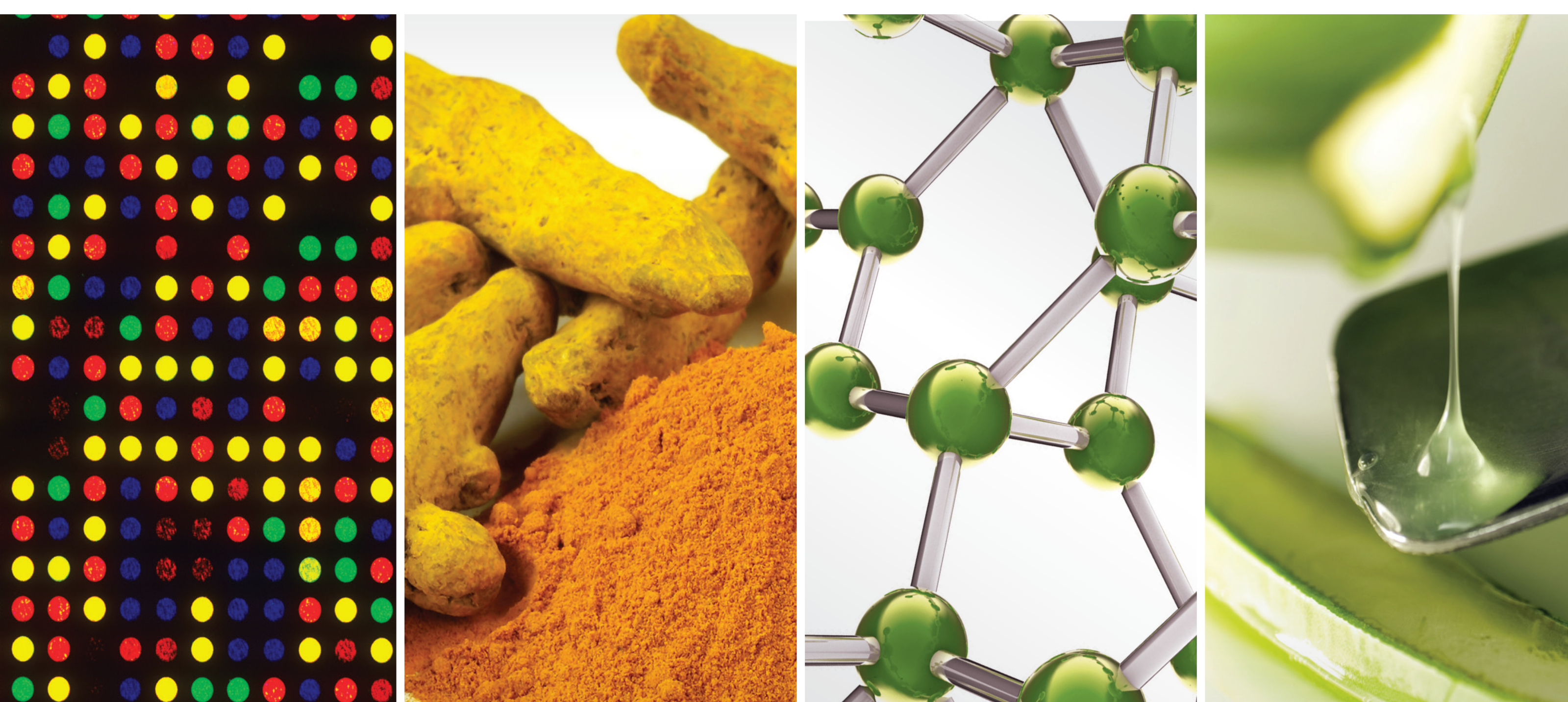
Evidence-Based Complementary and Alternative Medicine

Artificial Intelligence Device Development in Complementary and Alternative Medicine

Lead Guest Editor: Wen Si
Guest Editors: Lei Jiang, Boya Nugraha, and Lu Zhang



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Research Article

Decision Tree-Based Body Constitution Diagnosis System for Traditional Chinese Medicine

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This study aimed to establish a method for fast and accurate determination of body constitution types from the body constitution questionnaire (BCQ) by employing a decision tree model. The model was trained for 4 classes, namely, Yin-Xu, Yang-Xu, Phlegm and Blood Stasis, and Normal, and it achieved 67% accuracy for the testing dataset. The model also reduced the required number of BCQ questions from 44 to 3–6, depending on the responses. Lastly, we developed the Traditional Chinese Medicine (TCM) body constitution online diagnosis system using our model to collect data digitally and use it more practically and efficiently. This system can assist doctors to improve the diagnosis and treatment in TCM practice.

1. Introduction

In Traditional Chinese Medicine (TCM) practice, body constitution (BC) is the core theoretical basis for determining an individual's health status. The BC type affects individuals' susceptibility to specific diseases and strongly influences their prognoses. Therefore, being able to quickly and accurately determine a patient's BC is an important issue in TCM clinical practice. A body constitution questionnaire (BCQ) is an objective tool that can help bridge the gap between TCM's individualized medical features and scientific research methodology. Syndrome differentiation is one of the most important concepts in the diagnostic process of TCM. Decision tree algorithms are appropriate for this process as they can address a large amount of variable information to obtain more precise and accurate classifications. The algorithms can also handle incomplete data. Therefore, decision tree algorithms can help clinicians determine the relationship between symptoms/signs and syndromes, thereby improving the syndrome differentiation and treatment process in TCM.

In this study, we used the decision tree algorithm to optimize the process of using the TCM BCQ to determine patients' BC type. The study background and previous related research, materials and methods, results, discussion, conclusion, and future research directions have been presented herein.

1.1. Background and Previous Research. The four cardinal TCM diagnostic methods (seeing, smelling, asking, and touching) depend on the physician's subjective observations, knowledge, and clinical experience [1]. Moreover, TCM traditionally relies on subjective information—including the physician's perception and the patient's chief complaint—to reach a clinical diagnosis [2, 3]. Therefore, the objectivity of diagnosis in TCM practice and its scientific basis have often been contested [4]. To address this issue, several efforts have been made to improve TCM diagnosis methods. BC is the fundamental theory of TCM [5]. BC indicates the individuals' physiological characteristics: their susceptibility to pathogenic factors and tendency to develop certain types of pathological changes [6]. Because the BC type determines an individual's susceptibility to specific diseases and has prognostic relevance, it is used to guide treatment and disease-prevention measures [7]. Different BC types also have specific metabolic characteristics. Based on an individuals' BC, TCM practitioners advise personalized preventive and therapeutic measures, thereby achieving better treatment outcomes [5]. Currently, two Chinese Medical Constitution Questionnaire tools are widely used to determine the BC type: The Constitution in Chinese Medicine Questionnaire (CCMQ) [8] and BCQ [9, 10]. Lin [11] assessed the differences between the two questionnaires. Although clinical studies using the BCQ [9, 10] have reported promising results in recent years, these studies only evaluated and compared the questionnaires without addressing their ease of use.

The BCQ consists of 44 questions, each with a maximum score of 5 (ranging from 1 (never happened) to 5 (always happen)); the total score (calculated by summing the scores of all items) ranges from 44 to 220. The questions are aimed at determining the BC type, classified into 3 categories: Yang-Xu (19 questions), Yin-Xu (19 questions), and Stasis (16 questions). Some questions are used to determine more than one type. For Yang-Xu, a score exceeding 31 implies Yang-Xu BC; for Yin-Xu, a score exceeding 30 implies Yin-Xu BC; and for Stasis, a score exceeding 27 implies Stasis BC. The higher the score, the more obvious is the tendency to represent the BC. Scores less than the threshold for all three BC types are considered indicative of a peaceful constitution [9]. Previous studies have demonstrated satisfactory reliability (Cronbach's α: 0.85–0.92) and validity (z score: 3.3636–10.026) of the BCQ [12]. In recent years, the BCQ has been increasingly used in clinical research on several diseases, such as schizophrenia [13], breast cancer [14, 15], and diabetes [16, 17], and the assessment of the Yang-Xu constitution and clinical blood variables [18]. Although the 44 questions in the BCQ were used in these studies, the research did not attempt to make the process of using this tool simpler and more convenient.

In recent years, the concept of "big data" has been applied to assess the relationship between the intervention measures and the outcomes of diseases. The advent of big data technology provides great opportunities for the modernization of TCM [19]. A decision tree is a kind of inductive reasoning algorithm that uses the decision tree predictive model to show how the data are affected by various variables; in addition, it uses the dendrogram for automated data segmentation and evaluation [20]. Syndrome differentiation is one of the most important concepts in TCM practice, which is based on a series of diagnostic procedures. The process of syndrome differentiation entails an analysis of the symptoms and signs of the disease at the pathological stage. The syndrome information is complex and diverse and largely consists of qualitative variables. The decision tree can help process information with large amounts of variables and achieve more precise syndrome classification; moreover, it can handle incomplete data. Therefore, the decision tree technology can help determine the relationship of symptoms and signs with syndromes and improve the process of syndrome differentiation and treatment in TCM [21]. Many studies have demonstrated the applicability of decision trees to explain the rules of TCM diagnosis systems based on large TCM syndrome datasets [22]. However, these decision trees may produce huge branch systems, requiring further pruning of the excess branches to increase their efficiency.

The computational origins of decision trees, sometimes called classification trees or regression trees, are models of biological and cognitive processes. These are simple yet effective for predicting and explaining the relationship between some measurements of a variable and their target value. Quinlan developed Iterative Dichotomiser 3 (ID3) [23], C4.5, and C5.0 [24] algorithms. Those decision tree algorithms have helped improve the process of predicting variables and pruning technology.

Liu and Liu [25] used decision trees in the field of medicine, introducing several novel techniques and providing new research directions. Chen et al. [26] and Wang et al. [27] used the decision tree C5.0 module as the basis to construct a diagnostic model to analyze the complex characteristics of chronic hepatitis B in TCM. The decision tree is a tool not only for data analysis but also for extracting clearer judgment rules for physicians as a reference for clinical diagnosis. Although the decision tree theory cited was used in clinical settings, those researchers did not implement a real, operational system using the theory. In contrast, this study developed a mobile device system based on the decision tree theory to validate this theory.

The decision branch is illustrated as a figure much like the branch of a tree. Each node in the tree structure represents a conditional test for an attribute and each branch represents the result of the test; the offspring of the tree represents its final branch. The decision tree is also a type of establishment classification mode, which uses the existing data to produce a tree structure [23, 24, 28]. A tree structure is built by classifying a known instance (i.e., training paradigms), from which hidden rules between fields are summarized. The resulting decision tree can also be used to predict samples.

The decision tree is constructed from the root node from top to bottom and divides the data into subsets containing similar values. In Figure 1, ID3 uses entropy to calculate the uniformity of the sample. If the sample is completely uniform, its entropy is zero; if the sample is equally divided, its entropy is 1 [29].

Entropy using the frequency table of one attribute is expressed as equation (1), where p_i is the probability of class i appearing in a dataset S with c classes.

$$\text{Entropy}\,(S) = \sum_{i=1}^{c} \left(-p_i \log_2 p_i\right). \quad (1)$$

Classification and regression trees (CART) are decision tree algorithms that use the Gini index [30]. Gini impurity (calculated using equation (2)), like entropy, is a criterion for splitting nodes in decision trees. The methodology entails the calculation of the "impurity" or "information level" indicator. The node in the decision tree is split according to the information existing on the node using the following formula:

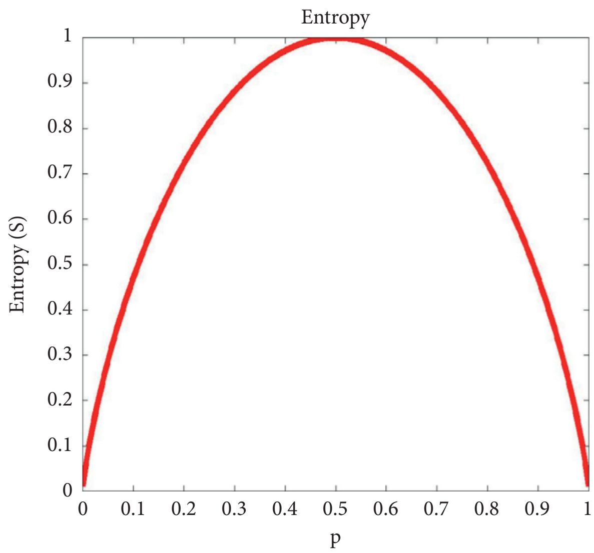

Figure 1: Decision tree entropy.

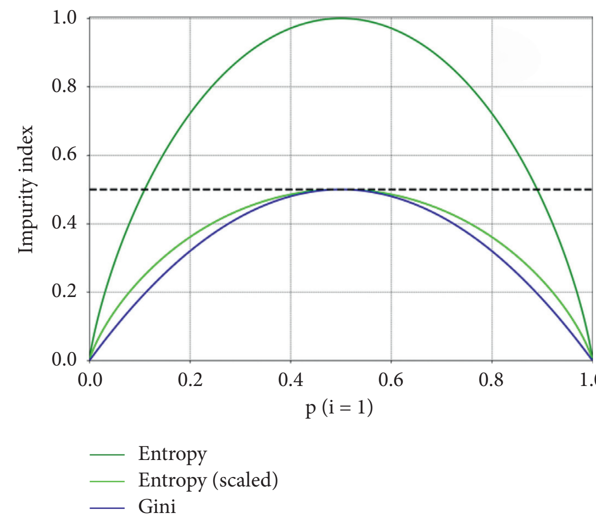

Figure 2: Gini coefficient and entropy.

$$\text{Gini}(S) = 1 - \sum_{i=1}^{c} p_i^2. \quad (2)$$

Different impurity measures (Gini coefficient and entropy) usually produce similar results. Figure 2 shows that the Gini coefficient and entropy are very similar impurity standards. One of the reasons why Gini is the default value of scikit-learn (Python library) is that the calculation of entropy may be slightly slower (because it uses logarithms).

In the process of optimizing the decision tree, the branches and leaves are pruned to simplify or compress the classification of the unnecessary and redundant parts. Pruning is also a method of compression, which selectively deletes insensitive noncritical and redundant connections in the model, such as noncritical weights or smaller absolute weights [31].

