies, seven different CHM formulas were used. Guipi Tang and Ningcao Wangyou Tang were each used in two studies, while other CHM formulas were only examined once. The frequently used single herbs for *dual deficiency of the heart and spleen* were Gan Cao (*Glycyrrhiza uralensis* Fisch.), Bai Shao (*Paeonia lactiflora* Pall.), Chai Hu (*Bupleurum chinense* DC.), Fu Ling (*Poria Cocos* (Schw) Wolf.), Bo Zi Ren (*Platyclatus orientalis* (L.) Franco), Da Zao (*Ziziphus jujua* Mill.), and Yu Jin (*Curcuma wenyujin* Y. H. Chen & C. Lin) (Table 2). The mean effective rate of CHM monotherapy for *dual deficiency of the heart and spleen* was 91.5% and the mean HAMD change score was 10.8 (Table 3); for CHM-antidepressant combination, it was 77.0% and 11.4, respectively (Table 4).

3.2.4. Liver Depression and qi Stagnation. *Liver depression and qi stagnation* is a pathological change in which *liver* is depressed, leading to impeded circulation of *qi* and stagnation of *qi* movement [21]. The most frequently used CHM formula for *liver depression and qi stagnation* was Chaihu Shugan decoction (Table 3). The commonly used single herbs were Bai Shao (*Paeonia lactiflora* Pall.), Yu Jin (*Curcuma wenyujin* Y. H. Chen & C. Lin), Chai Hu (*Bupleurum chinense* DC.), Chuan Xiong (*Ligusticum striatum* DC.), Xiang Fu (*Cyperus rotundus* L.), Zhi Ke (*Citrus* × *aurantium* L.), Xiang Fu (*Cyperus rotundus* L.), and He Huan Pi (*Albizia julibrissin* Durazz.) (Table 2). The mean effective rate of CHM monotherapy for *liver depression and qi stagnation* was 90.4% and the mean HDRS change score was 17.5 (Table 3); for CHM-antidepressant combination, it was 80.0% and 15.0, respectively (Table 4).

4. Discussion

This study is the first systematic review of English and Chinese literature, involving 61 studies and 2504 subjects on the classification and treatment of depression using the TCM diagnostic system. We found that the TCM pattern diagnoses for depression were diverse. Among 27 different TCM patterns identified, *liver qi depression* was the most commonly diagnosed TCM pattern in people with depression, followed by *liver depression and spleen deficiency*, *dual deficiency of the heart and spleen,* and *liver depression and qi stagnation*. With regard to CHM treatment, Xiaoyao decoction was the most frequently used herbal formula for the treatment of *liver qi depression* and *liver depression and spleen deficiency*, while Chaihu Shugan decoction was often used for *liver depression and qi stagnation*. For *dual deficiency of the heart and spleen*, no single formula could be regarded as commonly used across TCM practitioners. The results suggest that TCM practitioners may be more consistent in the treatment of depression involving *liver depression* than other patterns. The abundance of low-quality studies highlights that knowledge and experience in conducting high-quality RCTs may be limited. It further suggests that institutional review boards and publishing journals should play an active role in monitoring the standards of clinical trials.

The present paper found that Bai Shao (*Paeonia lactiflora* Pall.), which has a function of nourishing the *blood* and emolliating the *liver*, and Chai Hu (*Bupleurum chinense* DC.), which can sooth the *liver*, were commonly used to treat depression regardless of the TCM pattern. Animal studies have found that extract from Bai Shao produces antidepressant effects in chronic unpredictable stress-induced depression model in mice and rats [66]. The antidepressant effects are likely mediated by inhibition of the monoamine oxidase activity and oxidative stress, upregulation of neurotrophins, and modulation of the function of the hypothalamic-pituitary-adrenal axis [66]. Pharmacological studies of Chai Hu have shown that it has hepatoprotective, anti-inflammatory, antipyretic, analgesic, and immunomodulatory effects [67–70]; however, its antidepressant effects remain unclear. According to a TCM textbook, Chai Hu is a "Sovereign" herb in Xiaoyao decoction and Chaihu Shugan decoction [69]. The "Sovereign" herb is used for treating the principal diseases based on the TCM theory; the "Minister" herb has synergistic effects with "Sovereign" herbs and helps to alleviate other accompanying symptoms; the "Assistant" herb is for enhancing the therapeutic effects and modulating the adverse effects of "Sovereign" and "Minister" herbs, while the "Courier" herb is used for harmonizing the actions of the others [66]. Therefore, some of the commonly used herbs identified in this review may not primarily be targeted at depression; instead, they indirectly alleviate depression by enhancing or harmonizing the actions of other herbs. In view of the common use of Chai Hu in the treatment of depression, further studies on its antidepressant effects are warranted.

Xiang Fu (*Cyperus rotundus* L.) and He Huan Pi (*Albizia julibrissin* Durazz.) were specifically used for *liver depression and qi stagnation*, and Bo Zi Ren (*Platyclatus orientalis* (L.) Franco), which has a function of nourishing the *heart* and tranquilizing *shen*, was specific for *dual deficiency of the heart and spleen*. Yu Jin (*Curcuma wenyujin* Y. H. Chen & C. Lin) was commonly used for *liver depression and qi stagnation* and *dual deficiency of the heart and spleen*, Fu Ling (*Poria Cocos* (Schw) Wolf.) for *liver qi depression*, *liver depression and spleen deficiency,* and *dual deficiency of the heart and spleen*, and Dang Gui (*Angelica sinensis* (Oliv.) Diels) and Bai Zhu (*Atractylodes macrocephala* Koidz.) for *liver qi depression* and *liver depression and spleen deficiency*. Since three of the four commonly diagnosed TCM patterns in people with depression involve *liver* depression and two involve *spleen* deficiency, the prescription of Chinese herbs for different TCM patterns are inevitably overlapping. A lack of consistency across TCM practitioners in their selection of herbal formulas and pattern-based prescription of individual herbs may also lead to variation in CHM treatment [70]. Considering the limited number of studies available, further research on pattern-based CHM treatment for depression is warranted.

Due to the studies' variation in study design and inadequate methodological quality, it is difficult to conclude which herbal formulas have higher efficacy and which TCM patterns respond better to CHM. As a whole, there is no evidence to suggest CHM-antidepressant combination has higher efficacy than CHM monotherapy for depression. We found

that the effective rate was generally high for pattern-based treatment in *liver qi depression* and was similar between CHM monotherapy and CHM-antidepressant combination. For *liver depression and spleen deficiency*, the efficacy of CHM monotherapy and CHM-antidepressant combination was similar in terms of effective rate, but it was lower with CHM monotherapy in terms of mean HAMD change score (9.7 versus 20.1 for CHM-antidepressants combination). For *dual deficiency of the heart and spleen*, the efficacy of pattern-based CHM treatment was relatively weaker, especially CHM-antidepressant combination, which had a mean effective rate of 77.0% and mean HAMD change score of 11.4. For *liver depression and qi stagnation*, the efficacy of CHM monotherapy and CHM-antidepressant combination was similar, except for a relatively low mean effective rate of CHM-antidepressant combination (80.9% versus 90.4% for CHM monotherapy). It is clear that further studies with better methodological quality are needed to delineate the efficacy of pattern-based CHM treatment in depression.

There are some methodologic limitations of the study. First, there is no "gold standard" in the classification of TCM patterns, and the criteria for each pattern might be different between researchers. Future studies using both Western and Chinese medicine systems in diagnosis and severity assessment may facilitate Western-Chinese medicine integration in the understanding and treatment of depression. Although we reported the pattern diagnosis by the authors, the procedure and quality of the diagnostic process was uncertain. Such uncertainties would inevitably lead to discrepancies in the selection of herbs in treatment. Although a large number of studies were reviewed, this paper only summarized the effective rate and HAMD change score based on RCTs; meta-analysis was not possible due to difference in study design and low methodological quality of the studies.

Despite the limitations, the present study, for the first time, systematically and comprehensively summarized important data on pattern-based CHM treatment for depression. Our data should be useful for both clinical practice and future research. More high quality studies incorporating TCM pattern differentiation and treatment principle are needed to examine the efficacy of TCM treatments and the additional benefit of pattern differentiation.

5. Conclusion

We found that *liver qi depression*, *liver depression and spleen deficiency*, *dual deficiency of the heart and spleen*, and *liver depression and qi stagnation* were the most commonly studied TCM patterns in people with depression. In addition, Bai Shao (*Paeonia lactiflora* Pall.) and Chai Hu (*Bupleurum chinense* DC.) were commonly used across different TCM patterns regardless of the prescribed Chinese herbal formulas. Due to the limited number of studies on TCM pattern-based treatment of depression and their low methodological quality, we are unable to draw any conclusion regarding which herbal formulas have higher efficacy and which TCM patterns respond better to CHM.

Conflict of Interests

The authors have no conflict of interests to report.

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Research Article

Mining Symptom-Herb Patterns from Patient Records Using Tripartite Graph

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Unlike the western medical approach where a drug is prescribed against specific symptoms of patients, traditional Chinese medicine (TCM) treatment has a unique step, which is called syndrome differentiation (SD). It is argued that SD is considered as patient classification because prior to the selection of the most appropriate formula from a set of relevant formulae for personalization, a practitioner has to label a patient belonging to a particular class (syndrome) first. Hence, to detect the patterns between herbs and symptoms via syndrome is a challenging problem; finding these patterns can help prepare a prescription that contributes to the efficacy of a treatment. In order to highlight this unique triangular relationship of symptom, syndrome, and herb, we propose a novel three-step mining approach. It first starts with the construction of a heterogeneous tripartite information network, which carries richer information. The second step is to systematically extract path-based topological features from this tripartite network. Finally, an unsupervised method is used to learn the best parameters associated with different features in deciding the symptom-herb relationships. Experiments have been carried out on four real-world patient records (Insomnia, Diabetes, Infertility, and Tourette syndrome) with comprehensive measurements. Interesting and insightful experimental results are noted and discussed.

1. Introduction

Traditional Chinese medicine (TCM) has a long history and has been accepted as one of the main medical approaches in China [1]. Many of the herbal medicines used in today's clinical practice and some of the traditional Chinese medicine preparation has been used in human patients for thousands of years, which has been successfully applied to the treatment of many diseases, such as insomnia, diabetes, infertility, and Tourette syndrome. Unlike the western medical approach where a drug is prescribed against specific symptoms of patients, TCM treatment has a unique step, which is called syndrome differentiation (SD). It is argued that SD is, in fact, patient classification because, prior to the personalization of the most appropriate formula, a practitioner has to label a patient belonging to a particular class (syndrome) for a set of relevant formulae. Hence, to detect the patterns between herbs and symptoms via syndrome is a challenging problem; finding these patterns can help prepare a prescription that contributes to the efficacy of a treatment.

In recent years, interest in TCM has increased globally and the application of data mining to TCM [2–4] is also getting more attention. However, most of the previous research was related to the extraction of core herbs or to mine herb-herb relationships [1, 5, 6] from a network of herbs. We term this kind of network as a homogeneous information network, that is, network consisting of only one type of objects (herb in this example). When a network contains different types of objects (such as herbs, symptoms, and syndromes), we refer to them as heterogeneous information networks. Since heterogeneous information networks are not well studied, this has become the motivation of our work.

In general, a homogeneous information network can be derived from a heterogeneous information network, for

example, an herb-herb network can be derived from a symptom-syndrome-herb network by a projection on herbs only. A heterogeneous information network is different from a homogeneous information network because it carries richer information than its corresponding projected homogeneous information networks. Therefore, it aimed to discover herb-symptom patterns, via syndromes, from a heterogeneous information network, which contains different types of attribute values associated with objects. To the best of our knowledge, this is the first attempt towards mining herb-symptom patterns in TCM utilizing heterogeneous information networks.

In this research, we construct the heterogeneous information network leveraging the tripartite graph. Our heterogeneous information network contains multiple types of objects, such as herb, symptom, syndrome, and multiple types of links defining different relations among these objects, such as links existing between herbs and syndromes, between syndromes and symptoms, and between symptoms and herbs. Thus, the number of different types of objects there are in the network can be found out, as well as the identification of the possible links existing among objects. Furthermore, we can detect the patterns between herbs and symptoms.