Post-pruning is the most commonly used method for simplifying trees. Because leaves replace the nodes and subtrees, the complexity can increase. Pruning can significantly reduce the size as well as increase the accuracy of the classification. Although pruning is likely to reduce the accuracy of the allocation on part of the test set, the accuracy of the overall tree classification attributes increases [32–34]. Research on pruning methods requires more practical examples to confirm their efficacy. This study applies the pruning method to TCM to obtain a large amount of data that can be used to verify this method's accuracy.

2. Materials and Methods

2.1. Study Design and Subjects. This study was approved by the Institutional Review Board of Hualien Tzu Chi (IRB number: IRB107-08-B). A total of 439 healthy, mostly young volunteers were recruited from the local community via advertisements between March 2018 and June 2019. The inclusion criteria were as follows: age 20–65 years, no significant medical history, and no current use of medications for chronic illnesses. Written informed consent was obtained from all participants prior to their enrolment. All participants completed the BCQ. Some of the BCQ results represented mixed BC syndrome type. However, we only considered the single BC syndrome type in this study. Consequently, 168 pieces of the BCQ data were selected for the decision tree analysis.

2.2. BCQ. The TCM BCQ developed by the research team led by Prof. Yi-Chang Su of China Medical University was used in the study. The questionnaire contains 44 questions. People can understand their BCs by answering whether they are cold, tired, or thirsty. Table 1 shows the question numbers for each BC.

There are five response options for each question (1, not at all; 2, a little bit; 3, moderate level; 4, very high level, and 5, most serious level). The scores of individual subjects were summed to determine the BC type. For example, there are 19 questions for Yin-Xu, and subjects with >30 points were classified as having Yin-Xu. In this study, subjects with complex constitutions were excluded and only those with a single BC type were included. Table 2 shows the criteria for determining the BC type.

2.3. Decision Tree Analysis. In total, there were 168 pieces of the BCQ data. In this study, 134 pieces of data were used for training the decision tree, whereas 34 pieces of data were used for testing the decision tree. The decision tree was a CART tree that used the Gini index. Figure 3 shows one section of the decision tree. Each box is a node representing the result of an answer. Nodes on the left (under the word true) indicate that the judgment condition was satisfied. Nodes on the right (under the word false) indicate that the judgment condition was been satisfied. When there were no items on the left or right under a node, that node indicates the final judgment result. Each node has a specific background color, with brown indicating a normal constitution (normal), green indicating Phlegm and Blood Stasis (PaBS), purple indicating Yin-Xu (YinAC), and blue indicating

Table 1: Question numbers for each BC type.

BC type	#Test
Yin-Xu	2, 4, 8, 10, 11, 16, 18, 20, 23, 26, 29, 30, 31, 32, 35, 37, 38, 39, and 40
Yang-Xu	3, 5, 8, 9, 15, 16, 17, 22, 23, 24, 28, 31, 33, 36, 37, 41, 42, 43, and 44
Phlegm and blood stasis	1, 4, 5, 6, 7, 12, 13, 14, 16, 17, 19, 20, 21, 25, 27, and 34

Table 2: Criteria for determining the BC type.

BC type	Number of questions	Score	Judgment criteria
Yin-Xu	19	1–5	30
Yang-Xu	19		31
Phlegm and blood stasis	16		27

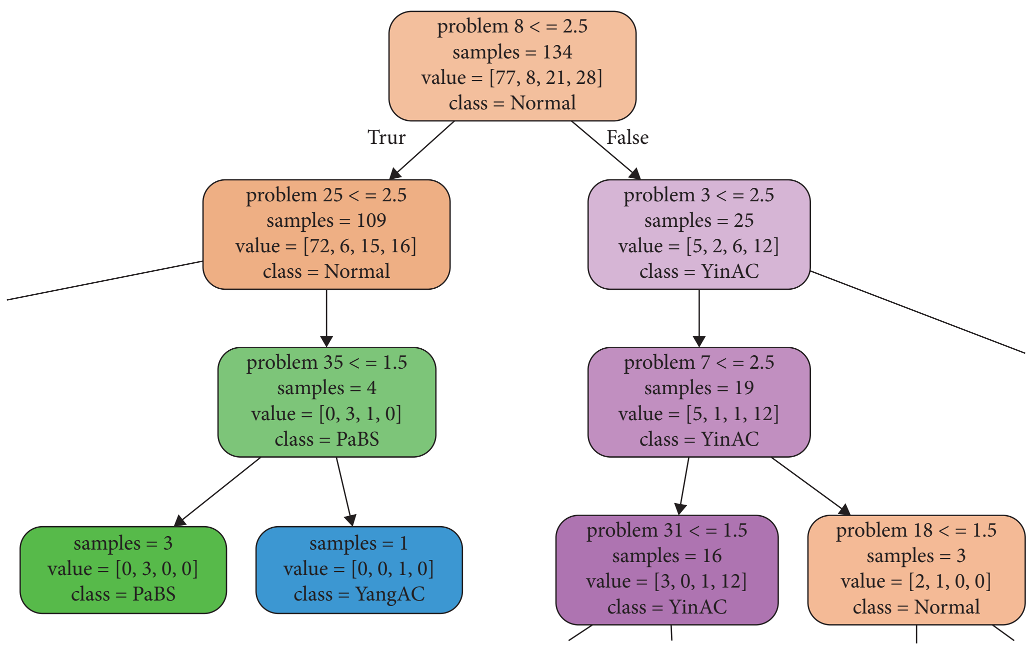

Figure 3: Sample decision tree section.

Yang-Xu (YangAC). The number after the word problem in the first row of each node represents the question number. The value after the greater than (>), less than (<), and/or = symbols represents the answer option (1, not at all; 2, a little bit; 3, moderate level; 4, very high level, and 5, most serious level).

In short, each node on the decision tree asks whether the given question (or condition) has been answered. Those meeting the condition proceed to the node below and left and those not meeting the condition proceed to the node below and right. Depending on the result, it follows the right or left path. The number after sample indicates the number of samples available at that point, and the list of numbers after value indicates how many samples belong to each option category at a given node. The category with the largest number of samples is the predicted value for that node, with a class representing the BC predicted by the node.

As an example, for the root node on the top of Figure 3, the problem number is 8. If the answer is ≤2.5 (true), one should proceed to the box below and to the left. If the answer is ≥3 (false), one should proceed to the node below and to the right. The line sample = 134 means this question has 134 samples. The line value = [77, 8, 21, 28] means the answers are 77 Normal, 8 PaBS, 21 YinAC, and 28 YangAC, respectively. The line class = normal means that the node predicts a BC of normal deficiency.

Figures 4 and 5 show the entire decision tree. The information in each node is simplified. To optimize this decision tree, we pruned the branches and reduced the redundant parts to obtain the highest accuracy of judgment.

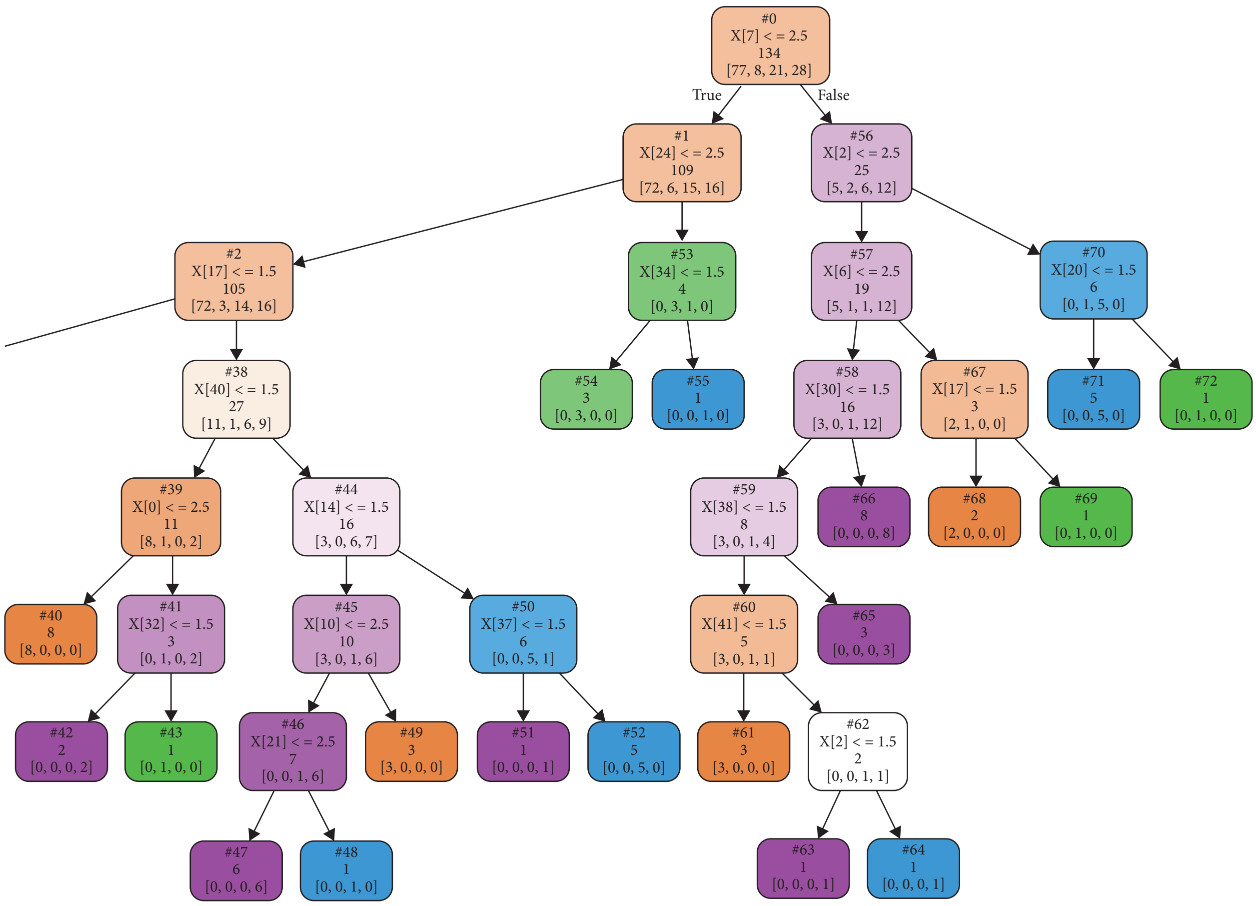

FIGURE 4: Right half of the entire decision tree.

We performed an experiment and attempted to use the maximum depth of the decision tree as an independent variable to judge the optimal depth of the decision tree for this study. The experimental result shows that the best accuracy, i.e., 0.67, was obtained with 12 leaves (Figure 6).

In the standard artificial intelligence (AI) system, a larger amount of data are used as a training dataset to establish a clearer and reliable model to verify the reliability and deviation of the system. Subsequently, a small test dataset is used to test the AI system from the perspective of the end-user and to check the accuracy of the results. We adopted the same approach in this study.

Based on the experiments, we found that the optimized decision tree can be reduced to 12 leaves after pruning the branches. As shown in Figure 7, this decision tree was greatly reduced in size without losing its accuracy. This optimization can help reduce the BCQ problems from a maximum of 10 problems to 6 problems for constructing the decision tree.

2.4. TCM BC Online Diagnosis System. The diagnosis system has two parts: the training system and the implementation system. The training system was used to build a decision tree and generate a database of more than 439 subjects for an online application (app). The implementation system was a BCQ app for mobile devices (Figure 8).

The TCM BC online diagnosis system architecture is presented in Figure 9. The system first trains the original BCQ data to the BCQ decision tree. Subsequently, the system displays the questions and options on the BCQ APP. Users can answer questions according to their own circumstances by clicking on the correct choice, as shown in Figure 8. The app then determines the next node based on the response. When a final leaf is reached, the system clearly shows the final judgment of the BC. The doctor may check the judgment in addition to the results of other medical tests to reach a diagnosis for the patient. If the doctor finds the determined BC to be wrong, the patient can be asked to complete the complete BCQ containing 44 questions. The obtained result can then be added to the BCQ data and the BCQ decision tree can be retrained. This may consequently increase the accuracy of the decision tree.

3. Results

A total of 439 healthy subjects volunteered to participate in this study. All subjects completed the BCQ without any

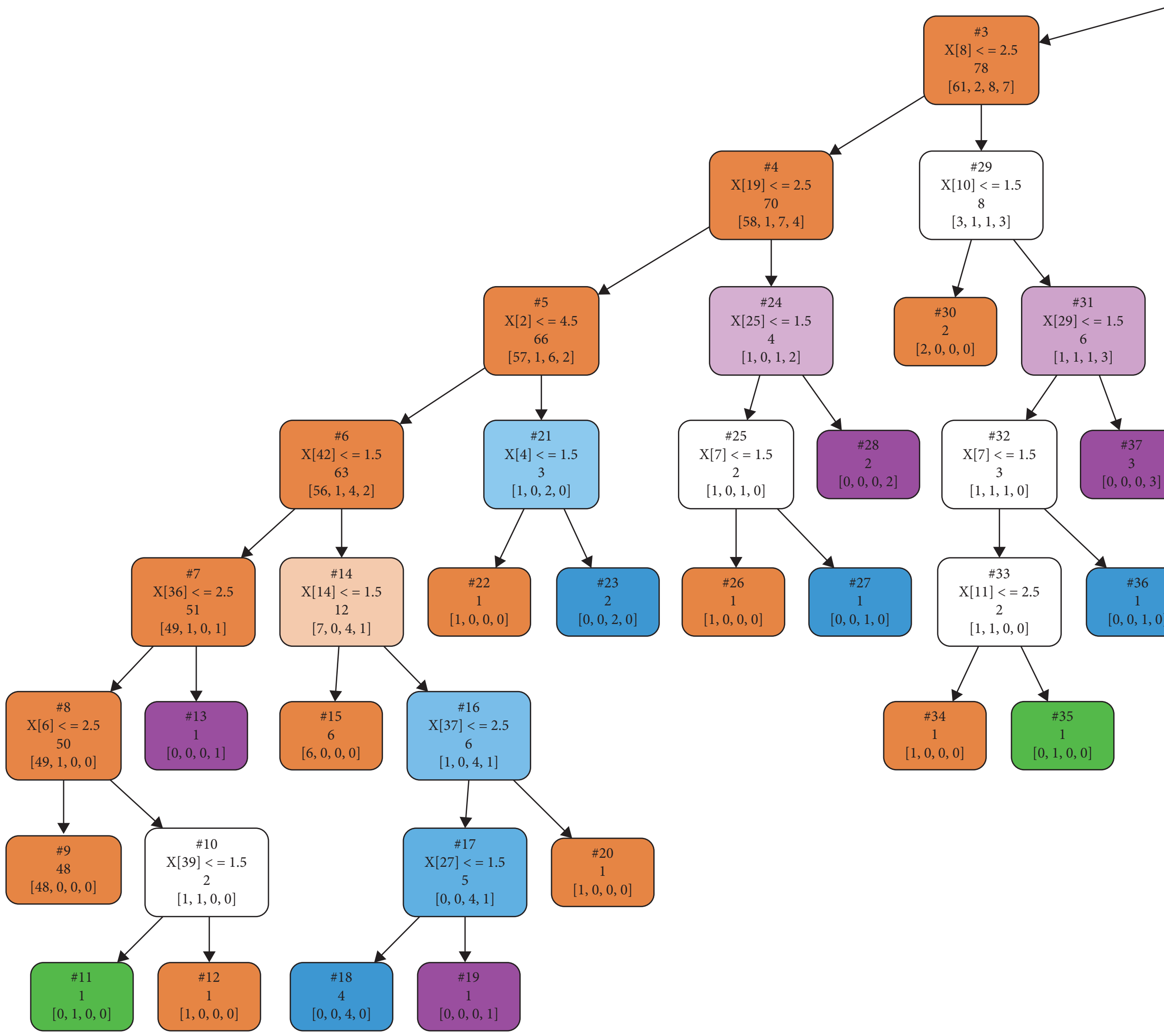

Figure 5: Left half of the entire decision tree.