The major contributions of this paper are summarized.

(1) We construct the TCM heterogeneous information network utilizing the tripartite graph.

(2) We study the problem of the symptom-herb relationship prediction in TCM heterogeneous information network.

(3) We propose a novel three-step prediction approach based on the TCM heterogeneous information network to discover symptom-herb patterns.

(4) Experiments on real TCM patient records indicate that our proposed method can mine symptom-herb relationships with high accuracy.

(5) Treatments are proven to be more effective than a direct symptom-herb relationship; that is, classifying patients into different syndromes is a crucial step in TCM treatment.

The remaining of the paper is organized as follows. We first introduce the background and preliminaries on TCM heterogeneous information networks and denote the task of symptom-herb pattern prediction in Section 2. In Section 3, we obtain some interesting observations based on TCM heterogeneous information network. We next present a novel three-step mining approach to discover the symptom-herb patterns in Section 4. We report our experiments and results in Section 5, discuss related work in Section 6, and conclude the study in Section 7.

2. Preliminaries and Problem Definition

2.1. Notations Definitions. In this work, we need to consider three types of entities: a set of herbs $H = \{h_1, h_2, \ldots, h_n\}$, a set of syndromes $D = \{d_1, d_2, \ldots, d_m\}$, and a set of symptoms $P = \{p_1, p_2, \ldots, p_q\}$. We assume that there are n herbs, m syndromes, and q symptoms. Here, symptoms refer to something that can be observed and measured, such as fever, nausea, coughing, and weight loss. Syndrome is a special phenomenon in TCM. A TCM doctor will base upon the patient's symptoms and classify them into one or two syndromes. After that, formulas will be prescribed according to the syndrome.

2.2. Heterogeneous Information Network. We first introduce the definitions of heterogeneous information network [7, 8], tripartite graph [9], and tritype information network, so as to study the characteristic of TCM and discuss how to find or predict symptom-herb patterns in TCM information network.

Definition 1 (heterogeneous information network). A heterogeneous information network is denoted as a directed graph $G = (V, E, W)$ with an entity type mapping function $\phi : V \rightarrow \mathscr{A}$ and a link type mapping function $\psi : E \rightarrow \mathscr{R}$, where each entity $v \subseteq V$ belongs to one particular entity type $\phi(v) \subseteq \mathscr{A}$, each link $e \subseteq E$ belongs to a particular relation type $\psi(e) \subseteq \mathscr{R}$, and $W : E \rightarrow R^+$ is a weight mapping from an edge $e \subseteq E$ to a real number $w \subseteq R^+$. Notice that, when the types of entities $|\mathscr{A}| > 1$ and also the types of relations $|\mathscr{R}| > 1$, the network is called heterogeneous information network.

Definition 2 (tripartite graph). A graph $\mathrm{TG} = \langle\{V_1 \cup V_2 \cup V_3\}, E\rangle$ can be called as tripartite, if a set of graph nodes decomposed into three disjoint sets such that no two graph nodes within the same set are adjacent; that is, $V_1 \cap V_2 \cap V_3 = \emptyset$.

Definition 3 (tritype information network). Given three types of objects sets X, Y, and Z, where $X = \{x_1, x_2, \ldots, x_m\}$, $Y = \{y_1, y_2, \ldots, y_n\}$, and $Z = \{z_1, z_2, \ldots, z_q\}$, graph $G = \langle V, E\rangle$ is called a tritype information network on types X, Y, and Z, if $V(G) = X \cup Y \cup Z$ and $E(G) = \{\langle o_i, o_j\rangle\}$, where $o_i, o_j \in X \cup Y \cup Z$.

Let $W_{(m+n)*(m+n)} = \{\langle w_{o_i o_j}\rangle\}$ (or $W_{(n+q)*(n+q)} = \{\langle w_{o_i o_j}\rangle\}$ or $W_{(m+q)*(m+q)} = \{\langle w_{o_i o_j}\rangle\}$) be the adjacency matrix of links, where $\langle w_{o_i o_j}\rangle$ equals the weight of link $\langle o_i, o_j\rangle$, which is the observation number of the link, and we thus use $G = \langle\{X \cup Y \cup Z\}, W\rangle$ to define this tritype information network with weight. In the following, we use X, Y, and Z denoting the object set and their type name. For convenience, we decompose the link matrix into four blocks: W_{XX}, W_{XY}, W_{YX}, and W_{YY} (or W_{YY}, W_{YZ}, W_{ZY}, and W_{ZZ} or W_{XX}, W_{XZ}, W_{ZX}, and W_{ZZ}), each denoting a subnetwork of objects between types of the subscripts. W can be denoted as

$$W = \begin{pmatrix} W_{XX} & W_{XX} \\ W_{YX} & W_{YY} \end{pmatrix} \quad \text{or} \quad W = \begin{pmatrix} W_{YY} & W_{YZ} \\ W_{ZY} & W_{ZZ} \end{pmatrix} \quad \text{or } W = \begin{pmatrix} W_{XX} & W_{XZ} \\ W_{ZX} & W_{ZZ} \end{pmatrix}. \tag{1}$$

This tritype information network, one of the heterogeneous information networks, denotes the rules of how entities exist and how links should be created. And, through

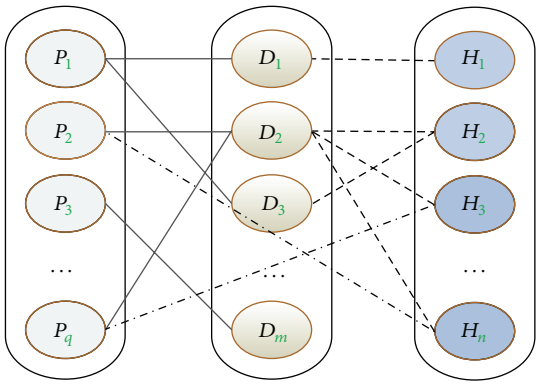


Figure 1: Tripartite graph structure of TCM. Here, instances of different objects are represented by different colour nodes and links among different objects are represented by different line styles. q, m, and n represent the number of symptom, the number of syndrome, and the number of herb, respectively.

Table 1: Properties of four TCM data sets. Here, "—" represents that this attribute can not be included in this data set.

	Insomnia	Infertility	Diabetes	Tourette
Number of prescriptions	460	852	1674	670
Number of herbs	111	251	204	189
Number of symptoms	155	389	186	—
Number of syndromes	—	106	178	98
Symptoms per herb	82.58	71.64	84.72	—
Syndromes per herb	—	24.34	29.56	20.56
Herbs per symptom	59.14	46.4	33.89	—
Herbs per syndrome	—	57.41	92.91	71.13

analyzing this tritype information network, we can know how many types of objects there are in the network and where the possible links exist. In the following, we give an example of tritype information network, which is showed in Figure 1. Here, as an abbreviation, we utilize the special letters to define these entity types, namely, H representing herbs, P representing symptoms, and D representing syndromes. Notations and similarity relations used in definitions as well as the rest part of the paper can be found in Notation section.

2.3. Target Relationship Prediction. Based on the previous definitions, our goal of this work can be summarized as follows: given a tritype network $G = \langle\{H \cup D \cup P\}, W\rangle$, the target type P, and a set of herbs $\{H_j\}$, our goal is to find or predict the most reasonable herbs for each symptom P_i, that is, how to predict the target relationship $E(G) = \{\langle P_i, H_j\rangle\}$, where $P_i, H_j \in P \cup H$.

Different from symptom-syndrome patterns and syndrome-herb patterns, which are directed relationships (because patients' syndromes are derived from a set of patients symptoms and herbs are configured by doctors according to the patients' syndromes, symptom-syndrome patterns and syndrome-herb patterns are directed relationships.), symptom-herb patterns are undirected relationships. Intuitively, the herb-symptom relationship detection is an implicit relationship mining, which is more difficult to detect than an explicit relationship mining. However, if new herb-symptom relationships can be discovered, they are beneficial for doctors configuring the prescriptions.

2.4. Dataset. In this work, our experiments were performed on four real TCM datasets: Insomnia, Infertility, Diabetes, Tourette. These four datasets were provided by Guang'anmen Hospital, China Academy of Chinese Medical Sciences. These four datasets include the symptoms, the syndromes, and prescription information of outpatients. Here, edges are formed among objects belonging to the same prescription. Properties of these four datasets are shown in Table 1.

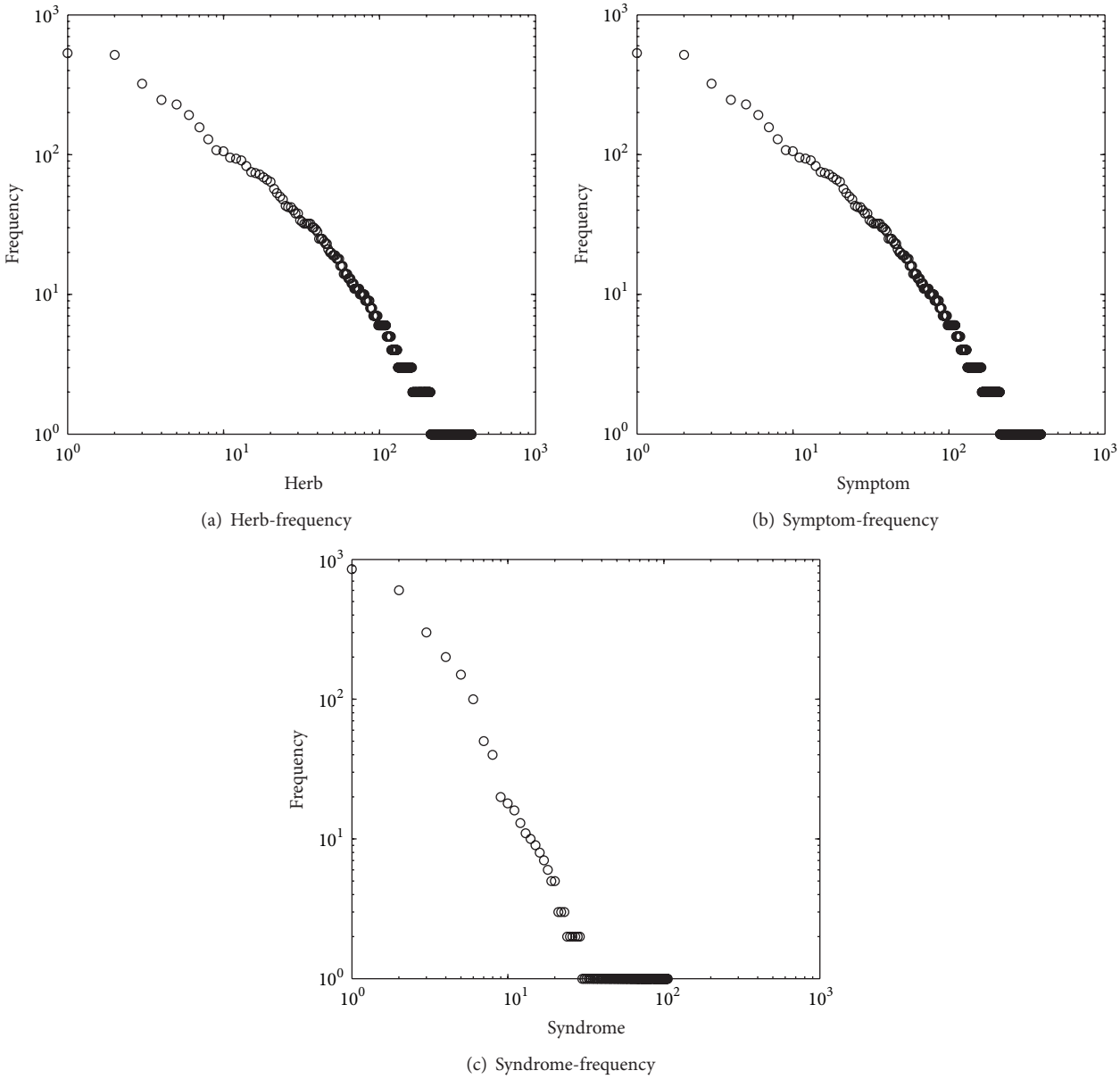
3. Observation

In this section, we conduct following observations based on the four TCM datasets in order to get a better understanding on the symptom-syndrome-herb patterns and structural properties of TCM tripartite network.

3.1. Entity Distribution. We first study the distribution of each entity frequency. Figure 2 plots the distribution in a log-log scale based on the Infertility dataset. In Figure 2(a), the x-axis represents the 251 unique herbs, ordered by descending herb frequency. The y-axis refers to the herb frequency. As reported by other authors [5, 10], we find the herb frequency to follow a power law distribution with few herbs being responsible for a high number of prescriptions. Here, the probability of a kind of herb having herb frequency x is proportional to $x^{-0.843}$. It indicates that most herbs are rarely used, while only a small number of the herbs are frequently used. In other words, the head of the power law contains herbs that would be used more frequently and the very tail of the power law contains the infrequent herbs. The most frequent herbs were used more than 530 times by different prescriptions altogether. Similarly, same distributions can be found in Figures 2(b) and 2(c).

In addition to the infertility dataset, we carried on similar statistical analysis with other three datasets, and the same pattern is observed in the vast majority of cases.

3.2. Link Distribution. So far, there is some existing work that explicitly addresses herb-herb patterns [5, 6]. They indicated that there are common herb pairs frequently used in the regular TCM herb prescriptions. However, few works focus on studying symptom-herb, symptom-syndrome, and



(a) Herb-frequency

(b) Symptom-frequency

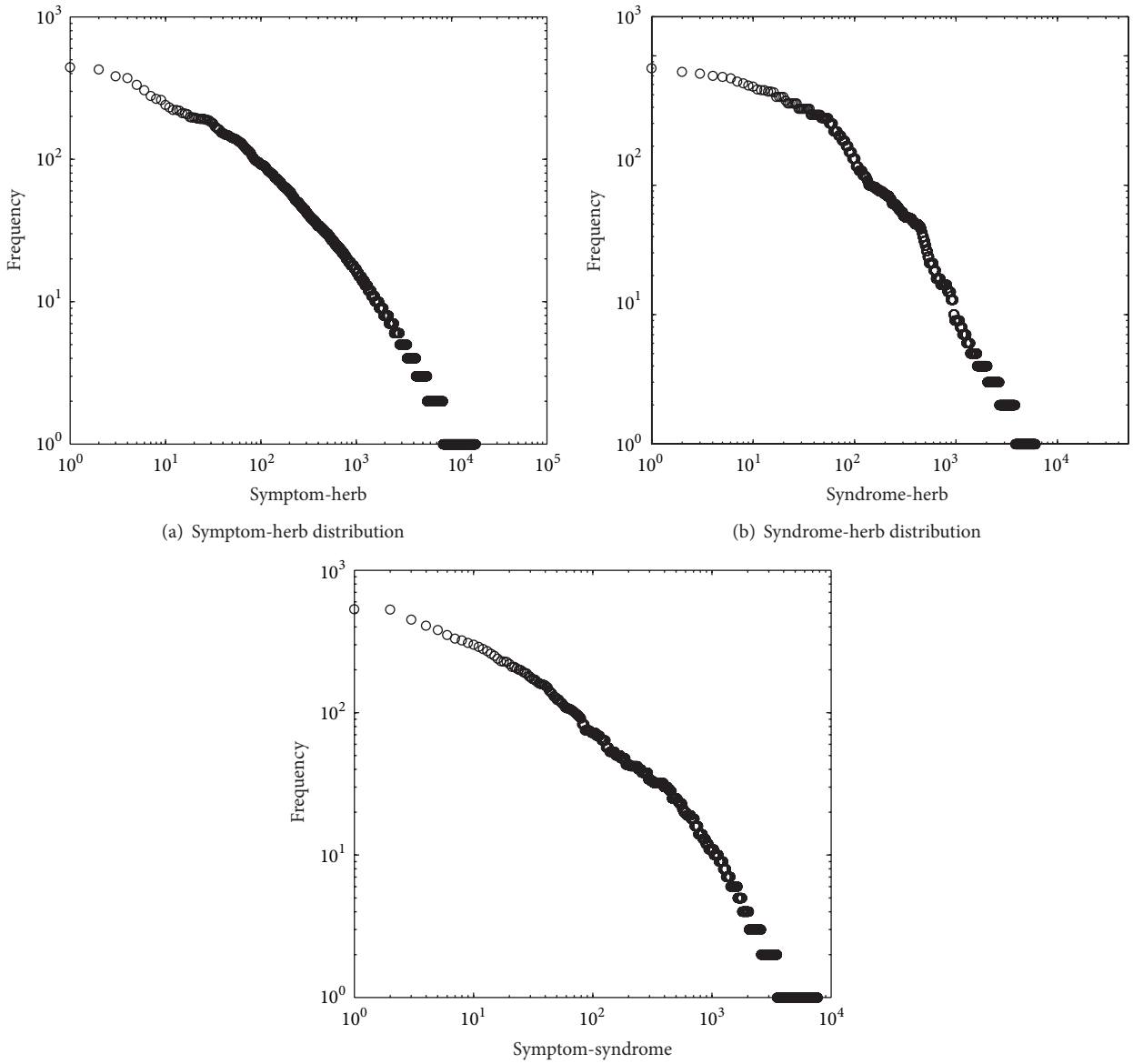
(c) Syndrome-frequency

Figure 2: Distribution of the entity frequency in Infertility Dataset. Here, in (a), the x-axis represents the 251 unique herbs, ordered by descending herb frequency. The y-axis refers to the herb frequency. In (b), the x-axis represents the 389 unique symptoms, ordered by descending symptom frequency. The y-axis refers to the symptom frequency. In (c), the x-axis represents the 106 unique syndromes, ordered by descending syndrome frequency. The y-axis refers to the syndrome frequency.

syndrome-herb patterns. In this work, we extract these patterns and analyze what distribution they obey.

Figure 3 shows that the distribution of these patterns (symptom-herb, symptom-syndrome, and syndrome-herb patterns) also follows a power law distribution. In Figure 3(a), the x-axis represents the 17,910 symptom-herb patterns, ordered by their cooccurrence frequency (descending). The y-axis refers to the symptom-herb frequency. Furthermore, we find that 80% of all symptom-herb patterns appear only 1–3 times in the infertility dataset. Here, the probability of a kind of symptom-herb pattern having symptom-herb pattern frequency x is proportional to $x^{-0.945}$. This indicates that there are common herb-symptom pairs frequently used in the regular TCM herb prescriptions. If we can predict these common herb-symptom pairs, it is very useful for a doctor configuring a formulae. Again, the same law distributions can be found in Figures 3(b) and 3(c).

3.3. Relationship Distribution. Furthermore, we study the relationship among symptom, syndrome, and herb. Here, the relationship also exists among symptom, syndrome, and herb. It is a one-to-many relationship, that is, the number of herbs each symptom is associated with, the number of



(a) Symptom-herb distribution

(b) Syndrome-herb distribution

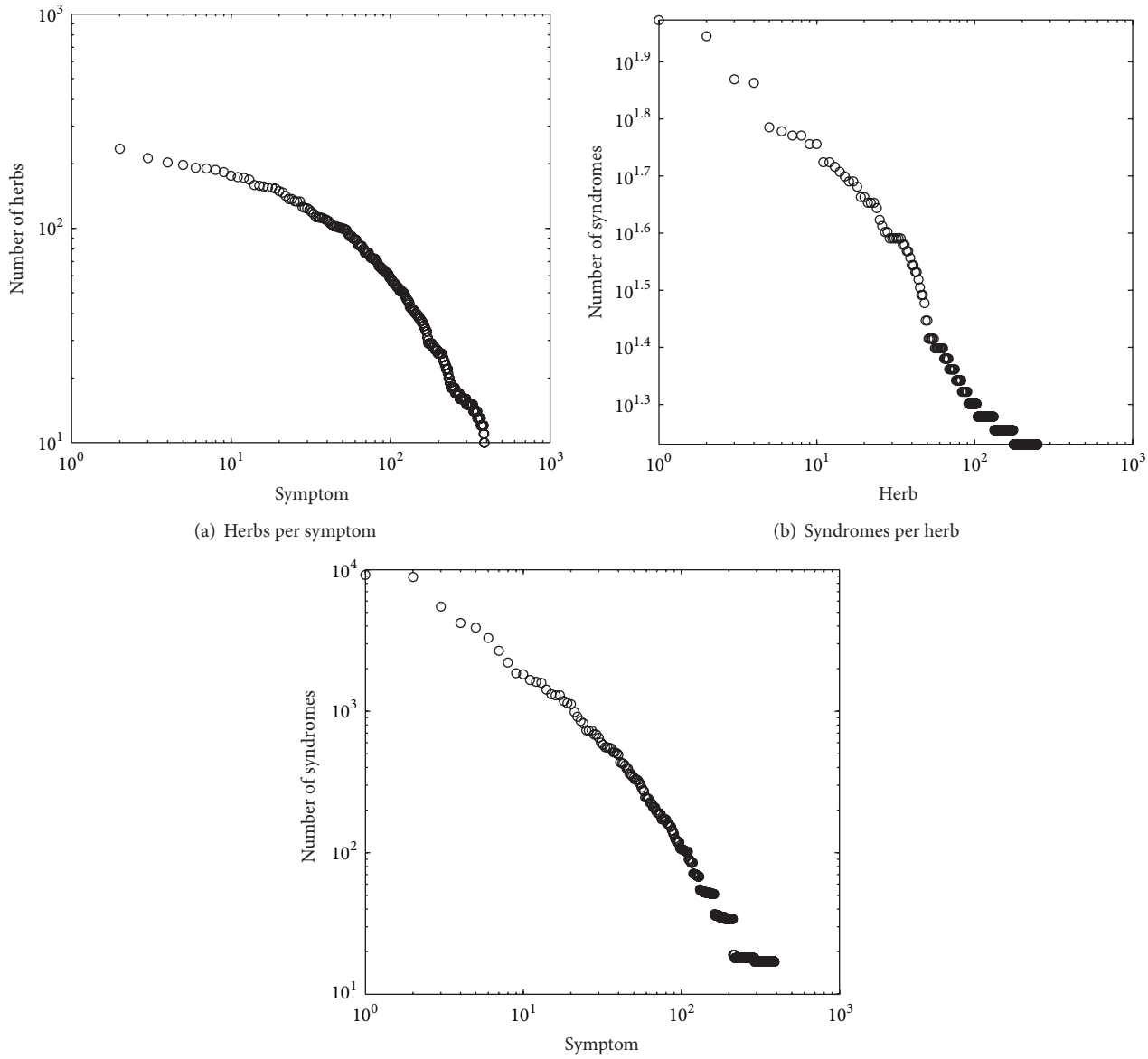
(c) Symptom-syndrome distribution

Figure 3: Distribution of the link frequency in Infertility Dataset. Here, in (a), the x-axis represents the 17,910 symptom-herb patterns, ordered by descending symptom-herb frequency. The y-axis refers to the symptom-herb frequency. In (b), the x-axis represents the 6,085 syndrome-herb patterns, ordered by descending syndrome-herb frequency. The y-axis refers to the syndrome-herb frequency. In (c), the x-axis represents the 7,897 symptom-syndrome patterns, ordered by descending symptom-syndrome frequency. The y-axis refers to the symptom-syndrome frequency.

syndromes each herb is associated with, and so forth. Figure 4 shows that the distribution of the number of herbs per symptom (syndromes per herb or syndromes per symptom) also follows a power law distribution. In Figure 4(a), the x-axis represents the 389 unique symptoms, ordered by the number of herbs per symptom (descending). The y-axis refers to the number of herbs per symptom. The probability of having x herbs per symptom is proportional to $x^{-0.51}$. We can find each symptom to be labeled with 46.4 herbs on average. Also, it can be found for the occurrence frequencies of herbs per symptom where 23.2% of all herbs link to the Top 1% of symptoms. Similarly, the same law distributions can be found in Figures 4(b) and 4(c).