missing values. Among these, 168 were found to have a single BC syndrome (95 with normal constitution, 25 with Yang-Xu, 36 with Yang-Xu, and 12 with PaBS), whereas 271 were found to have a mixed BC syndrome type. Therefore, we used the dataset of those with single BC and divided it into 2 parts: 134 subjects for training and 34 subjects for testing. We trained our decision tree model using the training dataset. Subsequently, we tested our model using the testing dataset. The prediction accuracy of our decision tree model for the testing dataset was 67%. In addition, we pruned the leaves of the decision tree during training to reduce the size and depth, which allowed us to reduce the number of questions from the original 44 BCQ questions to 3–6 questions for determining the BC type.

Furthermore, we developed a mobile phone app to change the interface for responding to the questionnaire from paper and pen to a mobile device. This innovation simplifies the entire process and allows us to collect more relevant data for future work. The BCQ app is not only helpful in the medical settings but also allows patients to conveniently check their fitness anytime and anywhere.

4. Discussion

To the best of our knowledge, this study is the first to apply a decision tree model to the TCM BC concept. As of now, our decision tree model can predict Yin-Xu, Yang-Xu, PaBS, and normal. The prediction result of our model can be used to improve diagnosis and treatment in TCM practice as well as prevent diseases. To accurately assess the BC type, patients need to answer 44 questions correctly. This can be cumbersome for patients, which compromises the reliability of their responses. Despite the fact that the accuracy of our model is not perfect (67%), it greatly reduces the number of required questions from 44 to 3–6. Furthermore, the development of our TCM BC online diagnosis system allows us to collect more data and increase the accuracy of our model for future work.

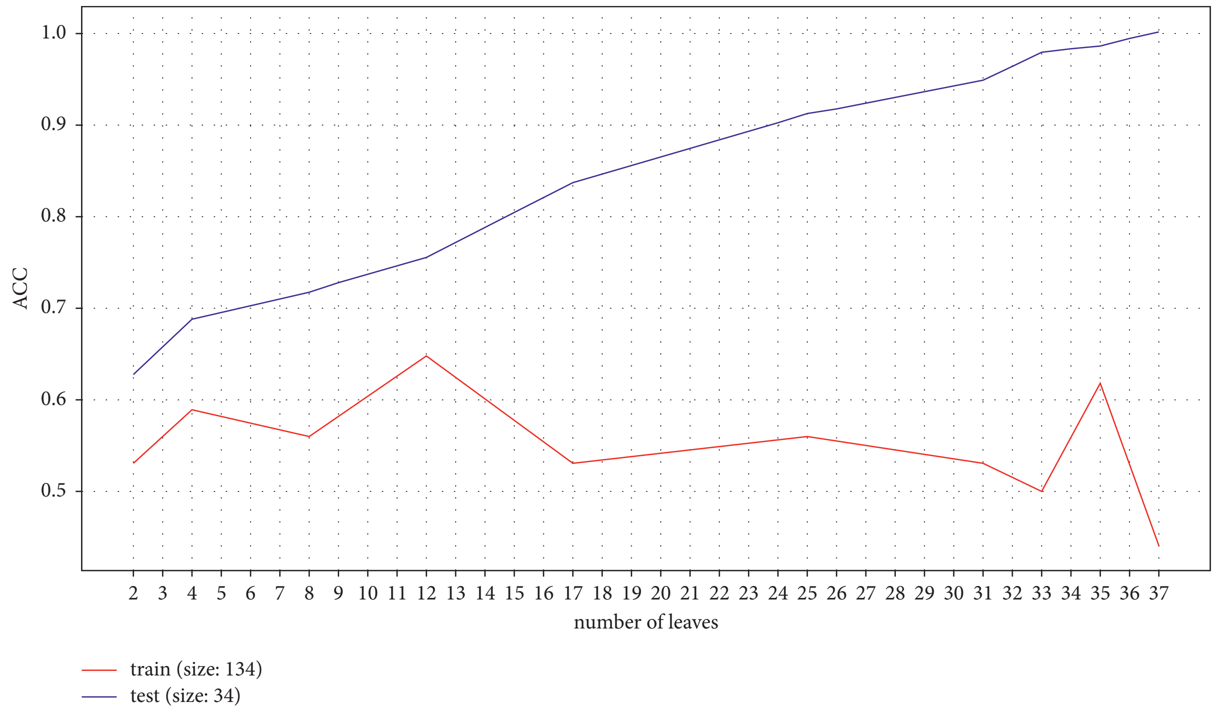

Figure 6: Accuracy of tree size.

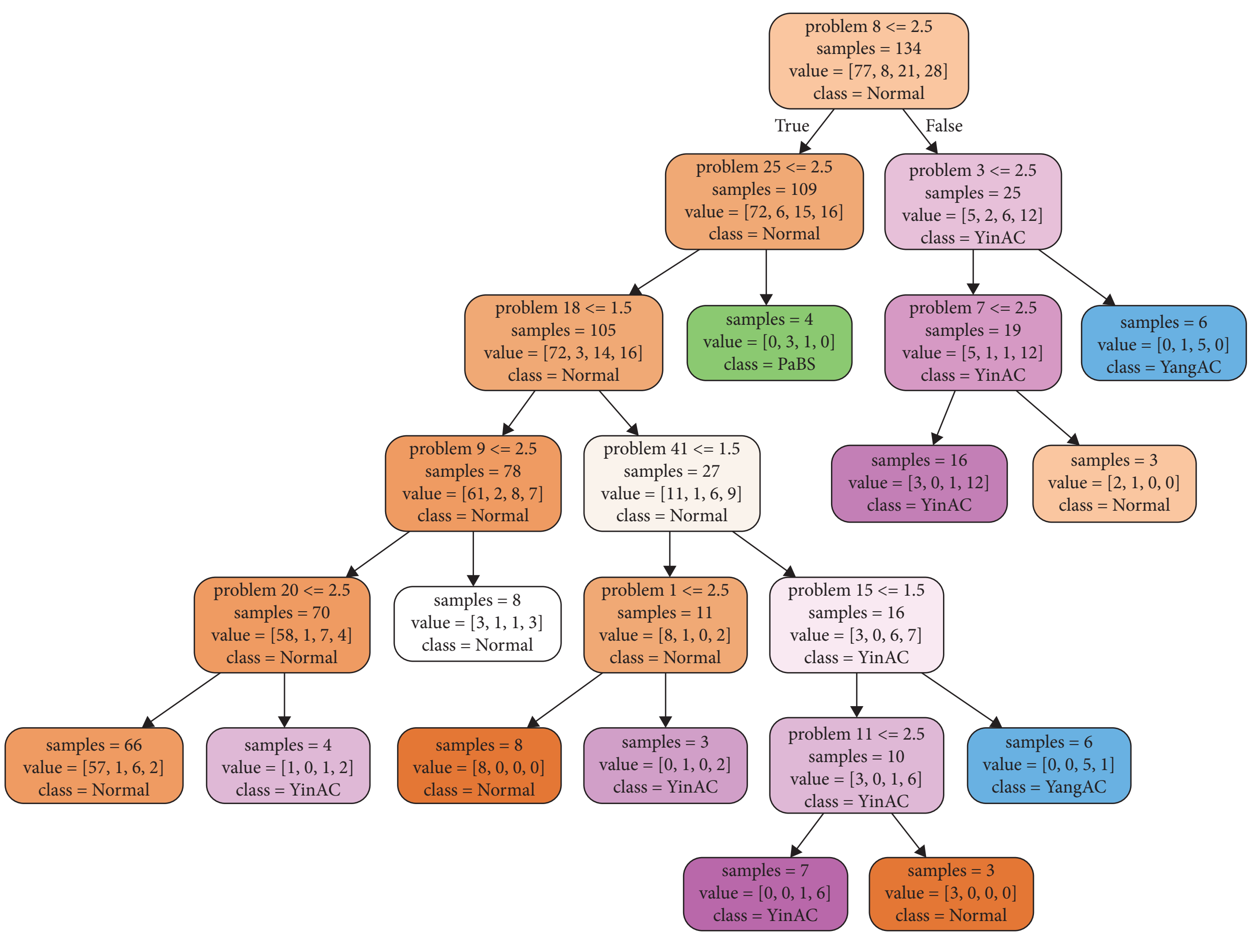

Figure 7: Decision tree after branches were pruned.

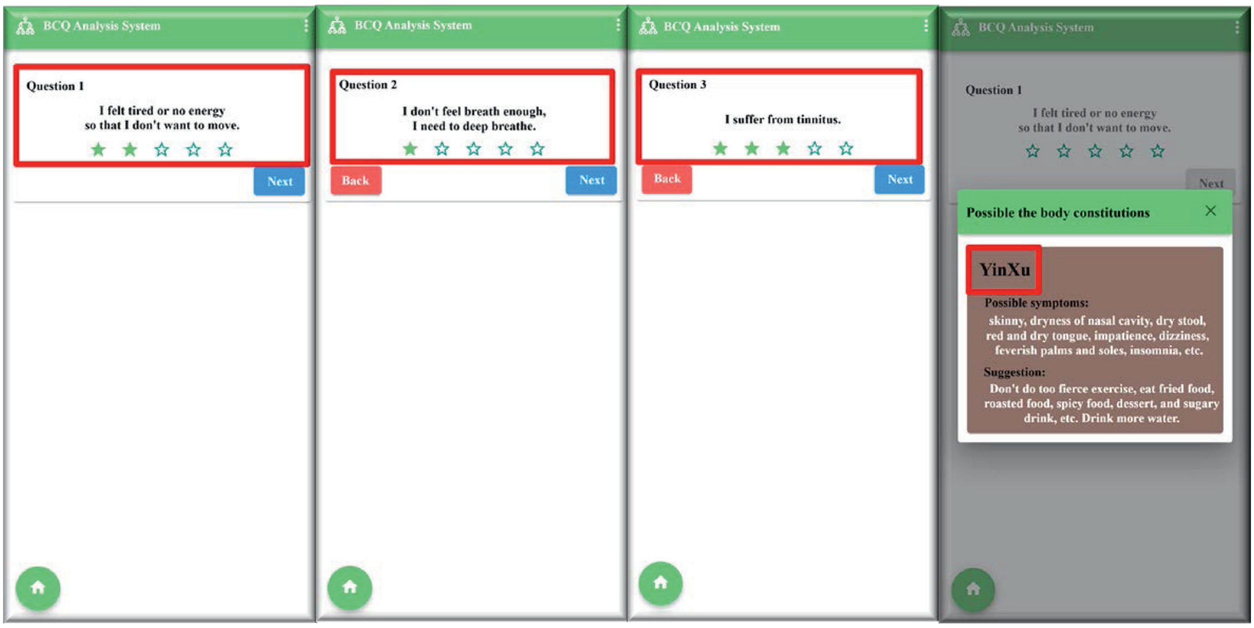

Figure 8: Screenshot of the BCQ app on a mobile device.

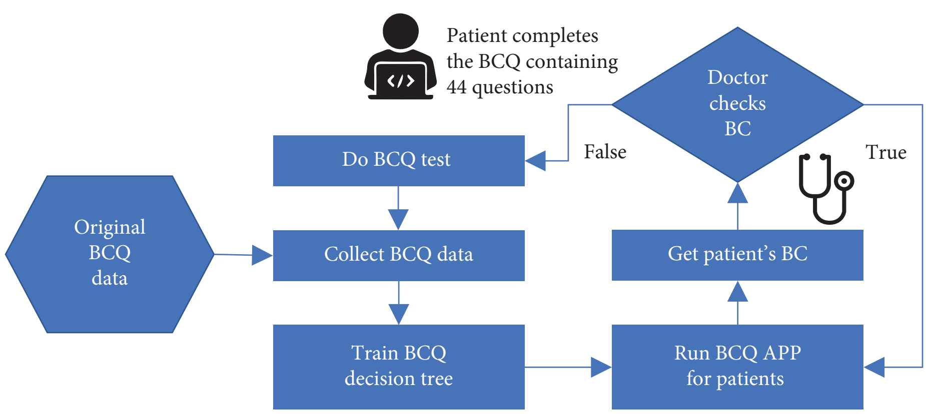

Figure 9: Architecture of the TCM BC online diagnosis system.

Coupled with the development of the TCM BCQ online diagnosis system, the BCQ is not only more practical and efficient but also establishes a system to facilitate future research.

5. Conclusions

In this study, we briefly explained the TCM BC types and described how BC is determined using the BCQ. We created a decision tree model for determining the TCM BC type using the BCQ dataset. Our approach achieved 67% accuracy for 4 single BC types. Using the decision tree model, we reduced the required number of the BCQ questions from 44 to 3–6. This allows our approach to considerably expedite the assessment process. In addition, we created a mobile phone app using this approach for practical and efficient usage. Using the app is more efficient in medical settings and helps improve the model by collecting more data.