4. Prediction Method Based on Tripartite Graph

In this section, we will introduce a novel three-step prediction approach based on the tripartite graph (Tri-TSPA). First, we extract two types of paths, which carry different semantic meanings. In terms of these two paths, we draw three matrices, which represent different cooccurrence relationship. And



(a) Herbs per symptom

(b) Syndromes per herb

(c) Syndromes per symptom

Figure 4: Distribution of relationship of objects in Infertility Dataset. Here, in (a), the x-axis represents the 389 unique symptoms, ordered by the descending number of herbs per symptom. The y-axis refers to the number of herbs per symptom. In (b), the x-axis represents 251 unique herbs, ordered by descending number of syndromes per herb. The y-axis refers to the number of syndromes per herb. In (c), the x-axis represents the 389 unique symptoms, ordered by the descending number of syndromes per symptom. The y-axis refers to the number of syndromes per symptom.

then, we propose an unsupervised prediction method in order to discover symptom-herb patterns.

4.1. Extracting Paths. In a tripartite network, two entities can be connected by different paths, which carry different semantic meanings. In this work, we choose two kinds of paths in order to find the reasonable symptom-herb patterns. These two kinds of paths are taken as follows:

$$\begin{aligned} &PH\_\text{Path: Symptom} \longrightarrow \text{Herb} \\ &PDH\_\text{Path: Symptom} \longrightarrow \text{Syndrome} \longrightarrow \text{Herb}. \end{aligned} \tag{2}$$

Path $PH_$Path extracts the direct target relationship; it looks like the way western medicine often adopts. In western medicine, medical doctors and other healthcare professionals (such as nurses, pharmacists, and therapists) treat diseases using drugs, radiation, or surgery according to symptoms [11]. Path $PDH_$Path extracts the indirect target relationship, it is a common way TCM often adopts. In TCM, doctors first choose a series of syndromes in terms of patients' symptoms, and, then, configure herbs on the basis of syndromes.

4.2. Constructing Matrix. After extracting paths from the tripartite graph, we can further construct matrices describing

the relationship among different entities, such as symptom-herb, symptom-syndrome, and syndrome-herb. In this work, we build the three matrices, namely, symptom-herb matrix based on the path *PH*_Path, symptom-syndrome matrix, and syndrome-herb matrix based on the path *PDH*_Path.

In addition, we also build matrices depicting the relationship among same entities, such as herb-herb, symptom-symptom, and syndrome-syndrome, in order to promote the similarity measure and find some useful symptom-herb patterns. These three matrices can be extracted based on the homogeneous information networks (here, if two herbs (or symptoms, syndromes) belong to the same prescription and they produce the positive effect when used together, we can connect these two herbs. According to this rule, the homogeneous information networks can be constructed), including herb, symptom, and syndrome homogeneous information networks.

In order to build aforementioned matrices, we define and implement multiple measurement strategies in this work. These strategies can be introduced as follows.

(i) *Frequency* (F). Frequency is a basic strategy, which is an observation number of cooccurrence of two entities (A_x and A_y), such as symptom-herb, symptom-syndrome, and syndrome-herb. It can be defined as $F(A_x, A_y)$:

$$F\left(A_x, A_y\right) = \left|\left\{\left\langle A_x, A_y\right\rangle : A_x, A_y \in P \cup D \cup H\right\}\right|. \quad (3)$$

(ii) *Jaccard Coefficient* (JC). According to the Jaccard coefficient [12], we can normalise the cooccurrence of two entities A_x and A_y by calculating

$$\mathrm{JC}\left(A_x, A_y\right) = \frac{\left|A_x \cap A_y\right|}{\left|A_x \cup A_y\right|}. \quad (4)$$

The coefficient takes the number of intersections between the two entities, divided by the union of the two entities. The Jaccard coefficient is known to be useful to measure the relevance between two objects or sets. In general, we can use symmetric measures, like Jaccard, to induce whether two entities have a related meaning.

(iii) *Asymmetric Measure* (AM). The cooccurrence of two entities A_x and A_y can be normalised leveraging the frequency of one of the entities [13–15], for instance, using equation

$$\mathrm{AM}\left(A_x \mid A_y\right) = \frac{\left|A_x \cap A_y\right|}{\left|A_y\right|}. \quad (5)$$

AM captures how often the entity A_y cooccurs with entity A_x normalised by the total frequency of entity A_y. We can interpret this as the probability of a patient being diagnosed with entity A_x given entity A_y occuring.

(iv) TfIdf. It is often used as a weighting factor in information retrieval and text mining [16]. In this work, we denote $\mathrm{Tf}(A_x, A_y) = F(A_x, A_y)$, which is the frequency of two entities (A_x and A_y) cooccurrence and define $\mathrm{Idf}(A_x, A_y) = \log(N/F(A_x, A_y))$, which measures the importance of A_x-A_y patterns for the entity A_x (or A_y). Thus, $\mathrm{TfIdf}(A_x, A_y)$ can be denoted as follows:

$$\mathrm{TfIdf}\left(A_x, A_y\right) = F\left(A_x, A_y\right) \log \frac{N}{F\left(A_x, A_y\right)}, \quad (6)$$

where N is the frequency of A_x (or A_y).

4.3. Symptom-Herb Patterns Prediction Method. In this subsection, we first show two similarity measures. And then, we introduce a relevance function. Finally, we proposed an unsupervised prediction method.

4.3.1. Similarity Measures. A similarity measure is a real-valued function that quantifies the similarity between two objects. In this work, taking the symptom as an example, if two symptoms are similar, they are likely to have similar frequency of symptom-herb patterns. Given symptom p_1, p_2, and herb h_1, if p_1 is similar to p_2, and there exists the p_1-h_1 pattern, we can infer that there exists the pattern p_2-h_1.

As mentioned previously, we have extracted two kinds of paths and built three matrices. Also, we have built other three homogeneous matrices. Based on them, we proposed two strategies measuring the similarity of entities of the same type.

(i) *PH*_Path based similarity: On basis of the symptom-herb matrix and symptom-symptom matrix, we use cosine similarity sim*PH* and sim*PP* to compute symptoms similarity, respectively. By combining sim*PH* and sim*PP*, we can get *PH*_Path based similarity. It can be denoted as

$$\mathrm{sim}PH\_\mathrm{Path}\left(p_x, p_y\right) = \lambda_0 \mathrm{sim}PH + \lambda_1 \mathrm{sim}PP, \quad (7)$$

where $\lambda_0, \lambda_1 > 0$ and $\lambda_0 + \lambda_1 = 1$. sim*PH* reflects the frequency similarity of symptom-herb patterns. In other words, if two symptoms are similar, they are likely to have similar frequency of symptom-herb patterns. sim*PP* reflects the frequency similarity of symptom-symptom patterns. In other words, if two symptoms belong to the same prescription, they are likely to be similar.

(ii) *PDH*_Path based on similarity: In terms of the symptom-syndrome matrix, syndrome-herb matrix, and syndrome-syndrome matrix, we can obtain two syncretic syndrome similarities, $\mathrm{sim}PDH_1(d_x, d_y)$ and $\mathrm{sim}PDH_2(d_x, d_y)$. Furthermore, through combining these two syncretic syndrome similarities, *PDH*_Path based on similarity can be formalized as

$$\mathrm{sim}PDH\_\mathrm{Path}\left(d_x, d_y\right) = \alpha \mathrm{sim}PDH_1 + \beta \mathrm{sim}PDH_2, \quad (8)$$

where the definition of $\text{sim}PDH_1$ and $\text{sim}PDH_2$ is simlar to $\text{sim}PH\_\text{Path}$, but their only difference is that $\text{sim}PDH_1$ and $\text{sim}PDH_2$ are based on the symptom-syndrome matrix, syndrome-herb matrix, and syndrome-syndrome matrix. Here, $\text{sim}PDH_1(d_x, d_y) = \alpha_0 \text{sim}PD(d_x, d_y) + \alpha_1 \text{sim}DD(d_x, d_y)$ and $\text{sim}PDH_2(d_x, d_y) = \beta_0 \text{sim}DH(d_x, d_y) + \beta_1 \text{sim}DD(d_x, d_y)$. Note that, $\alpha, \alpha_0, \alpha_1, \beta, \beta_0, \beta_1 > 0$ and $\alpha + \beta = 1$ and $\alpha_0 + \alpha_1 = 1$, $\beta_0 + \beta_1 = 1$.

4.3.2. Relevance Function. In our datasets, the outcomes of all the prescriptions are classified into two categories: good and bad. When a treatment was effective, which means that if the patient recovered completely or partly from diseases in the next encounter, then the prescription of the current encounter would be categorized as "good"; otherwise, the prescription would be categorized as "bad." In other words, when the outcome of a prescription is good, the patterns in this prescription, such as symptom-herb, symptom-syndrome, herb-herb, and others, make the positive role; otherwise, the patterns make a negative role.

In this work, relevance function is used to filter out the patterns with bad outcome. Here, the relevance function is parameterized with "relevance threshold" $\theta \in [0, 1]$ to provide a range of tolerance to bad outcomes. In particular, given a relevance function $R(\langle A_x, A_y \rangle \mid \theta)$, the relevance threshold θ is used for creating the parameterized version of this relevance function, $R(\langle A_x, A_y \rangle \mid \theta)$, that is formalized as

$$R = \begin{cases} 1 & \text{if } A_x \cap A_y \neq \emptyset, \ \text{ratio} \in (\theta, 1] \\ 0 & \text{else,} \end{cases} \tag{9}$$

where θ changes over different datasets. $A_x, A_y \in X \cup Y \cup Z$ and ratio = Good_Outcome(Pattern)/(Good_Outcome(Pattern) + Bad_Outcome(Pattern)). Here, Good_Outcome(Pattern) refers to the total number of this pattern working effectively, and Bad_Outcome(Pattern) is the total number of this pattern having no effect on patients. In the next section, patterns of symptom-herb that are predicted above relevance threshold θ (i.e., $R(\langle A_x, A_y \rangle \mid \theta) = 1$) are sorted according to predicted rating, while patterns of symptom-herb that are below θ (i.e., $R(\langle A_x, A_y \rangle \mid \theta) = 0$) are ignored.

4.3.3. Proposed Method. Up to now, we have given a systematic way to extract and build the topological features in the tripartite networks. In this subsection, we will introduce our prediction algorithm (Tri-TSPA). Our prediction method is as follows: first, we discover K nearest entities according to the similarity measures, $\text{sim}PH\_\text{Path}(A_x, A_y)$ or $\text{sim}PDH\_\text{Path}(A_x, A_y)$; then, we predict rating for each potential entity pair; subsequently, we get Top-n predicted patterns by ranking prediction rating; lastly, we get Top-N list by filtering the patterns of bad outcome using relevance function. The pseudocode of Tri-TSPA is shown in Algorithm 1.

In Algorithm 1, we only show the F measurement strategy to calculate the rating. Actually, we can replace $F(\cdot, \cdot)$ with $\text{JC}(\cdot, \cdot)$, $AW(\cdot, \cdot)$, and $\text{TfIdf}(\cdot, \cdot)$, respectively. In addition, PH_Path based on symptom-herb patterns mining is shown in Line 4–line 7, and PDH_Path based on symptom-herb patterns mining is shown in Line 8–Line 11.

5. Experiments

In this section, we conduct many experiments to evaluate the effectiveness of the proposed algorithm. We show that our proposed three step prediction approach can mine a reasonable set for each symptom on the TCM networks.

5.1. Experiment Setup. We first convert these datasets into heterogeneous tripartite information networks. We construct four TCM networks from TCM datasets, which consist of three types of objects: symptoms, syndromes, and herbs. Links exist between symptoms and syndromes, syndromes and herbs, and herbs and symptoms.

In order to effectively mine symptoms-herbs patterns, we adopt two kinds of strategies: PH_Path based strategy and PDH_Path based strategy. For each strategy, we apply four different measurement methods to set each term of each matrix related to this PH_Path (or PDH_Path). By combining these two kinds of strategies and four measurement methods together, we get total 8 different predicted methods. In the following section, a series of experiments will be carried on in order to find which predicted method can get the best performance.

In this work, we adopt twofold cross-validation (i.e., half training and half testing) to evaluate the performance of the prediction for each TCM network. In the training stage, we first extract two kinds of paths, symptom-herb path and symptom-syndrome-herb path. In terms of these two paths, we further build five matrices (in Section 4) according to the measurement method aforementioned (F, JC, AM, and TfIdf). After collecting all associated features, a training model is then built to learn the best coefficients associated with different features in deciding the symptom-herb patterns by performing multiple experiments. In the test stage, we utilize the learned coefficients to predict the potential patterns between symptoms and herbs and record whether this pattern is to appear in the test dataset.

In addition, the Insomnia and Tourette dataset lacks the object of syndrome and symptom, respectively. In this case, we assume some virtual objects (representing syndromes or symptoms) which can be constructed according to the next method. Here, we take the Insomnia dataset as an example to explain how to construct the virtual objects, namely, syndromes. First, we can get the existing patterns based on the PDH_Path from Infertility and Diabetes datasets, such as p_1-d_1-h_1, p_2-d_1-h_1; meanwhile, we can obtain the existing patterns based on the PH_Path from Insomnia dataset, such as p_1-h_1, p_2-h_1. Second, we can further check whether the patterns based on the PH_Path from Insomnia dataset exist in the dataset Insomnia or Tourette. If they exist (i.e., p_1-h_1, p_2-h_1), we can assume a virtual syndrome d and construct

Input: Weight Matrix W
Output: Top-N List
(1) Define Tri-TSPA(W)
(2) Begin
(3) queue $\leftarrow$ Discover K nearest entities using the similarity measures
(4) *Case 1.* for $p_i \in P$ do
(5) $F(p_i, h_i) = \overline{F(p_i, \cdot)} +$
(6) $$\frac{\sum_{p_j \in \text{queue}(p_i)} \text{sim}PH\_\text{Path}(p_i, p_j) \times (F(p_j, h_i) - \overline{F(p_j, \cdot)})}{\sum_{p_j \in \text{queue}(p_i)} \text{sim}PH\_\text{Path}(p_i, p_j)}$$
(7) End for
(8) *Case 2.* for $d_i \in D$ do
(9) $F(d_i, h_i) = \overline{F(d_i, \cdot)} +$
(10) $$\frac{\sum_{d_j \in \text{queue}(d_i)} \text{sim}PDH\_\text{Path}(d_i, d_j) \times (F(d_j, h_i) - \overline{F(d_j, \cdot)})}{\sum_{d_j \in \text{queue}(d_i)} \text{sim}PDH\_\text{Path}(d_i, d_j)}$$
(11) End for
(12) Top-n list $\leftarrow$ Get the predicted patterns list in the term of
(13) $F(p_i, h_i)$ or $F(d_i, h_i)$
(14) Top-N list $\leftarrow$ Filter the Top-n list using relevance function
(15) Return Top-N list
(16) End

Algorithm 1: Tri-TSPA.

the edge between d and p_1 and the edge between d and h_1 (or the edge between d and p_2). Otherwise, we only assume a virtual syndrome d and produce the edges between d and other symptoms (or the edges between d and other herbs). Similarly, we can construct the tripartite graph based on the Tourette dataset.

5.2. Evaluation Metrics. Our proposed algorithm computes a ranking score for each candidate herb and returns the top-N highest ranked herbs as the predicted list for a target symptom. To evaluate the prediction accuracy, we focus on how many symptoms-herbs patterns previously removed in the preprocessing step reappear in the predicted results. Therefore, we apply two popular performance metrics, namely, Precision@N and Recall@N [17–20], to capture the performance of our proposed algorithm.

Precision@N is the ratio of recovered symptoms-herbs patterns to the N predicted symptoms-herbs patterns. Recall@N is the ratio of recovered symptoms-herbs patterns to the set of symptoms-herbs patterns deleted in preprocessing. We divide the symptoms-herbs patterns into two sets: the test set T_h and the Top-N set R_h. Symptoms-herbs patterns that appear in both sets are members of the hit set. Precision and Recall are defined as follows:

$$\text{Precision} = \frac{\text{Size of Hit Set}}{\text{Size of Top}N\text{ Set}} = \frac{|T_h \cap R_h|}{N},$$
$$\text{Recall} = \frac{\text{Size of Hit Set}}{\text{Size of Test Set}} = \frac{|T_h \cap R_h|}{|T_h|}. \quad (10)$$

5.3. Parameter Tuning. In our experiments, we divide each dataset into two parts: training set and test set. We further split the training data to validation data to optimize the parameters λ_0, λ_1, α, α_0, α_1, β, β_0, β_1, θ, and K. We have varied the neighborhood size from 10 to 50 by an interval of 10 and the other nine parameters from 0 to 1 by an interval of 0.1. Using the validation data (in Infertility dataset), we have found the best λ_0 to be 0.8, λ_1 to be 0.2, α to be 0.7, α_0 to be 0.8, α_1 to be 0.2, β to be 0.3, β_0 to be 0.8, β_1 to be 0.2, θ to be 0.5, and K to be 30. In addition, we have different values for these parameters in the other three datasets, but we get the similar experimental results. Here, we do not list all the values for these parameters because of the limitation of space.

In Figure 5, we take the neighborhood size K as an example to explain how to install optimal value for each parameter. From Figure 5(a), we can see that for each Top-N list the Precision changes over the neighborhood size K. We can further observe that when the neighborhood size K equals 30, our proposed method gets the best performance. Also, from Figure 5(b), we have the similar results. Therefore, we set the neighborhood size K as 30.

5.4. Result and Analysis. In this section, we first evaluate the performance of four different measurement methods for two kinds of paths. And then, we compare the performance of PH_Path based strategy and PDH_Path based strategy by using the optimal measurement method.

5.4.1. The Optimal Measurement Method. It is worth noting that a comprehensive set of experiments was conducted using every measurement method in conjunction with every evaluation metric on every dataset, and the results are very consistent across all experiments. Because of the space limitations, we show the results based on the Infertility dataset in

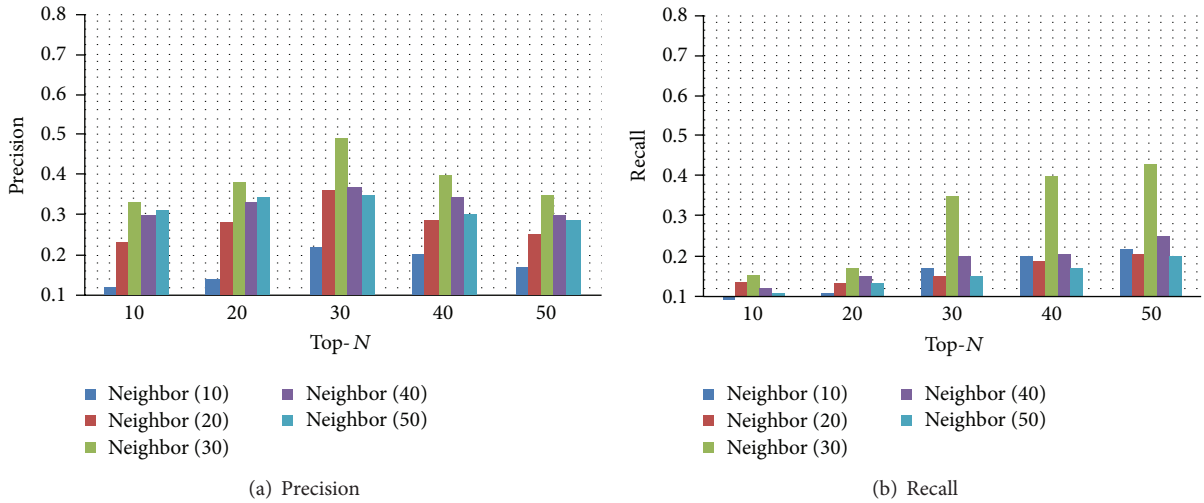


Figure 5: Selecting the optimal neighborhood size in Infertility Dataset. Here, in (a), the x-axis represents Top-N prediction. The y-axis refers to Precision. In (b), the x-axis represents Top-N prediction. The y-axis refers to Recall. These two figures can be obtained by using PH_Path based strategy, which applies the measurement method AM. In this experiment, we set λ_0, λ_1, and θ as 0.8, 0.2, and 0.5, respectively.

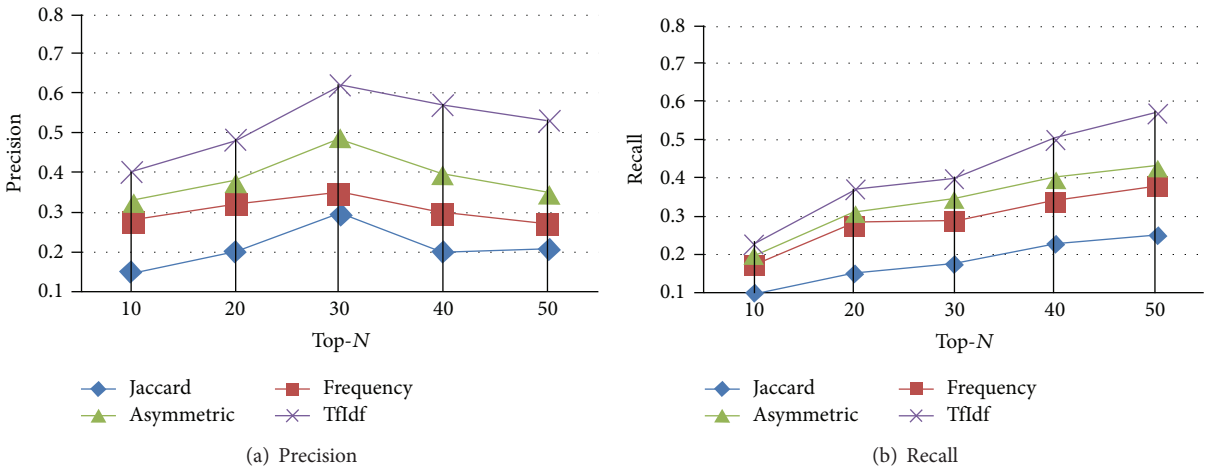


Figure 6: Selecting the optimal measurement method in Infertility Dataset. Here, in (a), the x-axis represents Top-N prediction. The y-axis refers to Precision. In (b), the x-axis represents Top-N prediction. The y-axis refers to Recall. These two figures can be obtained by using PH_Path based strategy.

the Figures 6 and 7. From Figure 6(a), we can see that the measurement method TfIdf apparently beats all the other three measures and produces the best prediction performance in terms of Precision. Specifically speaking, TfIdf has its average Precision 13%, 21.6%, and 30.8% better than AM, F, and JC, respectively. From Figure 6(b), according to Recall, TfIdf also significantly outperforms other three measures. TfIdf, respectively, achieves a 38%, a 61%, and a 116% improvement over AM, F, and JC. Here, an interesting result is observed that JC gets the worst performance. Contrary to JC being known to be more useful to measure the similarity between two same type of objects, it may be due to the existence of different type of objects. Similarly, from Figure 7, we can also observe that TfIdf is the best measurement method. Therefore, we should use TfIdf to help choose the best value for each term in each matrix so that the mining of symptoms-herbs patterns can produce the best results.

5.4.2. The Performance of Proposed Method. In this section, we will estimate the performance of our presented Tri-TSPA based on two kinds of paths.