5.1. Future Work. In subsequent studies, we plan to work with more doctors to use the BCQ app for collecting more BCQ data to create a more accurate BCQ decision tree model. Also, this paper only considers a single BC syndrome type. To improve reliability, mixed BC syndrome types can be analyzed after collecting a bigger dataset in the future. Additionally, the information obtained from analyzing a large amount of BCQ data can be used to revise the questions of the BCQ.

Data Availability

The data used to support the decision tree of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this study.

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Research Article

Power Spectrum Features of Acupoint Bioelectricity Signal

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Background. Since the 1950s, many studies have been conducted on the electrical properties of acupuncture points (acupoints), especially their bio-resistance characteristics. Results of such studies have been inconclusive due to factors such as sweat gland density and compounding factors of applying electrical stimulation. In this study, a power spectrum instrument was used to assess the power spectrum and power of acupoints and nonacupoints without electrical stimulation. Using such instrumentation, specificity of electrical signals of acupoints was also explored. *Methods*. Thirty-six subjects (29 females, 7 males) participated in the study. Stainless steel acupuncture needles (diameter 0.35 mm; length 50 mm) were used. Five acupoints were tested: ST 36, SP 6, GB 39, GB 37, and K I9. Four control sites 0.5–1.0 cm adjacent to each acupoint were chosen. After needle insertion into the acupoint and control sites, the needles were attached to the power spectrum instrument to acquire any electrical signals. Acquire signals were analyzed using self-written software. *Results*. Power spectrum difference between acupoint and nonacupoint signals was 0–2 Hz. Results of t-test or signed rank sum test ($\alpha = 0.05$) found that electrical signals between acupoints and nonacupoints were markedly different ($P < 0.05$). *Conclusion*. Acupoint bioelectricity signals are higher than adjacent nonacupoints. The most significant difference is distributed between 0 Hz and 2 Hz.

1. Background

A large volume of research has been conducted on acupuncture points (acupoints) and meridians (channels), focusing on the physiologic effects of acupoints and their electrophysiologic characteristics. The therapeutic effect of acupuncture has been confirmed by numerous clinical trials, showing that specificity of a given acupoint is associated with its efficacy. For example, acupuncture applied at ST 2, ST 25, and ST 36 increases gastric antral volume [1]. Copious randomized controlled trials have found treating acupoints is efficacious over treating nonacupoints (sham) [2]. However, studies have also shown no therapeutic differences between acupoints and nonacupoints [3, 4].

Since the 1950s, many studies have been conducted on the electrical properties of acupoints, especially their bio-resistance characteristics [5–7]. Such studies have suggested that acupoints maybe the particular channel transmitting electrical signals, compared with nonacupoints; acupoints can enhance conductivity, reduce electrical resistance or impedance, and increase electrical potential [8–10].

Many factors affect acupoint resistance properties, such as sweat gland density, acupoint location, electrode polarization, and frequency, among others [11]. To overcome these factors, Gow et al., for example, used a Kelvin probe that circumvented skin contact to detect acupoint resistance. However, applicability of this method may be limited as the probe is sensitive to ambient field and movement artifacts [12].

Instead, we propose that applying technology similar to electrocardiography or electroencephalography may detect the true nature of the electrical signal of acupoints. In this study, power spectrum instrumentation was used to collect electric signals at acupoints and nonacupoint control locations. External electrical stimulation was not applied, allowing better understanding of the difference, if any, between signals found at acupoints and nonacupoints, and specificity of the electrical signals.

2. Materials and Methods

2.1. Subjects. Thirty-six subjects (29 female, 7 male) between 23 and 30 years old were recruited to participate in the study during February–July 2018. Participants were recruited in Xiyuan Hospital of China Academy of Chinese Medical Sciences.

Subjects were excluded if they were under 18 years old and pregnant, had clear signs and symptoms of disease, and were suspected of having significant organic disease, lactating, or menstruating. On the day of the study, volunteers were queried about their previous day's emotional and dietary circumstances and those who experienced excess emotions (such as a bout of anger), ate cold or spicy food, or over-ate were excluded. Testing took place in the Nephrology Department of Xiyuan Hospital.

2.2. Acupoints Tested. Acupoints tested were located on the right side: ST 36, SP 6, GB 37, GB 39, and KI 9. Nonacupoint control points were situated 0.5–1.0 cm around the tested acupoints. The signal acquisition instrument required a reference electrode. A nonacupoint site on the right ulnar styloid process was chosen because of its limited number of sweat glands, allowing for voltage stability. A grounding electrode was also required, and the apex of the right lateral malleolus was selected for attachment (Figure 1).

2.3. Experimental Device. The study was conducted with a USB-ME16-FAI System (Multichannel Systems, Reutlingen, Germany), a highly sensitive electrical signal acquisition instrument (Figure 2). We wrote a MATLAB (MathWorks, Natick, MA) program to analyze the power spectrum of acquired signals.

2.4. Experimental Procedure. The experiment was performed in a quiet environment with minimal air flow and an ambient temperature of 18°C–24°C. Participants were shielded from any electromagnetic radiation.

Participants were asked to arrive 10 minutes before the start of the experiment so that they could sit quietly and relax. They were then asked to lie supine on a treatment table with the right upper arm and right lower leg exposed. Participants were also asked to stay awake during the experiment. In order to ensure the accuracy of the test, a single practitioner was responsible for a single acupoint.

To ensure good skin contact, the reference and ground electrodes were cleaned with 75% isopropyl alcohol before attachment to the skin. Disposable electrode pads were supplied by Beijing Tianhe Weiye Medical Equipment Factory (Beijing, China). The electrodes were then connected to the signal acquisition instrument with lead wires. The five acupoints were tested individually: ST 36, SP 6, GB 39, GB 37, and K I9. Four nonacupoint sites were selected to serve as controls. They were located 0.5–1.0 cm lateral, medial, superior, and inferior to each acupoint. These areas were cleaned with 75% isopropyl alcohol.

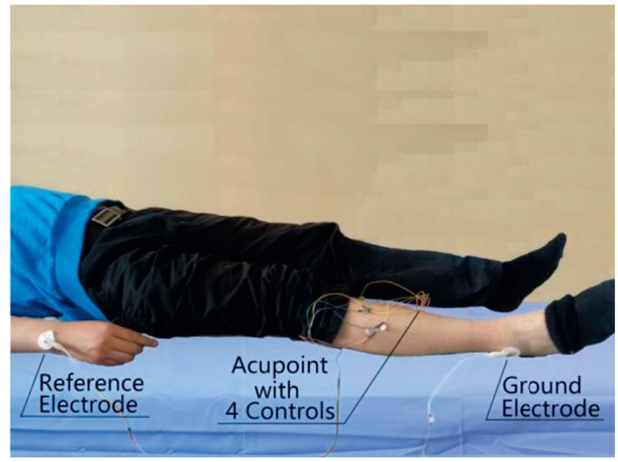

Figure 1: Reference and ground electrode sites.

Off-the-shelf disposable steel acupuncture needles (Suzhou Huanqiu Acupuncture Medical Appliance Co., Ltd., Suzhou, China) were used (diameter 0.35 mm; length 50 mm). The needle at the acupoint was inserted to a depth of 15 mm and *deqi* was obtained. To ensure reliability of the results, insertion depths of acupoint and control point needles were the same, though *deqi* was not apparent at the control points (Figure 3). One end of a lead wire was attached to the needle handle, with the other end attached to the signal acquisition instrument. Bioelectric signals of acupoints and control points were recorded synchronously by the USB-ME16-FAI instrument. Duration of each test was approximately 1 min. After all needles were removed, subjects were advised to rest quietly for 5 min.

We denoised the signals with db5 wavelet. Using Welch's method, power spectral density (PSD) was evaluated. Analyzing the power spectrum of the signal after filtering, the sampling frequency of instrument was 1000 Hz, thus the power spectrum analysis range was to maximum of 500 Hz. To easily observe the specificity, 0–2 Hz, 0–10 Hz, 0–50 Hz, and 0–500 Hz were analyzed.

2.5. Statistics. The Shapiro–Wilk normality test was applied if the data were consistent with a normal distribution based on the *t*-test. If the data did not meet normal distribution, signed rank sum test was used. Differences between acupoints and nonacupoints were considered significant if $P < 0.05$ or less.

3. Results

Five acupoints and their associated nonacupoint control points were scanned on 36 participants. Typical signals recorded by the instrument on the right leg are shown in Figure 4.

Analyzing the power spectrum of the signal after denoising, results showed that the difference in power spectrum between acupoint and nonacupoint bioelectrical

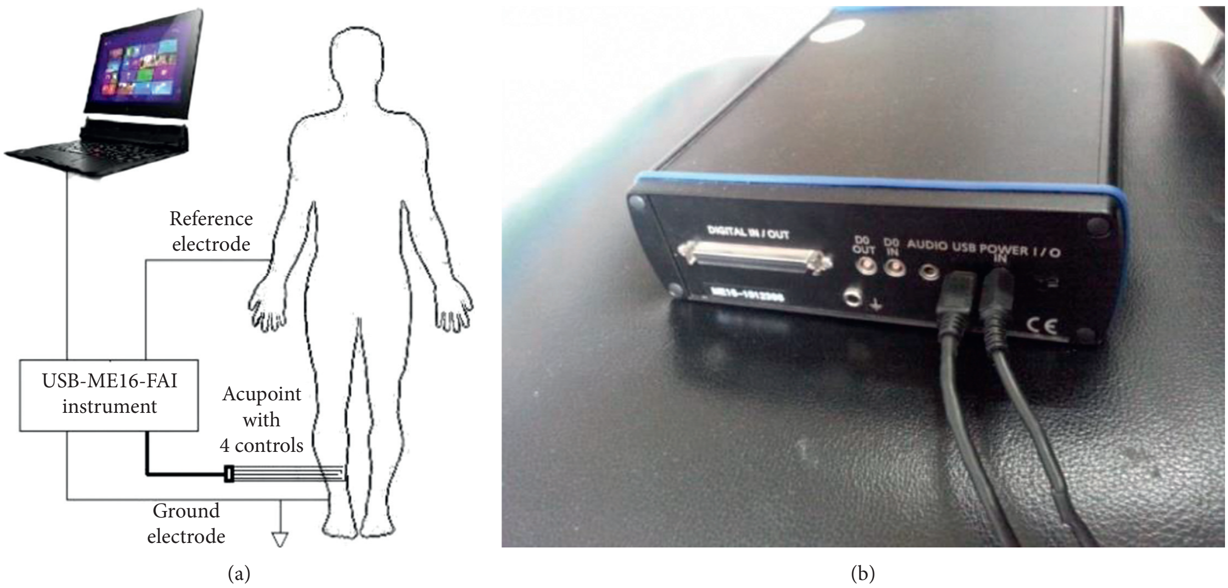

Figure 2: (a) Connections between computer and signal acquisition instrument and the subject. (b). USB-ME16-FAI signal acquisition instrument.

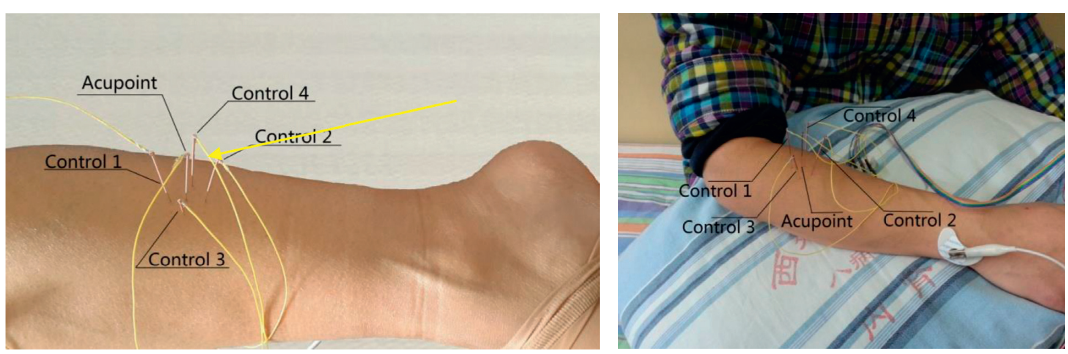

Figure 3: Placement of needles at acupoint and 4 surrounding control points.

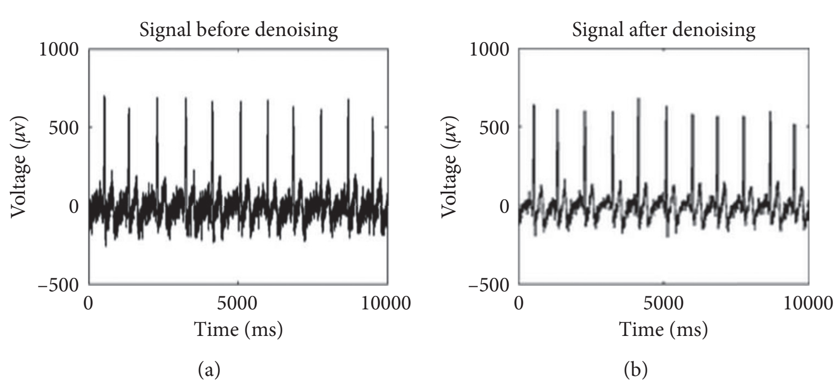

Figure 4: Typical signals from right leg. (a). Before denoising. (b). After denoising.

signals, most of the high power, is distributed in the 0–10 Hz, especially in the 0–2 Hz.

The first statistical analysis showed that the difference between bioelectrical output of acupoints and nonacupoints was significant ($P < 0.05$). ST 36, SP 6, GB 37, and GB 39 were considered different from their control points. With KI9, the data did not meet normal distribution, thus using signed rank sum test, the difference between this acupoint and its control points was significant ($P < 0.05$) (Table 1).