First, we illustrate how our Tri-TSPA can serve as a powerful model for predicting potential symptom-herb relationships. The prediction processing performance results can be found in Figures 8(a) and 8(b). We use two prediction processing measures to evaluate the performance of each method on four TCM datasets, which are Precision at top 30 prediction results and Recall at top 30 prediction results, denoted as Precision@30 and Recall@30, respectively. In terms of these two measurements, one can observe that

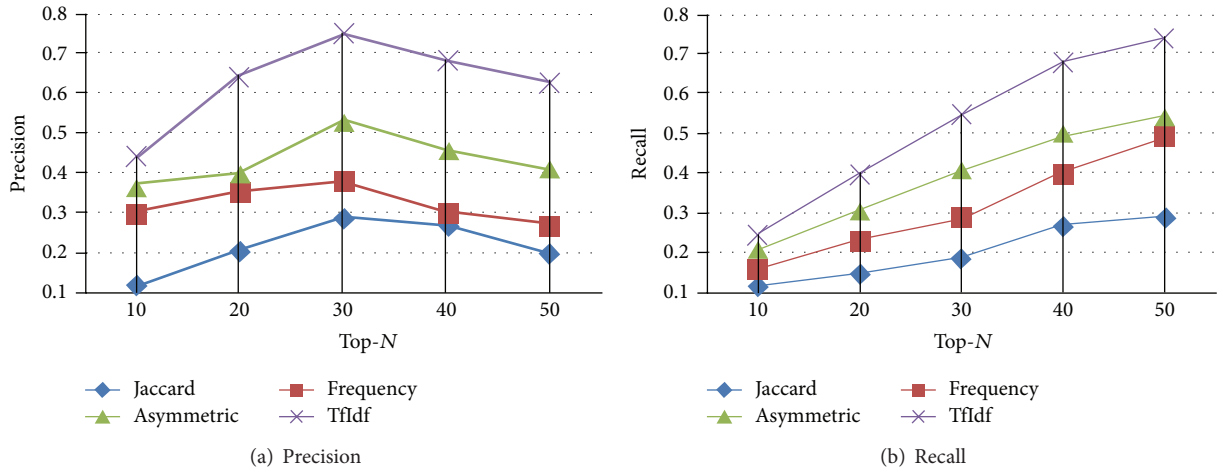


FIGURE 7: Selecting the optimal measurement method in Infertility Dataset. Here, in (a), the x-axis represents Top-N prediction. The y-axis refers to Precision. In (b), the x-axis represents Top-N prediction. The y-axis refers to Recall. These two figures can be obtained by using *PDH*_Path based strategy.

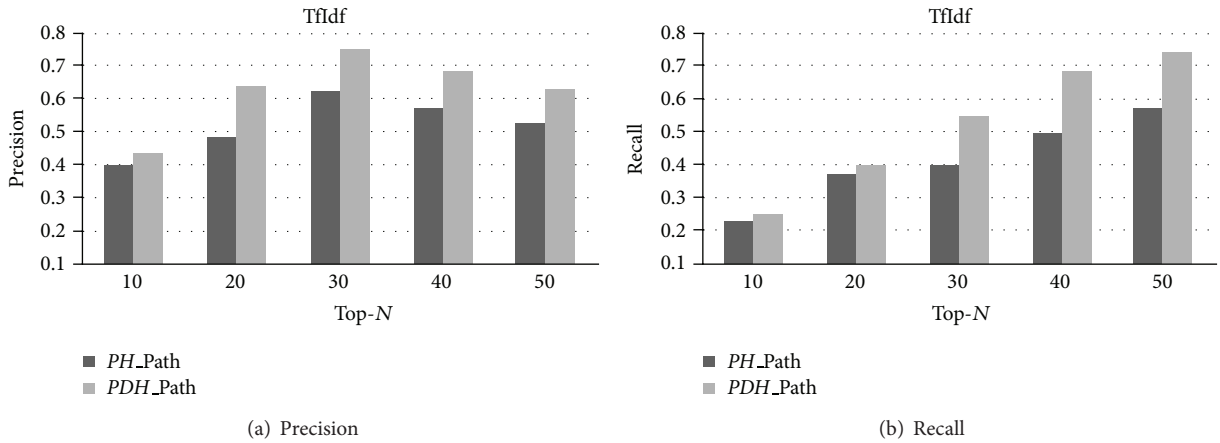


FIGURE 8: Prediction performance of our proposed method Tri-TSPA. Here, in (a), the x-axis represents Top-N prediction. The y-axis refers to Precision. In (b), the x-axis represents Top-N prediction. The y-axis refers to recall. Tri-TSPA adopts TfIdf to install the reasonable value to each term for each matrix.

our proposed Tri-TSPA based on *PDH*_Path can find more symptom-herb relations than the one based on *PH*_Path, in general.

From Figure 8(a), we notice that our proposed method Tri-TSPA based on *PDH*_Path improves Precision@30 by 10.8% compared with the one based on *PH*_Path. In addition, from Figure 8(b), we also see that our proposed method Tri-TSPA based on *PDH*_Path improves Recall@30 by 11% when compared with *PH*_Path. Therefore, we can conclude that *PDH*_Path based prediction method gives a good performance overall. Here, we can see that when N reaches 30, the precision of both algorithms is optimal. Meanwhile, although Recall@50 of both algorithms reaches optimal value, the gap between Recall@30 of both algorithms and Recall@50 of both algorithms is very small. So we take $N = 30$ as an optimal value to achieve optimal prediction power for the Infertility dataset.

In addition to the Infertility dataset, we tested the proposed algorithm with other three datasets, and the same pattern is observed in the vast majority of cases.

5.4.3. Discussion. The symptoms in TCM are related to the body as a whole. A certain subset of symptoms belongs to a certain syndrome, and the typical treatment of a syndrome usually follows a therapeutic principle, which refers to the use of a certain combination of herbs [21].

So far, we have mined a Top-N list of herbs for each symptom (see Table 2). However, our aim is to discover an effective combination of interacting herbs for each symptom, which is useful for healing the sick. In this section, we will introduce a matching function (MF) in order to achieve our aim.

Our matching function is as follows: first, we find all the patterns of good outcome in the dataset and then, we

Table 2: An Example of Top-30 List. This table can be obtained by using *PDH*_Path based strategy. Here, the third column represents symptom-herb ranking rating produced by Algorithm 1.

Symptom	Herb	Rating
Stomachache	Chiretta	7.567
	Radix Paeoniae Rubra	6.765
	Bupleurum	6.70
	Ligustrum Japonium	6.43
	Epimedium Herb	6.397
	Paeonia sterniana Fletcher in Journ	6.396
	Radix Polygoni Multiflori	6.167
	Rhizoma Atractylodis Macrocephalae	6.0
	Salvia	5.989
	Astragali Radix	5.973
	Tuckahoe	5.915
	Licorice Roots Northwest Origin	5.899
	Dioscoreae	5.659
	Homo sapiens	5.549
	Rehmannia root	5.438
	Motherwort Fruit	5.357
	Tortoise Shell	5.347
	Himalayan Teasel Root	5.327
	Tangerine Peel	5.209
	Nutgrass Galingale Rhizome	5.176
	Palmleaf Raspberry Fruit	5.165
	Diverse Wormwood Herb	4.97
	Plantain Seed	4.934
	Bitter Orange	4.92
	Safflower	4.905
	Hyacinth Bean	4.876
	Finger Citron	4.844
	Towel Gourd Vegetable Sponge	4.819
	Common Macrocarpium Fruit	4.736
	Zedoary	4.736

match the Top-N list with each existed pattern, and find a longest chain, namely, a maximum effective set of interacting herbs. Our matching function is described in Algorithm 2. Here, the differences between the relevant function and the matching function are as follows: the relevant function is used for filtering the bad patterns (i.e., symptom-herb); the matching function is used for finding a maximum effective set of interacting herbs for each symptom. By using MF, we get an effective combination of interacting herbs for each symptom (see Table 3). Stomachache is a manifestation of various syndromes according to Chinese medicine diagnosis. The aim of Chinese medicine is to address the root cause of disease that is a syndrome rather than a single symptom; as a result, multiple herbs are used to treat a particular syndrome. According to the assessment from a TCM practitioner, the herbs in Table 3 are appropriate to stomachache and they have the properties of relieving pain or stomach-related problems. Each of these herbs has different functions, including Regulate Qi (Nutgrass Galingale Rhizome, Tangerine Peel, Dioscoreae, Rhizoma Atractylodis Macrocephalae, Bupleurum), Regulate fluid (Plantain Seed, Tuckahoe), Clear heat (Radix Paeoniae Rubra, Chiretta), Regulate blood (Motherwort Fruit, Salvia), and Nourish Yin (Himalayan Teasel Root). Here, we think our approach works in view of TCM, because when we check the original Infertility dataset, we find that most of the combinations of our Top-N list of herbs exist in the original dataset.

Table 3: An effective combination of interacting herbs for symptom *Stomachache*. Based on Table 2, this table can be obtained by using Algorithm 2.

Symptom	Herb	Rating
Stomachache	Chiretta	7.567
	Radix Paeoniae Rubra	6.765
	Bupleurum	6.70
	Ligustrum Japonium	6.43
	Epimedium Herb	6.397
	Paeonia sterniana Fletcher in Journ	6.396
	Rhizoma Atractylodis Macrocephalae	6.0
	Salvia	5.989
	Tuckahoe	5.915
	Licorice Roots Northwest Origin	5.899
	Dioscoreae	5.659
	Motherwort Fruit	5.357
	Himalayan Teasel Root	5.327
	Tangerine Peel	5.209
	Nutgrass Galingale Rhizome	5.176
	Palmleaf Raspberry Fruit	5.165
	Plantain Seed	4.934
	Hyacinth Bean	4.876
	Common Macrocarpium Fruit	4.736

6. Related Work

TCM network and its properties are researched in many fields. One of these fields is how to explore the complex relationships amongst different components of TCM clinical prescriptions. So far, there are some attempts that explicitly address this aspect.

In [22], authors proposed a new methodology of clinical decision of pulmonary tuberculosis, which can adapt the features of TCM and can be applied to other contagious diseases. This method increased the possibility and accuracy of online diagnosis and treatment especially on contagious diseases. In [23], they presented a new approach to systematically generate combinations of interacting herbs that might lead to good outcome. Their approach was tested on a dataset of prescriptions for diabetic patients to verify the effectiveness of detected combinations of herbs. Their approach is able to detect effective higher orders of herb-herb interactions with statistical validation. In this work, we also consider the factor of good outcome, but we focus on how to improve the algorithm accuracy using good outcome. In [24], they introduced a framework to explore the complex relationships

```
Input: Dataset (D) and Top-N List (L)
Output: A set of herbs (S)
(1) Define MF(D, L)
(2) Begin
(3) set ← Discover the existed patterns of good outcome in D
(4) S ← Match L with each one of set, and delete patterns of bad
(5)       outcome in L.
(6) Return S
(7) End
```

Algorithm 2: MF.

amongst herbs in TCM clinical prescriptions using Boolean logic. In [25], authors put forward a framework which can be used to extract synergistic herbal combinations in a variety of clinical situations. They found that not only the herbs (present herbs) necessary for a positive outcome, but the choice of some other herbs (absent herbs) may have a negative impact on the outcome. In [5], they introduced a two-stage analytical approach. This method first uses hierarchical core subnetwork analysis to preselect the subset of herbs that have high probability in participating in herb-herb interactions and, then, detects strong attribute interactions in the preselected subset by applying MDR. In [26], a new parameter-free algorithm was designed to systematically generate a set of combinations of interacting herbs that leads to good outcome. So far, most of these researches were related to how to extract core herbs or mine herb-herb relationships, which focused on the homogeneous information networks consisting of only one type of objects. In this work, we try to extract the symptom-herb relationships based on the heterogeneous information network.

Another line similar to our research problem is the relationship mining task in heterogeneous information network [27, 28], which involves different types of objects and relations. However, these studies have a different focus compared with our work. In [27], they constructed a heterogeneous biological information network by combining multiple different databases and interaction information in order to find multidrug prescriptions that are effective and safe. In [28], they proposed MedRank, a new network-based algorithm that ranks heterogeneous objects in a medical information network. In this work, we aim at mining symptom-herb patterns in the TCM heterogeneous information network.

7. Conclusion

In this work, we put forward a novel three-step prediction approach to mine symptom-herb relationships effectively and efficiently. Experiments on the TCM network show that our method can find symptom-herb relationships with much higher accuracy using heterogeneous topological features. The results have shown that the performance is indeed superior when the symptoms are mapped to herbs via syndromes, rather than a direct mapping between symptoms and herbs. In other words, syndrome differentiation (patient classification) is a crucial step to a successful treatment in TCM. In the future, we intend to extend our work in the following three directions. Firstly, a new measure to estimate the performance in the proposed method should be explored. Secondly, another novel similarity measure method should be studied to capture the rich topological features. Thirdly, a new matching function to improve the predictive performance should be sought.

Notations

P:	Symptom
D:	Syndrome
H:	Herb
PH_Path:	The path of symptom-herb
PDH_Path:	The path of symptom-syndrome-herb
SimPH_Path:	The similarity based on PH_Path
SimPP:	The similarity based on P-P matrix
SimPH:	The similarity based on P-H matrix
SimPDH_Path:	The similarity based on PDH_Path
SimPD:	The similarity based on P-D matrix
SimDH:	The similarity based on D-H matrix
SimDD:	The similarity based on D-D matrix.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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Research Article

Yang Deficiency Body Constitution Acts as a Predictor of Diabetic Retinopathy in Patients with Type 2 Diabetes: Taichung Diabetic Body Constitution Study

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Objective. Diabetic retinopathy (DR), the most common microvascular complication of diabetes mellitus (DM), can cause severe visual impairment and blindness. To prevent the development of DR, identifying the associated risk factors for patient classification is critical. We conducted a cross-sectional study to determine whether body constitution (BC) is an independent predictor of DR. *Method*. 673 type 2 DM (T2DM) patients were recruited from a medical center, all received DR examination and body constitution questionnaire to assess BC. Other risk factors for DR were also recorded, including life style, history of diabetes, and blood pressure, etc. Multiple logistic regression analysis was conducted to calculate the odds ratios (ORs) for DR. *Results*. The prevalence of DR was significantly lower in Yang deficiency patients compared with non-Yang deficiency patients (24.69% versus 38.18% $P = 0.02$). After adjusting for other risk factors, we observed that patients exhibiting Yang deficiency BC were less likely to present with DR (OR = 0.531; 95% confidence interval = 0.312–0.903, $P = 0.018$). *Conclusion*. In addition to traditional risk factors, Yang deficiency BC might be an independent predictor of DR among T2DM patients and the results can be used as evidence for traditional Chinese medicine patient classification.

1. Introduction

Diabetic retinopathy (DR), the most common microvascular complication of diabetes mellitus (DM), has become a major cause of visual impairment and blindness worldwide [1–4], thus imposing a heavy burden on health care systems [5, 6]. The number of people with DM worldwide is estimated to continue increasing from 171 million in 2010 to 366 million in 2030 [7]; the prevalence of DR may also rise and cause an even greater socioeconomic burden [8]. The WHO multinational study on vascular disease in diabetes revealed that Chinese diabetes populations have a higher prevalence of DR [9]. Hence, reducing the risk of DR is an essential health concern for the ethnic Chinese diabetes populations in Taiwan, Hong Kong, Singapore, and mainland China, which comprise more than 25% of the global population.

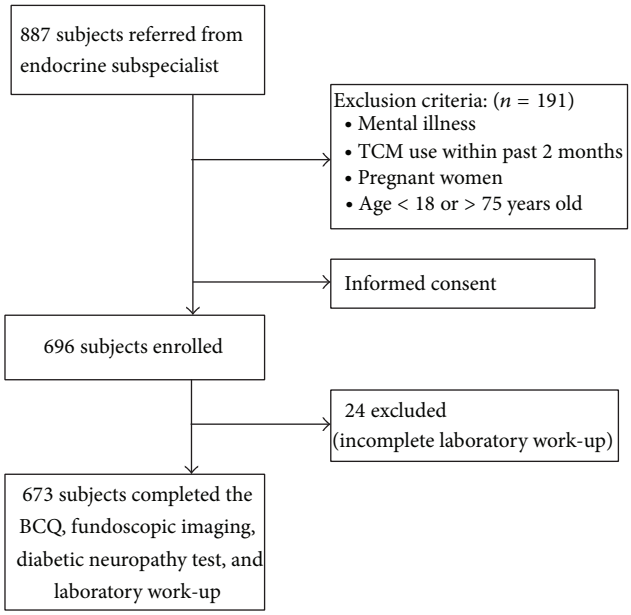

Figure 1: The flowchart of the study.

The pathogenesis of DR is complex and not fully understood, and considerable efforts have been expended in identifying the possible risk factors for the development and progression of this disease [10–15]. Effective control of blood pressure and serum glucose and early detection and timely treatment of DR have been suggested to reduce the risk of DR-related vision loss [16–18]. However, new strategies are still necessary for further and substantial reduction of the DR risk [19, 20].

Traditional Chinese medicine (TCM), one of the most important and frequently used types of complementary and alternative medicine [21–23], is an ancient system of personalized medicine based on body constitution (BC) theory [24–26]. BC is the fundamental physiological component of a person, and different BC types are variously susceptible to disease and affect the development and prognosis of diseases [27, 28]. Patient classification is important in TCM, and different prevention and therapeutic methods for the same disease are used according to the BC type [29–31]; this is known as *tong bing yi zhi* in Chinese.

The relationships between BC and DM [32, 33], insulin resistance [34], diabetic nephropathy [35], and diabetic peripheral arterial disease [36] have been established, thus confirming TCM patient classification theory and verifying a new TCM treatment strategy for DM [37]. However, the association between BC and DR has yet to be determined. In the current study, we recruited type 2 DM (T2DM) patients and collected their BC types, a series of laboratory data, and fundus photographs for DR detection. We aimed to determine whether BC could be an independent predictor of DR in T2DM patients in ethnic Chinese populations.

2. Materials and Methods

2.1. Study Design and Subjects. We conducted this cross-sectional study form February 2010 to February 2011 at the Diabetes Health Promotion Center of Taichung Veterans General Hospital (Taichung, Taiwan). The study protocol was approved by the Institutional Review Board of Taichung Veterans General Hospital (C10007). A total of 887 individuals diagnosed with T2DM were referred by endocrinology and metabolism subspecialists from an outpatient clinic, and 191 subjects older than 75 years were excluded. Written informed consent was obtained from each subject prior to participation in the study. Every subject received a diabetic retinopathy examination and was included in the enrollment group only when the possible risk factors for DR were completely collected: body constitution measurement, sociodemographic history (including sex, age, body mass index, and waist circumference), lifestyle, diabetic related history, blood pressure, lipid profile, renal parameters for diabetic nephropathy, and diabetic neuropathy examining results. Twenty-four subjects were excluded because of incomplete laboratory tests, and 673 T2DM patients were included in the final analysis. Figure 1 shows the recruitment of the study subjects.

2.2. Measurements

2.2.1. Body Constitution Measurement. All of the participants were administered a body constitution questionnaire (BCQ) consisting of three independent constitution subscales, including 19 items on Yang deficiency [24, 38], 19 items on Yin deficiency [39, 40], and 16 items on Phlegm stasis [27].

Because some items belonging to these three scales overlapped, the BCQ comprised 44 items on a 5-point Likert-type scale from 1 (*never happened*) to 5 (*always happens*). The final score of each constitution was calculated by summing the scores of all items on each subscale, with a higher score implying a greater deviation from the constitution. The diagnostic cut-off points for Yang deficiency, Yin deficiency, and Phlegm stasis were 30.5 [38], 29.5 [40], and 26.5 [27], respectively. BCQ demonstrates favorable factorial validity [27], and Cronbach's α of each constitution subscale in previous studies has been between 0.88 and 0.90 [27, 38, 40].

2.2.2. Detection of DR. Central fundus photographic imaging was performed following the standardized protocol. Both eyes of each subject were photographed using a nonstereoscopic 45° digital nonmydriatic camera (CR-DGi, Canon, Inc., Tokyo, Japan). The fundus photographs were examined in a masked manner by experienced and trained endocrinology and metabolism subspecialists. The DR severity of each eye was graded according to the International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales [41]. Because nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) were considered early and late stages of DR, respectively, study participants who had at least one eye with either NPDR or PDR were assigned to the DR group for analysis.

2.3. Data Collection. Several critical risk factors for DR were derived to control for the confounding influence. The sociodemographic and biological characteristics of the 673 participants, including sex, age, height, waist, lifestyle, duration of DM, oral hypoglycemic agent use, and insulin usage, were investigated through personal interviews at the Diabetes Health Promotion Center of Taichung Veterans General Hospital. After more than 12 hours of fasting, a series blood samples were collected for measuring fasting blood sugar, glycosylated hemoglobin (HbA1c), total cholesterol, total triglyceride, high density lipoprotein, low density lipoprotein (LDL), and creatinine (Cr). The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease four-variable equation: eGFR = 186 × serum creatinine − 1.154 × age − 0.203 × 1.212 (if black) × 0.742 (if female) [42]. We also collected a spot urine from each participant to analyze urine protein, and the estimated daily urine protein output was calculated using the following equation: albumin in spot urine/serum creatinine (ALB/Cr). A diabetic neuropathy examination was performed based on the physical examination protocol of the Michigan Neuropathy Screening Instrument (MNSI) [43].

2.4. Statistical Analysis. The data were presented as mean ± SD for continuous variables and as number (%) for categorical variables. Differences between groups were compared using a chi-square test for categorical variables and a t-test for continuous variables. We used multiple logistic regression analysis to calculate the odds ratios (ORs) for DR. Hierarchical models for covariant variables were considered for determining whether BC is an independent predictor of DR. First, crude ORs were calculated without adjustment. We then sequentially entered sociodemographic factors, lifestyle, diabetic factors, blood pressure, and lipid profiles into the model. Finally, renal parameters and diabetic neuropathy were added into the final model. A two-sided significance level was set at $P < 0.05$. We performed all analyses using SAS version (SAS Institute Inc., Cary, NC, USA).

3. Results

A total of 343 (51%) males and 330 (49%) females composed the study group. Of the 673 participants, 81 (12%), 174 (25.9%), and 86 (12.8%) patients were diagnosed with Yang deficiency, Yin deficiency, and Phlegm stasis BC, respectively. Table 1 shows a comparison of sociodemographic factors, lifestyle, diabetic factors, lipid profile, blood pressure, renal parameters, and diabetic neuropathy between subjects with and without Yang deficiency, Yin deficiency, and Phlegm stasis BC. Sex differs in all BCs. Patients with Phlegm stasis BC had higher BMI, LDL level, and lack of exercise habits as compared with the non-Phlegm stasis patients. Participants with Yang or Yin deficiency BC tended to have higher percentage of insulin usage. Among individuals with Yin deficiency BC, higher percentage of diabetic neuropathy and lower GFR level were also noted.

A total of 226 (33.6%) patients have DR, including PDR and NPDR. Table 2 shows the prevalence of DR according to BC status. The prevalence of DR was significantly lower in Yang deficiency patients compared with non-Yang deficiency ones (24.69% versus 38.18%, $P = 0.02$).

The unadjusted and hierarchically adjusted ORs for DR associated with different BC were shown in Table 3. Individual with Yang deficiency BC was less likely to have DR (crude OR = 0.531; 95% CI = 0.312–0.903, $P = 0.018$). After adjusting for all of the variables, including Yin deficiency, Phlegm stasis, sociodemographic factors, lifestyle, diabetic factors, blood pressure, lipid profile, renal parameters, and diabetic neuropathy, Yang deficiency BC remained significantly associated with DR (OR = 0.453; 95% CI = 0.234–0.875, $P = 0.019$).

4. Discussion

Substantial efforts have been expended to discover the risk factors associated with DR among T2DM patients. Male sex, blood pressure, duration of diabetes, HbA1c, and albuminuria had been identified to be associated with DR among T2DM patients across different ethnic groups [11–13, 44, 45]. In our study, we considered all of the aforementioned risk factors as well as other confounding factors. After adjusting for other variables, this cross-sectional study suggests that Yang deficiency BC is an independent predictor of DR. T2DM patients with Yang deficiency BC had a 55% reduced likelihood of DR.

An individual's BC is formed by Yin and Yang and the imbalance between Yin and Yang renders individuals more prone to certain diseases [24, 46]. Yang consists of the energy for maintaining body function, and the diminishing energy level is defined as Yang deficiency. Several research and

Table 1: Participant characteristics.