A second statistical analysis assessed all 48 pieces of data using Shapiro–Wilk method, finding that the results did not meet normal distribution. Next, using the *t*-test (alpha 0.05),

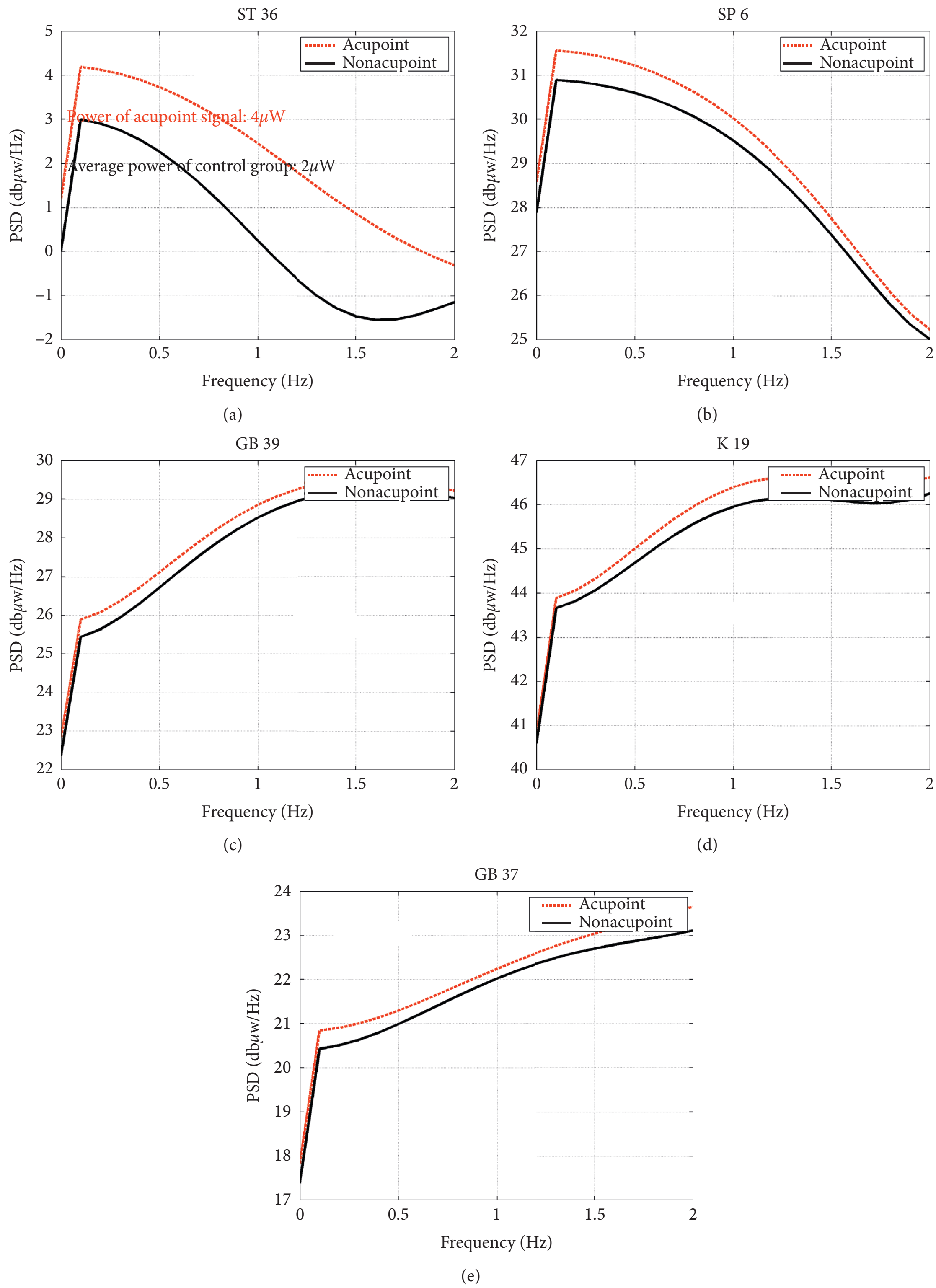

Figure 5: Average power spectrum of acupoints and control points.

Table 1: Specific measurement values.

Name	ST 36		SP 6	
Num	Acupoint power value	Nonacupoint power value	Acupoint power value	Nonacupoint power value
1	1135.70	1106.30	3403.90	3265.60
2	882.03	848.60	378.62	344.47
3	1925.30	1853.80	893.47	849.89
4	1474.80	1422.70	1892.60	1633.20
5	1194.00	1127.50	125910.00	121480.00
6	1949.50	1850.30	43357.00	39865.00
7	2195.40	2103.70	372670.00	348470.00
8	685.83	663.23	153120.00	155470.00
9	2745.40	2588.20	88900.00	85157.00

Name	GB 39		GB 37		KI 9	
Num	Acupoint power value	Nonacupoint power value	Acupoint power value	Nonacupoint power value	Acupoint power value	Nonacupoint power value
1	1468.40	1397.90	327.34	304.29	105550.00	97348.00
2	2212.90	2126.00	923.11	921.77	137760.00	93227.00
3	1353.40	1269.20	489.34	480.80	276340.00	271600.00
4	3030.80	2960.90	474.53	478.75	124010.00	118280.00
5	187040.00	177190.00	125.24	118.73	139560.00	134240.00
6	18194.00	17260.00	202.84	205.50	11833.00	11103.00
7	96560.00	91971.00	193870.00	188840.00	75489.00	69825.00
8	638580.00	612650.00	50471.00	48380.00	85692.00	82349.00
9	417290.00	407530.00	84470.00	83119.00	692280.00	662160.00
10			577420.00	556300.00	313710.00	271070.00
11			438300.00	415470.00		

Table 2: Percentage of difference between acupuncture and nonacupuncture points.

Name	Num	ST 36 (%)	SP 6 (%)	GB 39 (%)	GB 37 (%)	KI 9 (%)
Each volunteer point power value percentage higher than the nonacupoints	1	2.66	4.24	5.04	7.58	7.77
	2	3.94	9.91	4.09	0.15	32.33
	3	3.86	5.13	6.63	1.78	1.72
	4	3.66	15.88	2.36	−0.88	4.62
	5	5.90	3.65	5.56	5.48	3.81
	6	5.36	8.76	5.41	−1.29	6.17
	7	4.36	6.94	4.99	2.66	7.50
	8	3.41	−1.51	4.23	4.32	3.90
	9	6.07	4.40	2.39	1.63	4.35
	10				3.80	13.59
	11				5.49	
Average		4.36	6.38	4.52	2.79	8.58

it was revealed that the difference between acupoint and nonacupoint bioelectrical output was significant ($P < 0.05$) (Table 2).

4. Discussion

Numerous studies on the characteristics of acupoints have shown that they do in fact possess bioelectric properties, including increased conductance, reduced impedance and resistance, and increased capacitance. Recent studies have focused on the volt-ampere characteristics of acupoints [13], using electrical impedance methodology [14, 15]. Yet the majority of instruments employed measure electrical skin resistance, which differs from detecting and monitoring acupoints. Controversial findings may be due to different measuring methods. Most studies have focused primarily on the efficacy and electrical characteristics of acupoints and their active response to external electric stimulation. This cannot be equated with acupoints' own bioelectrical properties. We believe that applying signal acquisition methods similar to ECG and EEG testing to detect bioelectrical signals at acupoints may lead to understanding the true nature of the bioelectrical characteristics of acupoints.

So, we designed this experiment to test this idea. From the test results, we can basically affirm that acupoints have certain electrical properties, which are an aspect of the specificity of acupoints. The study of the electrical properties inside acupuncture points should ensure their objectivity and reproducibility, which is of great importance to fully reveal the electrical properties of meridian points.

The instrument used in this experiment, the first of its kind in China, was used to directly collect acupoint bioelectricity signal. The specific details will be explained one by one as follows:

(1) Why the acupoints on the right side of the limb were chosen: firstly, to avoid the influence of cardiac electricity, we chose the reference electrode, the grounding electrode, and the test acupoints on the same side of the limb; secondly, we chose all the acupoints on the right side of the limb because of the lying position of the volunteers and the convenience of the acupuncturist. Of course, this is the limitation of this test, and we can select the left limb acupoints for comparison in the future.

(2) It was observed that the conductivity of electrical conduction between LI 4 and LI 11 was significantly higher than that between nonacupuncture points 1 cm outside of LI 4 and LI 11. Because of the differences in body size of the volunteers, we chose 0.5–1.0 cm of the adjacent acupuncture point, but it was still appropriate for the volunteers to be free of needle sensation. To ensure the accuracy of the test, one acupuncturist was fixed to operate.

(3) In Table 1, nine volunteers participated in the test of ST 36 point, nine volunteers participated in the test of SP 6 point, nine volunteers participated in the test of GB 39 point, 11 volunteers participated in the test of GB 37 point, and 10 volunteers participated in the test of KI 9 point. It is worth clarifying that when testing the above five acupuncture points, the same volunteer could participate in the testing of different acupuncture points and their nonacupuncture points. The power values for the nonacupuncture points were taken as the average of the four points tested. The same acupuncture point and its nonacupuncture points can vary greatly in the data tested by the instrument due to the different body sizes of the volunteers. At the same time, the data from the instrument also vary greatly from point to point and from nonpoint to nonpoint. For the sake of data authenticity, we present the complete data in the table. In Table 2, the ratio of the power values of the acupuncture points is measured by each volunteer to the power values of the nonacupuncture points. A value greater than "0" indicates that the power value of the acupuncture point is higher than the power value of the nonacupuncture point; a value less than "0" indicates that the power value of the acupuncture point is lower than the power value of the nonacupuncture point. The average power value in the last row is the percentage of all power values measured at the point compared to all power values at the nonacupuncture points.

Our current experiment with five acupuncture points showed that the power of acupuncture points differs from nonacupuncture points, and in the next experiment, we are planning to increase the number of acupuncture points to 10 to continue to take evidence and demonstrate the difference between acupoints and nonacupoint. It is a strong proof of the theory of Chinese medicine and one of the foundations for further research.

5. Conclusions

There are two main findings in the article. First, it was shown that bioelectricity signals of ST 36, SP 6, GB 37, GB 39, and KI 9 have high power values; second, we found the most significant differences in the frequency range of 0–2 Hz. Also, we could evaluate the power spectrum and power of acupuncture points and how they differ from nonacupuncture points. In addition, we can explore the specificity of the bioelectricity signals of acupuncture points in the future.

Data Availability

The data of the figures used to support the findings of this study are included in the article. The data of the tables used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors have no conflicts of interest.

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Research Article

Application of Wireless Dynamic Sleep Monitor in Acupuncture Treatment of Insomnia after Ischemic Stroke: A Retrospective Study

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Purpose. Retrospective analysis of the clinical effect of acupuncture on insomnia after ischemic stroke by using a wireless sleep monitor as an innovative evaluation method. *Methods*. From March 1, 2018, to September 30, 2019, 105 cases of insomnia after ischemic stroke were extracted from the inpatient medical record system of Shenzhen Longhua District Central Hospital. According to differences in the treatment plan, the cases were divided into an acupuncture group (57 cases) and a drug group (48 cases). The acupuncture group was given acupuncture treatment on the basis of usual care, while the drug group was given estazolam oral treatment on the basis of usual care. Under the ICF framework, the related items of sleep function and emotion function were selected for evaluation. As outcome parameters, the alterations of the Pittsburgh sleep quality index (PSQI), the self-rating anxiety scale (SAS), and the self-rating depression scale (SDS) were used before the treatment, after treatment, and in a follow-up; meanwhile, the ActiSleep-BT wireless sleep monitor was used to measure total sleep time (TST), sleep efficiency (SE), and sleep arousal (SA) of the two groups before and after treatment and at follow-up. *Results*. Within-group comparison showed significant differences in the acupuncture group before treatment and after treatment on the ActiSleep-BT wireless dynamic sleep monitor data as well as in PSQI and ICF. Comparing the acupuncture group with the control group also showed significant differences in the ActiSleep-BT wireless dynamic sleep monitor data, PSQI, and ICF. *Conclusion*. By evaluation using ActiSleep-BT wireless sleep monitor, acupuncture treated insomnia after ischemic stroke; the effect is better than usual care.

1. Introduction

Insomnia is one of the common diseases after stroke, which is characterized by difficulty in falling asleep, difficulty in sleeping, and difficulty in recovering energy through sleep. 50%–68% of stroke patients are accompanied by insomnia and sleep dysfunction to varying degrees, accounting for about 10% of the total number of patients with chronic insomnia [1]. Insomnia can not only affect patients' physical and mental health, quality of life, and nerve function, but also aggravate the risk of a recurrence of a cerebral infarction or cerebral hemorrhage [2]. Most drugs used in clinical treatment of insomnia cause dependence and tolerance. Long-term use can lead to drug resistance or addiction, and the recurrence rate is high after stopping medication [3–5]. Therefore, considering the defects of insomnia drugs and various adverse reactions, non-drug treatment has gradually become the key treatment for insomnia after stroke [6, 7]. Our group retrospectively analyzed the medical records of acupuncture treatment of insomnia after ischemic stroke, in order to further evaluate its clinical efficacy.

2. Clinical Data

2.1. Research Object and Grouping. Patients with insomnia after ischemic stroke who were hospitalized in the

Rehabilitation Department, Traditional Chinese Medicine Department, or Neurology Department of the Shenzhen Longhua District Central Hospital from March 1, 2018, to September 30, 2019, were extracted from the inpatient medical record system of Shenzhen Longhua District Central Hospital. Finally, according to the inclusion and exclusion criteria, a total of 105 subjects were determined, including 57 cases in the acupuncture group and 48 cases in the drug group.

2.2. Diagnostic Criteria

2.2.1. Diagnostic Criteria of Ischemic Stroke. The diagnostic criteria of ischemic stroke were formulated with reference to the Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2014 [8, 9]: (a) acute onset; (b) focal neurological deficit (weakness or numbness of one side of the face or one limb, language disorder, etc.), or comprehensive neurological deficit; (c) unlimited duration of symptoms or signs (when imaging shows responsible ischemic lesions), or duration of symptoms for more than 24 hours (when lack of imaging responsible lesions); (d) elimination of nonvascular causes; (e) brain CT/MRI examination having excluded cerebral hemorrhage.

2.2.2. Diagnostic Criteria for Insomnia. The diagnostic criteria of insomnia are in line with the diagnostic criteria of insomnia proposed in the Chinese Classification and Diagnostic Criteria for Mental Disorders (CCMD-3). The typical symptoms of patients are sleep disorders such as difficulty in falling asleep, dreaminess, insufficient sleep depth, easy waking from sleep, early waking, and difficulty in falling asleep after waking up, accompanied by daytime sleepiness and fatigue. Sleep disorders occur more than 3 times a week and last for more than 30 days. Insomnia induces a series of emotional problems or part of activity efficiency is obviously reduced, or it is accompanied by mental disorder and even hinders the performance of social function.

2.3. Inclusion Criteria. The inclusion criteria were as follows: (a) the diagnostic criteria above are met; (b) inclusion into the study within 2 weeks to 6 months of onset; (c) medical records are complete, the acupuncture prescription is entered at least once a week, and there are assessment scales for admission and hospitalization; (d) the length of hospitalization is at least 7 days; (e) participation is voluntary and informed consent has been signed.

2.4. Exclusion Criteria. The exclusion criteria were as follows: (a) patients with severe cardiovascular/cerebrovascular diseases, severe liver, kidney, hematopoietic system, or other diseases; (b) patients with mental illness in acute attack; (c) patients who are afraid of acupuncture and do not cooperate with acupuncture treatment; (d) incomplete medical records and lack of important diagnosis and treatment information; (e) the case records cannot meet the Guidance Revised Standards Reporting Interventions Clinical Trials Acupuncture (STRICTA) requirements.

3. Treatment

3.1. Basic Treatment. Both groups were given basic treatment for primary diseases, such as controlling blood pressure, improving cerebral circulation, resisting platelet aggregation, etc., accompanied by corresponding comprehensive nursing and targeted rehabilitation physiotherapy for limb function, and most patients were given comprehensive nursing for ischemic stroke. Comprehensive nursing should include nursing countermeasures for insomnia, such as creating conditions and environment conducive to sleep, training subjects to develop good sleeping habits, teaching and explaining the correct use of sleeping pills, conducting necessary psychological counseling, and highly cooperating with rehabilitation and nursing of limb functions to relieve insomnia caused by limb factors.

3.2. Acupuncture Treatment Group. According to the Guidance Revised Standards Reporting Interventions Clinical Trials Acupuncture (STRICTA), the selection of acupoints, operator, needles, the background and clinical experience of the operator were standardized to ensure the quality control of the acupuncture treatment. The following acupoints were used for the standardized acupuncture treatment: Baihui (DU20), Shenting (DU24), Yintang (Hall of Impression), Anmian bilateral (Peaceful Sleep), Shenmen bilateral (HT7), and Sanyinjiao bilateral (SP6). Patients were lying on their back during acupuncture treatment, and all acupoints were disinfected routinely. Acupuncture was performed with a $0.30\,mm \times 40\,mm$ Huatuo stainless steel filiform needle. The needles were left for 20 min for each treatment, for 3 treatments per week for 4 weeks, which made for a total of 12 treatments.

3.3. Control Group. The control group was treated with benzodiazepine pills (Huazhong Pharmaceutical Co., Ltd., approval number: Sinopharm Zhunzi H42021522, 1 mg) oral, with the initial dose of 1 mg taken 30 minutes before going to bed every night, and the adjusted dose of 1-2 mg every night.

4. Outcomes

We set ActiSleep wireless dynamic sleep monitor data as primary outcome; and the secondary outcome was Pittsburgh Sleep Quality Index (PSQI), and the International Classification of Functioning, Disability and Health Rehabilitation Set (ICF-RS).

5. Evaluation

5.1. ActiSleep Wireless Dynamic Sleep Monitor. The ActiSleep sleep monitor made by Beijing Baianji Technology Co., Ltd., was worn on one arm by patients, and the sleep efficiency (SE), sleep awakening times (SA), and total sleep times (TST) of patients were monitored before, during (2^{nd} week of treatment), and after treatment.

5.2. Pittsburgh Sleep Quality Index (PSQI). Before and after treatment, the sleep quality of the subjects was evaluated from 7 aspects: subjective sleep quality, time to fall asleep, sleep time, sleep efficiency, sleep disorder, hypnotic drugs, and daytime dysfunction [10].

5.3. The Patients Life Quality Was Evaluated by the World Health Organization Quality of Life (WHOQOL) Questionnaire. The WHOQOL is used to quantify patient's health-related quality of life. This scale was chosen, because it allows for international comparability, because the achieved scores of health-related quality of life are comparable between patients of different cultural backgrounds [11].

5.4. The International Classification of Functioning, Disability, and Health Rehabilitation Set (ICF-RS). The ICF-RS was developed by the WHO and is based on an international expert investigation and systematic large-scale data analysis: 30 items are selected from more than 1400 categories of the International Classification of Functioning (ICF) to describe the key functions of patients (from acute stage, recovery stage to chronic stage). The quantitative standard evaluation of ICF evaluates rehabilitation combination of adult rehabilitation population according to ICF, including the composition of rehabilitation combination, evaluation rules, judgment of result grade, handling of special circumstances, and precautions for use, etc. [12]. According to the level 1 limit value general scale (grades 0–4) formulated by ICF R&D Center, each item is divided into five grades: no dysfunction (grade 0), mild dysfunction (grade 1), moderate dysfunction (grade 2), severe dysfunction (grade 3), and complete dysfunction (grade 4). At the same time, considering the special circumstances such as the gender and condition of the assessed object, the original grades of 8 (unspecified) and 9 (not applicable) were also used [13, 14], as can be seen in Table 1.

5.4.1. b134 Sleep Function (Category 13)

(1) Category definition: the general mental function that produces periodic, reversible, and selective physical and psychological freedom from the environment characterized by physiological changes in which individuals live.

(2) Content description: the subject can selectively maintain proper time and quality of sleep to meet daily sleeping needs. This includes the amount, start, maintenance, and quality of sleep and takes into consideration pathologies of sleep, e.g., insomnia, lethargy, and narcolepsy. Excluded are consciousness function (b110), energy and driving force function (b130), attention function (b140), and psychomotor function (b147).

(3) Assessment language: have you had any sleep problems in the past 2 weeks?

(4) Assessment guidance: in this category, the assessed person needs to comprehensively consider three factors, sleep time, sleep quality, and the troubles caused by sleep problems to life, work, and study, and mark the corresponding numbers 0–10 by using the Numerical Rating Scale (NRS).

(5) Scoring rules: Numerical Rating Scale (NRS); please see Table 2.

Level 0: the above NRS score is 0. Level 1: the above NRS score is 1-2. Level 2: the above NRS score is 3–5. Level 3: the above NRS score is 6–9. Level 4: the above NRS score is 10. Level 8: unspecified. Level 9: not applicable.

5.4.2. b152 Emotional Function (Category 14)

(1) Category definition: special mental functions related to emotion: components in emotional and psychological activities.

(2) Content description: an individual's ability to generate appropriate emotions and manage various emotions. This includes emotional moderation, adjustment and range of emotions (such as sadness, happiness, love, fear, anger, hatred, tension, anxiety, happiness, and sadness), emotional variability, and a functional regulation of emotion, excluding temperament and personality function (B126), as well as energy and drive function (b130).

(3) Assessment language: in the past 2 weeks, how would you rate your own ability to generate, control, and regulate emotions?

(4) Assessment guidance: the aim is to evaluate whether the assessed individual can produce appropriate emotions and whether there is emotional inversion: can you control and adjust your emotions when you are happy, angry, or sad? Evaluate whether the mood is stable, whether there is temper tantrum, improper speech, disordered expression, physical attack, reticence, etc. The assessed person can be guided to think about the ability to generate, control, and adjust emotions when encountering specific situations or in the current environment (such as a hospital ward). Answers are marked in the following assessment criteria 0 to 10 (NRS).

(5) Scoring rules: Numerical Rating Scale (NRS); please see Table 2.

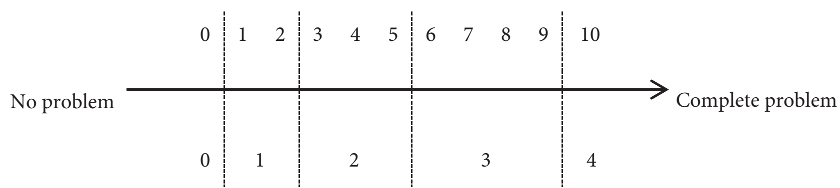
6. Statistical Methods

The data were analyzed by SPSS 25.0. The measured data are expressed as mean values and standard deviation (SD). Paired *t*-tests were used for intra-group comparison, and independent sample *t*-tests were used for inter-group comparison. The counting data were expressed by rate or

Table 1: ICF first qualifier generic scale.

Value	Problem severity	Impact of the problem	Occurrence frequency %
0	No problem	Can be ignored, negligible	0–4
1	Mild	A little	5–24
2	Moderate	Medium	25–49
3	Severe	High, very much	50–95
4	Completely	Totally	96–100
8	Unspecified	Lack of sufficient information	
9	Not applicable	Unsuited	

Table 2: Numerical Rating Scale (NRS).



Level 0: the above NRS score is 0. Level 1: the above NRS score is 1-2. Level 2: the above NRS score is 3–5. Level 3: the above NRS score is 6–9. Level 4: the above NRS score is 10. Level 8: unspecified. Level 9: not applicable.

composition ratio, and the comparison between groups was performed using the chi-square test. The comparison between the hierarchical data sets was done using Ridit analysis. Differences were considered as statistically significant if $p < 0.05$.

7. Results

7.1. Baseline. Baseline data shows the basic situation of all 105 subjects, and the comparison based on grouping. There was no significant difference after statistical analysis, and the two groups are comparable. See Table 3.

Table 3: Baseline of data.

	Acu. group	Ctrl. group	Total
N=	57	48	105
Age (mean)	52.06	50.77	51.69
Age (SD)	12.25	16.04	17.22
Male (*n*)	31	27	58
Female (*n*)	26	21	47
Living alone (*n*)	6	3	9
Living with others (*n*)	51	45	96
Still working (*n*)	49	37	86
Disease course (max)	24 w	24 w	24 w
Disease course (min)	2 w	2 w	2 w
Disease course (mean)	13.61w	12.18 w	13.49 w
Disease course (SD)	12.73	9.82	13.50
Hospitalization days (max)	28 d	32 d	29 d
Hospitalization days (min)	7 d	7 d	7 d
Hospitalization days (mean)	26.43	25.71	26.33
Hospitalization days (SD)	5.00	4.92	4.27

7.2. Comparison of Dynamic Sleep Monitoring Data. The dynamic sleep monitoring data can be found in Table 4. Three aspects are shown: sleep efficiency (SE), sleep awakening times (SA), and total sleep time (TST). Among the three assessment time points, there was a significant difference between groups. Meanwhile, within both groups, all three aspects showed improvement after treatment compared to before treatment. See Table 4.

7.3. Comparison of PSQI and ICF. Both PSQI and ICF data showed the treatment effect of acupuncture group is superior to control treatment. There were significant differences between groups at nearly all compared items. See Table 5.

8. Discussion

Insomnia is the most common symptom of stroke patients, and its incidence rate among stroke patients is much higher than in the general population. Insomnia has a great impact on the prognosis of stroke patients [15], as it increases the recurrence rate of stroke, induces psychological disorders and cognitive impairment, aggravates physical symptoms, and seriously affects the rehabilitation process and daily life [16]. The treatment of this late effect of ischemic stroke has not been paid enough attention. Sedative and hypnotic drugs are generally used for symptomatic treatment in clinic [17]. The benzodiazepine Estazolam, which was selected in this study, can block the impulse conduction from the limbic system to the brainstem reticular structure, reduce the conduction excitation in the cerebral cortex, and thereby have sedative and anticonvulsant effects. However, benzodiazepines are known to induce drug dependence and cause various adverse reactions [18].

Modern acupuncture experimental research has proven that the corresponding acupuncture points can increase the content of 5-hydroxytryptamine and aminobutyric acid in the rat brain and reduce the content of glutamate, the excitatory neurotransmitter, so as to improve the central inhibitory function and thus lead to improvement in case of

Table 4: ActiSleep-BT data comparison.

	Acu. group			Ctrl. group		
	Before t.	During t.	After t.	Before t.	During t.	After t.
N=	57	57	57	48	48	48
SE% (mean)	77.26	83.62	85.17	78.33	79.07	79.62
SE% (SD)	6.11	7.00	8.61	7.10	6.99	6.57
TST (min) (mean)	351.81	411.63	468.52	363.20	408.73	416.84
TST (min) (SD)	99.30	121.84	109.71	130.64	122.44	127.02
SA (mean)	18.15	17.71	14.20	19.05	16.79	17.83
SA (SD)	10.08	9.37	7.51	11.17	10.86	12.09

Table 5: Data comparison of PSQI and ICF.

	Acu. group		Ctrl. group	
	Before t.	After t.	Before t.	After t.
N=	57	57	48	48
PSQI (mean)	12.94	10.77	12.05	11.83
PSQI (SD)	4.72	3.08	6.42	5.50
ICF b134 (mean)	2.89	1.04	2.75	1.84
ICF b134 (SD)	1.05	1.31	1.62	1.96
ICF b152 (mean)	2.79	0.68	2.66	1.27
ICF b152 (SD)	1.17	1.29	1.38	1.54

insomnia [19]. According to the meridian syndrome differentiation of traditional Chinese medicine, insomnia is an ailment located in the brain, and the ascending of the governor vessel (Du Meridian) belongs to the brain. Therefore, the Baihui acupoint (Du20) is selected as the main acupoint for this treatment, and the Shenting (Du24) and Yintang acupoints (Hall of Impression) are combined to regulate the governor vessel, regulate the mind, and tranquilize the mind. Anming, as the name implies (Anming means peaceful sleep), has a special therapeutic effect on insomnia, can calm and induce sleep, and is a commonly used acupoint for sleep disorders. The Shenmen acupoint (HT7) is the Yuan (primary) acupoint and acupoint of hand-shaoyin heart meridian, which is mainly used for treating heartache and insomnia [20]. Acupuncture of Shenmen (HT7) can regulate the original qi of heart meridian and tranquilize the mind. Sanyinjiao (SP6) refers to the intersection point of three yin meridians and is effective against various diseases which are caused by yin deficiency, such as palpitation and insomnia [21].