	Yang deficiency (n = 673)			Yin deficiency (n = 673)			Phlegm stasis (n = 673)		
	Yes (n = 81)	No (n = 592)	P value	Yes (n = 174)	No (n = 499)	P value	Yes (n = 86)	No (n = 587)	P value
Age (years)	57.57 ± 11.97	59.21 ± 10.60	0.20	60.01 ± 11.18	58.67 ± 10.63	0.16	59.21 ± 11.13	58.98 ± 10.74	0.86
Female, n (%)	59 (72.84)	271 (45.78)	<0.001‡	100 (57.47)	230 (46.09)	<0.01†	57 (66.28)	273 (46.51)	<0.001‡
BMI (kg/m^2)	26.05 ± 4.26	25.67 ± 4.07	0.44	25.64 ± 3.69	25.74 ± 4.23	0.76	27.11 ± 4.68	25.51 ± 3.97	<0.01†
WAIST (cm)	88.04 ± 10.77	89.01 ± 10.46	0.43	87.83 ± 10.10	89.27 ± 10.61	0.12	91.98 ± 11.93	88.44 ± 10.20	0.01*
Lifestyle factors									
Smoke history, yes, n (%)	4 (4.93)	34 (5.74)	0.77	8 (4.59)	30 (6.01)	0.49	6 (6.97)	32 (5.45)	0.57
Alcohol usage, yes, n (%)	0 (0)	21 (3.54)	0.09	2 (1.14)	19 (3.80)	0.08	0 (0)	21 (3.57)	0.07
Exercise habits, yes, n (%)	59 (72.83)	475 (80.23)	0.12	132 (75.86)	402 (80.56)	0.19	56 (65.11)	478 (81.43)	<0.001‡
Diabetic factors									
FBS (mg/dL)	149.68 ± 60.61	144.98 ± 45.72	0.50	147.71 ± 53.87	144.8 ± 45.43	0.52	147.84 ± 41.99	145.21 ± 48.53	0.63
HbAlc (%)	7.87 ± 1.78	7.78 ± 1.67	0.67	7.86 ± 1.86	7.77 ± 1.61	0.58	8.08 ± 1.73	7.75 ± 1.67	0.08
DMH (year)	8.20 ± 7.40	8.28 ± 7.28	0.93	8.61 ± 7.34	8.15 ± 7.27	0.48	8.02 ± 6.82	8.31 ± 7.36	0.74
OHA use, yes, n (%)	75 (92.59)	562 (94.93)	0.38	165 (94.82)	472 (94.58)	0.90	81 (94.18)	556 (94.71)	0.84
Insulin usage, yes, n (%)	32 (39.51)	147 (24.83)	<0.01†	61 (35.06)	118 (23.65)	<0.01†	28 (32.56)	151 (25.72)	0.18
Lipid profile									
TC (mg/dL)	177.79 ± 39.74	175.46 ± 36.26	0.59	173.32 ± 35.84	176.58 ± 36.95	0.31	180.95 ± 41.93	174.97 ± 35.81	0.21
TG (mg/dL)	160.1 ± 120.29	156.82 ± 180.37	0.83	149.73 ± 91.91	159.82 ± 194.46	0.37	163.88 ± 136.23	156.24 ± 179.13	0.64
HDL (mg/dL)	52.24 ± 13.49	52.96 ± 14.78	0.68	51.68 ± 13.68	53.29 ± 14.93	0.21	51.51 ± 14.17	53.07 ± 14.69	0.36
LDL (mg/dL)	110.37 ± 31.97	106.9 ± 32.47	0.37	106.64 ± 33.85	107.56 ± 31.91	0.75	114.08 ± 36.41	106.33 ± 31.69	0.04*
Blood pressure									
SBP (mmHg)	131.14 ± 17.05	131.58 ± 14.37	0.82	131.35 ± 15.57	131.59 ± 14.41	0.85	131.90 ± 16.21	131.47 ± 14.49	0.80
DBP (mmHg)	78.91 ± 11.31	78.38 ± 8.74	0.68	77.68 ± 9.93	78.70 ± 8.76	0.23	77.50 ± 10.09	78.58 ± 8.93	0.30
GPT (U/L)	29.28 ± 30.00	29.00 ± 23.53	0.94	28.43 ± 28.99	29.24 ± 22.57	0.74	32.52 ± 30.82	28.52 ± 23.27	0.25
Renal parameters									
Microalbumin (mg/dL)	27.85 ± 86.83	21.97 ± 72.16	0.56	28.12 ± 92.32	20.77 ± 66.49	0.34	27.47 ± 89.66	21.97 ± 71.52	0.59
Cr (mg/dL)	1.09 ± 0.46	1.14 ± 0.63	0.39	1.19 ± 0.63	1.12 ± 0.61	0.19	1.09 ± 0.49	1.14 ± 0.63	0.34
eGFR (ml/min)	69.56 ± 24.42	71.01 ± 21.52	0.57	67.22 ± 23.72	72.10 ± 21.07	0.01*	70.64 ± 23.35	70.86 ± 21.67	0.93
ALB/CR (ug/mg)	475.24 ± 2008.6	233.91 ± 935.92	0.29	319.95 ± 1386.8	243.08 ± 1013.1	0.50	316.61 ± 1238.90	255.10 ± 1103.70	0.64
Diabetic neuropathy, yes, n (%)	63 (77.78)	14 (2.36)	0.08	48 (27.59)	29 (5.81)	0.01*	64 (74.42)	13 (2.21)	0.25

Data were presented as mean ± SD for continuous variable and as number (%) for categorical variable.

P values were calculated using the chi-square test for categorical variable and t-test for continuous variable $^{*}P < 0.05$, $^{\dagger}P < 0.01$, and $^{\ddagger}P < 0.001$.

BMI, body mass index; FBS, fasting blood sugar; HbA1c, glycosylated hemoglobin; DMH, duration of diabetic mellitus; OHA, oral hypoglycemic agent; TC, total cholesterol; TG, total triacylglycerol; HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; GPT, glutamic pyruvic transaminase; Cr, creatinine; eGFR, estimated glomerular filtration rate; ALB/CR, microalbumin to creatinine ratio.

Table 2: Prevalence of diabetic retinopathy according to body constitution.

BC	DR n (%)	non-DR n (%)	Total N (%)	P value
Yang deficiency				
Yes	20 (24.69)	61 (75.31)	81 (100)	0.02*
No	226 (38.18)	366 (61.82)	592 (100)	
Yin deficiency				
Yes	62 (35.63)	112 (64.37)	174 (100)	0.77
No	184 (36.87)	315 (63.13)	499 (100)	
Phlegm stasis				
Yes	24 (27.91)	62 (72.09)	86 (100)	0.07
No	222 (37.82)	365 (62.18)	587 (100)	

BC: body constitution; DR: diabetic retinopathy. *$P < 0.05$.
P values were calculated using the two-sided chi-square test.

clinical trials have indicated the association between disease or discomfort and Yang deficiency [32, 47–51]. Persisting lack of Yin is called Ying deficiency[39], and Phlegm stasis means when the transportation of Yin and Yang is obstructed [52]. In our study, the results revealed that patients with Yang deficiency BC might have a lower risk of DR, and further research is necessary for exploring the mechanism of how Yang deficiency BC influences DR development in T2DM patients.

Hemodynamic abnormalities, including increased retinal blood flow and blood pressure, might lead to the development and progression of DR [53–57]. Yang deficiency is regarded as a decrease in energy level, including the force of circulation [38]. Traditional therapeutic methods of TCM for Yang deficiency are termed *yi qi wen yang* and demonstrate the effect of promoting blood circulation [58]. Blood pressure did not differ significantly between patients with or without Yang deficiency BC in this study and was considered in our multiple logistic regression analysis. Thus, the retinal blood flow of patients may explain the effect of Yang deficiency on DR observed in our study.

Angiogenesis is another vital pathogenic pathway in diabetic retinopathy [55, 57] and the effect of antivascular endothelial growth factor therapy has been clinically studied. Several studies have found that single-herb or herbal remedies used based on the principle of replenishing Qi and Yang, thus increasing the energy level, has the therapeutic effect of ischemic damage [59, 60] and wound healing [61] through angiogenesis. Whether patients with Yang deficiency BC have less angiogenesis or fewer vascular endothelial growth factors that might result in the decreased risk of DR is a topic of scientific interest.

Previous studies have successfully provided evidence for TCM patient classification by using machine learning algorithms [62–64], and by using epidemiology module, our study results confirm that people with certain BCs might be more susceptible to some diseases. We launched the Taichung Diabetic Body Constitution Study to evaluate the effect of BC on T2DM patients. Previous results have shown that T2DM patients with Yang deficiency, Yin deficiency, or Phlegm stasis BC had reduced health-related quality of life [65]. The BC concept can guide TCM physicians to treat patients according to different BCs and improve health conditions by helping patients to adjust their BC status. A previous randomized controlled trial reported that higher life quality, reduction of antihypertensive medication, and a significant difference in systolic blood pressure could be attained by using Chinese food therapy to restore Ying-Yang imbalance in hypertensive patients with Yin deficiency BC [66]. Studies have identified certain Chinese herbs that demonstrate antidiabetic [67–69] and antihyperglycemic [70, 71] effects, which can be useful in future clinical research when combined with TCM patient classification.

The questionnaire, BCQ, with favorable reliability and validity can be easily applied by Western physicians to assess the BC status and has been used in clinical research [36, 50]. In this study, we focused on the independent influence of BC on DR; hence, we considered other focal complications of DM, including diabetic neuropathy and nephropathy. Further clinical research based on the study results is necessary to investigate the effect of preventing or treating DR by adjusting BC.

Our study has three major limitations. First, the abnormal constitution theoretically occurs before a disease, but the time sequence of a cross-sectional study design cannot determine the causal relationship between BC and DR. A cohort study might be necessary to mitigate this doubt. Second, because the patients willing to join the study might have been more aggressive in improving their health conditions, a potential selection bias exists. To mitigate the impact of bias, we considered the lifestyle and sociodemographic factors in the multiple logistic regression analysis. Finally, although we included major confounding factors, other unmeasured variables might exist because this was an observational study.

5. Conclusion

Distinguishing T2DM patients who exhibit a high or low risk of complication development is crucial for health management. This study suggests that BC is independently associated with DR. T2DM patients with Yang deficiency BC had a 55% significantly reduced likelihood of DR. For patient classification, using BCQ to assess the BC is convenient, inexpensive, and noninvasive and should be adopted in clinical practice. Identifying the association between DR and BC confirms BCQ construct validity. Our study results might guide future study to survey the longitudinal association between DR and BC.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Table 3: Unadjusted and adjusted odds ratios and 95% CI for diabetic retinopathy according to constitution.

	Diabetic retinopathy, OR (95% CI)					
	Yang deficiency		Ying deficiency		Phlegm stasis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Model 1	0.531 (0.312–0.903)	0.018*	0.948 (0.662–1.358)	0.770	0.637 (0.386–1.049)	0.075
Model 2	0.536 (0.289–0.995)	0.048*	1.263 (0.832–1.917)	0.273	0.735 (0.409–1.323)	0.305
Model 3	0.529 (0.282–0.995)	0.048*	1.164 (0.761–1.780)	0.485	0.779 (0.427–1.422)	0.416
Model 4	0.531 (0.282–0.999)	0.049*	1.154 (0.754–1.768)	0.510	0.746 (0.407–1.366)	0.342
Model 5	0.498 (0.262–0.947)	0.034*	1.099 (0.712–1.697)	0.670	0.768 (0.415–1.421)	0.401
Model 6	0.472 (0.247–0.902)	0.023*	1.108 (0.715–1.717)	0.645	0.812 (0.436–1.512)	0.511
Model 7	0.453 (0.234–0.875)	0.019*	1.057 (0.677–1.648)	0.810	0.824 (0.438–1.550)	0.548

Model 1 is unadjusted. Model 2 is adjusted for BC. Model 3 is additionally adjusted for sociodemographic factors. Model 4 is additionally adjusted for lifestyle. Model 5 is additionally adjusted for diabetic factors. Model 6 is additionally adjusted for blood pressure and lipid profile. Model 7 is additionally adjusted for renal parameters and diabetic neuropathy.
Analysis by logistic regression. $^{*}P < 0.05$.
BC: body constitution, including Yang deficiency, Ying deficiency, and Phlegm stasis. Sociodemographic factors: gender, age, BMI, and waist. Lifestyle: smoke and alcohol drinking history and exercise. Diabetic factors: FBS, HbA1c, DM duration, oral hypoglycemia agent, and insulin use. Blood pressure: SBP and DBP. Lipid profile: TG, HDL, and LDL. Renal parameters: GFR and microalbumin to creatinine ratio.

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