To evaluate the curative effect of the acupuncture treatment, a subjective scale was combined with objective data. As a standard and recognized objective evaluation index of sleep quality, kinescope can effectively ensure the reliability of curative effect evaluation. Previous methods of sleep quality assessment include polysomnography (PSG), or subjective assessment methods such as sleep diary and sleep scale. Although PSG can accurately analyze sleep and waking state, its relatively high price and inability to record sleep in a natural state limit its clinical application. Although the sleep diary can reflect the sleep status in a natural state to a certain extent, its accuracy has not been recognized. However, the kinescope can accurately and continuously record the patient's sleep time and movement during sleep, making it an objective monitoring index that can replace PSG to evaluate sleep quality. As the subjects of this experiment are insomnia patients after stroke, there are many potential influencing factors in the experiment, such as medication baseline of stroke patients, acupuncture experience of patients, etc. [22]. These influencing factors were not controlled in this experiment. However, these factors will be the focus for the improvement of high-quality randomized controlled clinical trials with strict specifications, which are to follow up on this study.

Data Availability

The study data are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Yujuan Song was the leader of the project of "high-level medical team project" and the main author in this paper. Xuebing Wang was a member of the project and she was responsible for data collation and data processing. Friedrich Schubert was the project technical and English language support.

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Review Article

Resting-State fMRI in Studies of Acupuncture

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Research exploring the mechanism of acupuncture has been a hot topic in medicine. Resting-state functional magnetic resonance imaging (rs-fMRI) research is a noninvasive and extensive method, which is aimed at the research of the mechanism of acupuncture. Researchers use fMRI technologies to inspect the acupuncture process. The authors reviewed the application of rs-fMRI in acupuncture research in recent 10 years from the aspects of studying acupoints, subjects, acupuncture methods, and intensities. The results found that the application of rs-fMRI in acupuncture research mainly includes research on the onset mechanism of acupuncture treatment; visual evidence of diagnosis and treatment of dominant diseases; efficacy assessments; physiological mechanism of acupoint stimulation; and specific visualization of acupoints.

1. Introduction

Acupuncture has been used as a traditional treatment method and is now becoming popular rapidly in clinical medicine practice because of its undeniable therapeutic effects [1, 2]. However, the effect of the acupuncture mechanism on the central system is still unclear, so the exploration of the acupuncture efficacy mechanism has been a hot topic in the medical study [3, 4]. Nowadays, resting-state fMRI is a prominent technique to measure the activities in the brain caused by acupuncture [5, 6].

The objective of this study is to develop an artificial intelligence analysis algorithm and automatic result output system with the function of reading and analyzing fMRI images in acupuncture research. Based on this demand, we preliminarily collected the contents mentioned in this review.

2. Comparison of Acupoints

2.1. Comparison of a Single Acupuncture Acupoint vs. Acupoint or Nonacupoint. Eight recent studies showed that acupuncture at different acupoints could induce different activities of brain regions in resting-state networks (Table 1). Zhong et al. [7] found that the connectivity between the superior temporal gyrus and anterior insula was enhanced by acupuncture at GB40 and the connection between the STG and postcentral gyrus was increased following acupuncture at KI3. Qiu et al. [8] reported the differences in wavelet transform coherence characteristic curves in the declive, precuneus, postcentral gyrus, supramarginal gyrus, and occipital lobe with acupuncture at LR3 and nonacupoint, and the posteffect can last for 5 minutes. Feng et al. [9] found that compared to nonacupoint, the increase in correlations for acupoints was related with the limbic/paralimbic and subcortical regions and the decrease in correlations was related with the sensory and frontal cortex. Long et al. [10] found that the areas with significant changes in functional connection values after acupuncture at ST36 were mainly concentrated in the middle temporal gyrus and parahippocampal gyrus, which are the main hubs of the default network. The therapeutic effect of acupuncture on pain may be related to the enhanced connection between these two areas. Yu et al. [11] observed that acupuncture at LR3 mainly activated the brain functional network in visual function, associative function, and emotional cognition, which was consistent with the therapeutic effect of LR3 in traditional medicine; furthermore, it had specific values to interpret the acupoint specificity of the LR3. Cai et al. [12]

Table 1: Research studies on a single acupuncture acupoint vs. acupoint or nonacupoint.

Acupoints	Main findings
GB40 vs. KI3 [7]	Superior temporal gyrus (STG), auditory network, and anterior insula vs STG and postcentral gyrus
LR3 vs. nonacupoint [8]	Declive, precuneus, postcentral gyrus, supramarginal gyrus, and occipital lobe; post-ACU can lasted for 5 minutes
ST36 vs. nonacupoint [9]	Limbic/paralimbic regions
ST36 vs. nonacupoint [10]	Parahippocampal gyrus and middle temporal- major hubs of the default mode network
LR3 vs. nonacupoint [11]	Network: visual, emotion, and cognition
Back-shu + front-mu vs. single [12]	ReHo: thalamus, the posterior cingulate gyrus, and the precuneus
ST36 vs. nonacupoint [13]	Somatosensory and saliency processing regions
Combinations vs. single [14]	More widely activate areas; new brain areas; and curative effects

found that needling at the back-shu and front-mu points of the stomach can induce the ReHo changes in the thalamus, the posterior cingulate gyrus, and the precuneus brain regions compared with the single point, and these areas are the important brain regions for points to regulate gastric motility. Nierhaus et al. [13] considered that the stimulation about ST36 can obviously modulate somatosensory and saliency processing activities than nonacupoint. Liu et al. [14] addressed that the combined acupoints activate a wider range of brain areas than single points. In addition, the association of acupoints could activate a few new brain areas and engender new curative effects.

2.2. Comparison of before Acupuncture vs. after Acupuncture. More and more results suggested the brain activity after acupuncture was different from that before acupuncture, needing at points could change inherent activities of the cerebral cortex (Table 2). Zhang et al. [15] revealed that needling at LR3 and KI3 specifically promoted the function of brain areas, which are related to vision, emotion, and cognition, and inhibited associated with attention, phonological, and semantic processing. Zhou et al. [16] found that acupuncture at the points of the Lung Meridian could significantly strengthen ALFF in the right gyrus subcallosum and inferior frontal gyrus and weaken in the right postcentral gyrus, left precuneus, superior temporal gyrus, and middle temporal gyrus and needling at the Lung Meridian points could alter inherent activities of the cerebral cortex. Liu et al. [17] observed that compared with before acupuncture, the ReHo in cognitive network, motor network, default network, and limbic system encephalic changed after acupuncture at GB34.

2.3. Comparison of Verum Acupuncture vs. Sham Acupuncture. Table 3 presents that verum acupuncture was superior to sham acupuncture. Verum acupuncture stimulated acupoints to produce the sensation of Deqi. Zyloney et al. [18] reported that verum acupuncture (ACU) generated the connectivity in the PAG, PCC, and precuneus, contrasting with sham ACU, and significantly promoted the changes of functional connectivity regions in the pain matrix and default mode network by acupuncture at LR3. Zhao et al. [19] indicated that a true acupuncture effect had more extensive and more significant brain reactions in the long-term stimulation than sham ACU. Adopting the ALFF and ReHo approach, Wu et al. [20] observed that acupuncture at LR3 can modulate the activities of functional brain regions, such as vision, movement, sensation, emotion, and analgesia, but sham ACU does not show correlations in regions with functions. Liu et al. [21] found that poststimulus effects showed a more significant characteristic through verum ACU, and the insula plays a crucial role in the switch process of immediate- and delayed-effect neural responses of acupuncture.

2.4. Comparison of Contra-Acupuncture vs. Ipsiacupuncture. The authors used contra-acupuncture vs. ipsiacupuncture to measure the mechanism of acupoints (Table 4). Using ReHo as the observation index, Zhang et al. [22] found that ACC plays an essential role in the regulation of contralateral ST38, on the other pathway of the brainstem-thalamus-cortex, which is an important region on the ipsilateral ST38. Yan et al. [23] revealed the different changes of brain functional connectivity modes after acupuncture at contralateral or ipsilateral ST38, which supported the hypothesis of acupoint specificity.

Two studies designed the comparison of individual differences. Yang et al. [24] found the decreased connectivity in the left middle frontal gyrus in Val/Val homozygous subjects compared with the Val/Val homozygous subjects. The change of ReHo in different brain regions may be related to different constitution groups, and the acupuncture feeling of physical differences may be an important factor affecting acupuncture analgesia [25].

3. Comparison of Different Acupuncture Methods

Ten studies to investigate the verity of brain activities used different acupuncture methods (Table 5). The DMN was observed to have a more extensive connectivity following MA and EA, and the connectivity in the sensorimotor network was specifically increased by TEAS [26]. Lv et al. [27] found the changes in the ReHo or ALFF value in brain region functions related to cognitive after-laser acupuncture at TGA. Jiang et al. [28] reported more prominent connectivity between the DMN and the SMN during 30 minutes transcutaneous electrical nerve stimulation (TEAS) compared with MTEAS. Motor function regions

Table 2: Research studies on before acupuncture vs. after acupuncture.

Study	Main findings
Zhang et al. [15]	ALFF: increased cerebral occipital lobe and middle occipital gyrus Decreased gyrus rectus of the frontal lobe and posterior lobe
Zhou et al. [16]	ALFF: right gyrus subcallosum, postcentral gyrus, inferior frontal gyrus left precuneus, superior temporal gyrus, and middle temporal gyrus
Liu et al. [17]	ReHo: cognitive, motor, default network, and limbic system

Table 3: Research studies on verum acupuncture vs. sham acupuncture.

Study	Main findings
Zyloney et al. [18]	PAG, PCC, and precuneus; pain matrix and default mode network
Zhao et al. [19]	More extensive and remarkable cerebral response
Wu et al. [20]	ALFF + ReHo: vision, movement, sensation, emotion, and analgesia
Liu et al. [21]	Insula

Table 4: Research studies contra-acupuncture vs. ipsiacupuncture.

Study	Main findings
Zhang et al. [22]	ReHo: ACC, brainstem-thalamus-cortex
Yan et al. [23]	Increased: anterior cingulate and insula Decreased: anterior/paracingulate cortex

connectivity was changed by the xingnaokaiqiao method [29]. Chung et al. [30, 31] pointed out that scalp acupuncture can remarkably enhance the regulation system of the brain network involved in cognition and implementation and the correlation with adjacent brain regions. EA of the auricular concha has an instant effect in modulating the brain default mode network in PI patients, and it may be a brain mechanism underlying improvement of PI [32]. An abdominal acupuncture method could improve the functional connectivities in the cognition network [33]. After electrical stimulation of acupoints, the activities in the frontal lobe, cingulate gyrus, and cerebellum had local changes. In addition, the intensity of changes after 15 minutes were higher than 5 minutes, indicating that the effect of EA on brain functional areas was continuous and strong [34]. Compared with SNA, TENS, TNA, or SNA plus SNA + MS methods showed that the most extensive DMN modulation induced by TNA acupuncture methods can be used as a way of regulating brain activity [35].

4. Comparison of Different Stimulation Intensities

Two studies compared the impact of needling at different intensities on brain functional connectivity (Table 6). Shi et al. [36] reported that deep acupuncture with Deqi sensation could regulate neural activity at multiple levels, but no one had Deqi sensation when undergoing shallow acupuncture. Increased connectivity in the MPFC/rACC and dorsolateral prefrontal cortex after enhancement acupuncture compared to standard acupuncture in KOA patients certificated the underlying treatment of the KOA brain mechanism was significantly associated with stimulation intensities [37].

5. Dominant Diseases

5.1. Nervous System Diseases. Table 7 shows research on the onset acupuncture mechanism of diagnosis and treatment of dominant diseases. Zheng et al. [38] found that needling LIV3 and LI4 can regulate the functional activity of cognition-related regions in AD patients. Acupuncture at LIV3 and LI4 can increase the hippocampal connectivity in AD disease [39]. Wang et al. [40] demonstrated that acupuncture can achieve antidepressant treatment through modulating limbic system activity, particularly the amygdala and the ACC. The changes of DMN connectivity can be used to monitor CM and acupuncture modulate effects after acupuncture [41]. Stroke patients showed decreased FC in the motor cortex, and the decreased FC was increased after acupuncture [42]. Acupuncture at motor-implicated acupoints specifically modulates the motor-related network in stroke patients and enhances the connectivity between the cerebellum and primary sensorimotor cortex. What's more, acupuncture at motor-implicated acupoints could compensate for the decreased connectivity between the cortex and subcortical areas, thus improving motor coordination and subcortical motor learning ability in stroke patients [43]. Tan et al. [44] indicated that acupuncture at tiaoshenyizhi acupoints can improve cognitive function in mild cognitive impairment disease. Chen et al. [45] demonstrated that ACU at TE5 increased the connectivity of the bilateral sensorimotor networks in ischemic stroke patients. Wang et al. [40] included the action of acupuncture on antidepressant patients may be actualized through regulating the areas of the limbic system. After acupuncture at GB34, the functional connectivity between the PM/SMA and SMG was enhanced in stroke patients, suggesting that acupuncture delays the progression of the disease by increasing the communication connection between the damaged white-matter tracts. [46]. Li et al. [47] observed decreased FC in the RFPN could be reversed by acupuncture. Compared with healthy controls, the connectivity between ACC and PCC was enhanced after acupuncture, and the functions of ACC and PCC were associated with cognitive and motor ability that could be interpreted the modulatory effects of acupuncture [48].

Table 5: Research studies on different acupuncture methods.

Methods	Main findings
MA + EA, TEAS [26]	MA + EA: more secure and spatially extended connectivity; TEAS: sensorimotor network
Laser acupuncture [27]	Cognitive functions
TEAS [28]	DMN and SMN
XNKQ acupuncture [29]	Motor function
Scalp acupuncture [30, 31]	Cognition, implementation network, and adjacent brain regions
EA [32]	DMN
Abdominal acupuncture [33]	Allomeric function
EA [34]	Higher intensity at 15 minutes than 5 minutes
SNA, SNA + MS, and TENS [35]	Different acupuncture methods to induce different DMN modulatory effects

Table 6: Research studies on different stimulation intensities.

Intensities	Main findings
Deep **vs.** shallow [36]	LPNN and DMN
Enhancement **vs.** standard [37]	MPFC/rACC and dorsolateral prefrontal cortex

Table 7: Research studies on different dominant diseases.

Dominant diseases	Main findings
AD [38]	Cognition regions
AD [39]	Hippocampal
Depression [40]	Limbic system, amygdala, and the ACC
CM [41]	DMN
Stroke [42]	Bilateral motor cortex
Stroke [43]	Motor-related network
MCI [44]	Cognition regions
Ischemic stroke [45]	Sensorimotor network
Depression [40]	Limbic system, amygdala, and ACC
Stroke [46]	PM/SMA and SMG RFPN
Migraine [47]	ACC and PCC
Stroke [48] chronic pain [49–51]	Networks: DMN, salience, central executive, and sensorimotor
ALBP [52]	Limbic, pain, attentional and somatosensory system, and DMN
CD [53]	Afferent processing network and DMN
Smoking craving [54]	SN
Hypertension [55]	Frontal lobe, cerebellum, and insula
PMS [56]	Aberrant neural activity
Cardiovascular [57]	Cortical, hypothalamus and brainstem

5.2. Motor System Diseases. Imaging studies evidenced that acupuncture may achieve its therapeutic effect through regulating the connectivity of DMN, salience, central executive, and sensorimotor networks in chronic pain patients [49–51]. Wu et al. [52] showed that acupuncture causes extensive inactivation of almost all limbic systems, pain systems, and DMN in patients with acute lower back pain, which indicated that multiplex networks involved in the treatment of motor system diseases by acupuncture.

5.3. Other Diseases. Bao et al. [53] found that the efficacy of acupuncture on CD may involve the regulation of the afferent processing network and DMN in the brain. The effects of acupuncture in treating smoking craving were remarkable, and the SN played an important role in the treatment course [54]. The efficacy of LR3 in connectivity was more concentrated in the frontal lobe, cerebellum, and insula [55]. Pang et al. [56] found that the aberrant neural activity of PMS patients could be regulated by acupuncture at SP6. Acupuncture may adjust the cardiovascular system through multiple brain networks with the cortical level, the hypothalamus, and the brainstem [57].

6. Conclusions

This review demonstrates the application of rs-fMRI in the study of the acupuncture mechanism from the aspects of study acupoints, subjects, acupuncture methods, and intensities and found that the application of rs-fMRI in acupuncture research mainly includes research on the onset mechanism of acupuncture treatment; visual evidence of diagnosis and treatment of dominant diseases; efficacy assessments; physiological mechanism of acupoints stimulation; and specific visualization of acupoints. Specifically, the following conclusions can be drawn from the physiological mechanism of acupuncture at acupoints and its specificity research: there are differences in the brain connectivity and local activities between single and different acupoints, and combination points have more wide activate areas than single point; the regulate areas are mostly related to the emotional, cognitive, and painful functions; limbic system and subcortical areas are found to be hubs after acupuncture; verum acupuncture may increase DMN, PAG, PCC, and pain matrix connectivity compared with sham acupuncture, and sham acupuncture influenced less functional areas than true acupuncture; the local brain functional activities of ipsilateral acupuncture are different from those of contralateral acupuncture; the effect of acupuncture has an obvious individual difference; and there are different degrees of changes in brain functional connectivity among different acupunctures, intensities, methods, and different subjects, and an adjusting acupuncture approach can be used as a means of regulating brain activity. In addition, in the study of the onset mechanism of acupuncture treatment, diagnosis and treatment of dominant diseases, and curative effect evaluation, we can see that the brain functional connectivity is not the same in several dominant diseases, acupuncture can treat diseases by regulating the brain network related to cognitive and motor functions, rs-fMRI has an important meaning for the evaluation of the therapeutic effect after acupuncture, and there is a great significance for the establishment of disease-specific biomarkers.

A good technical platform has been offered by the development of medical imaging for the study of acupuncture mechanisms. With the help of fMRI, the inherent and spontaneous neural activities of neurons can be observed from the microscale, mesoscale, and the entire brain area, and it will contribute to depict the organization and mechanism of the brain. However, the sample size is relatively small. In the future, we will collect more samples to expand the database for developing an artificial intelligence algorithm and automatic result output system of fMRI images to explore the cerebral mechanism of acupuncture.

Abbreviations

STG: Superior temporal gyrus
ReHo: Regional homogeneity
ALFF: Low-frequency fluctuations
PAG: Periaqueductal gray
PCC: Posterior cingulate cortex
ACC: Anterior cingulate cortex
MA: Manual acupuncture
EA: Electroacupuncture
TEAS: Transcutaneous electrical acupoint stimulation
TGA: Thirteen ghost acupoints
MTEAS: Minimal TEAS
PI: Primary insomnia
DMN: Default mode network
SNA: Single-needle acupuncture
TENS: Transcutaneous electrical nerve stimulation
TNA: Three-needle acupuncture
LPNN: Limbic-paralimbic-neocortical network
MPFC: Medial prefrontal cortex
rACC: Rostral anterior cingulate cortex
KOA: Knee osteoarthritis
CM: Chronic migraine
SMA: Supplementary motor area
SMG: Supramarginal gyrus
RFPN: Right frontoparietal network
PMS: Premenstrual syndrome

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Authors' Contributions

Xiaoling Li, Lina Cai, and Xiaoxu Jiang contributed equally to this work.

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Review Article

Overview of Artificial Intelligence Applications in Chinese Medicine Therapy

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To evaluate the importance of AI technologies in modernizing traditional Chinese medicine (TCM) therapy, this article presents the systematic review of the relevant literature and explains the beneficial effects of AI technology on the TCM treatment outcomes from the experience of famous and veteran Chinese medicines, including acupuncture, Tui Na massage, and Qigong practitioners. This study also focuses on the urgent necessity to apply AI technologies to develop therapeutic models on the theme "treating the disease before it happens." Furthermore, the study also discusses the major bottlenecks and future prospects for the development of intelligent TCM treatment strategies.

1. Artificial Intelligence and Chinese Medicine

Artificial intelligence (AI) refers to the technical simulation of human intelligence by computer-based programs and/or robotics mimicking biological thought processes and physical expressions. AI-related research and development involve high levels of interdisciplinary application-oriented toolboxes, including machine learning, deep learning, robotics, gesture, facial expression, and cognitive and language processing. In this way, each and every minute aspect of biological communication and expression patterns are used as inputs to train the algorithm-based simulations with varying degrees of complexity to support multipurpose human necessities as required. The concept of AI was first formally defined at the Dartmouth Summer Research Project workshop in 1956 [1, 2]. Later in 1972, Stanford University in California first developed an AI-guided early expert system, MYCIN, which was used to treat patients with blood infections based on the archived medical test results and reported symptoms [3]. The application of AI technology in the field of medicine has been becoming more extensive and detailed. In recent years, AI technology finds its extensive applications in almost every aspect of healthcare and allied fields, such as robotics-mediated complex surgical procedures, robotics in high-throughput clinical diagnosis and therapy, telemedicine, developing universal coding systems for exchange, storage, interpretation, and quick retrieval of healthcare-associated information in an uninterrupted and highly secured way [4]. During the 1970s and 1980s, Chinese scholars attempted to combine AI technologies with traditional Chinese medicine (TCM) for the first time to develop an AI-guided assistive diagnostic and therapeutic system within the realm of TCM [5]. AI technology has been found quite helpful to the TCM practitioners to promptly and precisely realize the optimization and objectification of four diagnostic methods to provide more efficient clinical treatments and standardized health management [6–11]. Despite rapidly emerging technological advances in the fields of data science and AI in healthcare, there has not been enough interest in modernizing TCM diagnosis and therapy with the help of AI-guided skills. In the era of next-generation technological breakthroughs, it is of utmost importance to blend AI skills with TCM-based treatment strategies making it easily acceptable, reliable, and affordable to all needing people to keep pace with the rapid advancement of healthcare facilities worldwide.

2. AI System of the Experience of Famous and Veteran Chinese Medicine

The development of the TCM has a history of inheritance for over a thousand years. Unequivocally, the knowledge system of the TCM has been highly enriched with invaluable pathological, clinical, and medical experiences of the predecessors and is continuously being updated with novel therapeutic information. Amongst the archived experiences of TCM, the TCM-based clinical experience represents the top-level diagnosis and treatment strategies for most diseases and acute illnesses, which reflects the inheritance of the profound wealth of knowledge over generations.

Scholars have made substantial efforts to exploit the power of AI in aggregating the experience-based knowledge from the very beginning of TCM to the modern era in order to form a potentially influential and effective knowledge system that can facilitate modern-day treatments by retrieving the information on the ancient Chinese medicine [5]. Functionally, AI can be trained on the desired human experiences through the databases to perform in dialectical thinking mode mimicking human thought processes, while simultaneously it can also collect new information from the contemporary diagnosis and treatment experiences to provide more focused as well as highly enriched healthcare solutions in a geographical location, ethnicity, and/or disease-specific manner. Liu Fan [12] has reported the utility of the knowledge mapping technology to analyze the retrospective data of curative effects of the TCM in chronic gastritis treatments based on syndrome differentiation, comparisons of prescribed medicines, and core symptoms by the groups of famous TCM practitioners, Drs. Yao Naili and Zhang Runshun. This analysis yielded four superior diagnosis and treatment schemes in the form of knowledge mapping, further supporting the fact that the applications of AI in the TCM could effectively utilize the invaluable experiences of famous veteran TCM practitioners to provide more organized and precise diagnostic platforms. Furthermore, the knowledge mapping technology is not only essential for building databases for the TCM-associated clinical diagnosis and treatment outcomes but also assists with the visualization and deep analysis of novel ideas and therapeutic rules before their implementations. The clinical application of knowledge mapping can provide multiple potential treatment options to the physicians based on the diagnostic results, thereby accelerating the treatment procedures, which in turn will be automatically included in the database if proven efficient, forming a virtuous circle.

TCM scholars have been continuously digitizing the classic books of the TCM, literature on diagnosis and treatment experiences, and physiological mechanisms, gradually forming databases for the TCM expert system along with user-friendly and reliable data-sharing platforms.

Moreover, Chen Qingwen [13] has developed an automatic diagnosis and treatment system based on neural network technology. By using this symptom-oriented search tool, physicians not only can promptly access important medical records to learn about the therapeutic outcomes of previously employed TCM in treating related diseases but also are able to precisely execute e-prescriptions for rapid distribution to relevant departments and the patient as well. This system can immensely benefit the physicians from all sectors to share and learn the experiences of expert TCM practitioners in order to improve the overall diagnosis and treatment standards of TCM.

3. Acupuncture and AI

According to the statistics of the World Health Organization and the World Federation of Acupuncture and Moxibustion Societies, acupuncture has been applied in 142 countries or regions by 2002. In recent years, wide acceptance of acupuncture as a highly effective noninvasive therapeutic platform has made it possible to amend the medical guidelines to include acupuncture as a standard medical practice worldwide, which in turn has been attracting the long-term interests of the healthcare industry to commercialize acupuncture globally. Moreover, with the help of the web-based learning tools, acupuncture "cloud lecture" has been educating people globally about its wide ranges of applications in treating almost all types of diseases in a noninvasive way and without worrying about long-term harmful side-effects, giving this therapy an international recognition and popularity [14]. Hence, it is obvious that blending acupuncture therapy with AI technologies will further improve the diagnostic precision and treatment outcomes at international standards. The robot-controlled acupuncture (RCA) technology [15] has been developed by the Department of Computer Science and Information Engineering, Tainan National Cheng Kung University, to investigate the therapeutic effects of acupuncture from three broad perspectives: (1) localization of the acupuncture points, (2) timely robot arm activation for the acupuncture point stimulation, and (3) AI-guided automatic detection of therapeutic efficacy of acupuncture point stimulation. To do so, an automatic acupuncture system was established with a 2D monocular camera and a robotic arm determining the degree of Qi gain by real-time monitoring of electroencephalographic (EEG) changes. Notably, RCA focuses on the most challenging aspects of facial acupuncture point localization using a 3D morphable model (3DMM) for reconstructing subject's 3D facial model precisely labeled with acupuncture points by following the sequential steps: facial image capture, labeling the facial acupuncture points, merging into an Isomap texture, and loading the 3DMM texture along with the average model into 3D graphics software to perform the precision facial acupuncture. Indeed, medical robots can perform these tasks with much higher accuracy than humans, allowing acupuncturists to locate hard-to-reach acupuncture points with the help of

RCA and make them get their essential Qi energy [16–19]. It is worth mentioning that combining acupuncture with modern medical technologies and AI tools can significantly reduce the controversy of acupuncture safety issues seriously considered in Western countries. Moreover, these interdisciplinary approaches have prompted international medical research on acupuncture technology to develop advanced methods such as purple laser acupuncture, two-color laser needles, and ultra-thin permanent needles [20–23]. However, there are still shortcomings in acupuncture machine-based research, such as the design of the machine model which is relatively simple yet without the incorporation of refined features and also remains unsuitable for deep treatments. In future research, traditional machine learning algorithms containing clustering algorithms, the law of association algorithms, and deep learning algorithms of neural network class should be combined and extended to build targeted predictive models to mine significant identifying features, which have positive impacts on achieving higher accuracy in treatment prediction for acupuncture therapy [24]. Increasing therapeutic means and applications of acupuncture have enhanced the efficacy of the simple acupuncture methods providing the impetus for the modernization of this therapeutic platform.

4. AI's "Preventive Treatment of Diseases" Thinking

The idea of "preventive treatment of diseases" has been originated from the Yellow Emperor's Canon of Internal Medicine [25] during the Spring and Autumn period and Warring States periods, representing the highest level of physicians. The idea has three meanings: first, to prevent illness before it occurs; second, to discover signs and early treatment; and third, to prevent changes after the illness. Through the wisdom of successive generations of physicians, the theory of "preventive treatment of diseases" has become increasingly and reasonably acceptable. In the case, we want to aware our community about any upcoming disease outbreaks or keep our community under constant health surveillance. We need to aggregate the big data and employ AI technologies to collect and analyze people's health records on a large scale. Xia Shujie et al. [26] have analyzed the health management model of "preventive treatment" using AI to establish a key technical model and have summarized the process into three steps: first, collecting macro-, meso-, and microhealth data; second, applying AI, such as multi-label learning, Ada Boost, neural networks, and fuzzy mathematics to construct the state identification model; and finally, intervening into the state to evaluate and summarize the dynamics to arrive at the best intervention solution with the help of AI. By virtue of AI, Snowy Technology [27] has digitized the ancient methods of pulse diagnosis in TCM into an AI-guided user-friendly system, like a health-tracking watch, for heart-brain function monitoring by collecting data on heart rate, blood pressure, and other effective indicators and analyzing the health status of 14 vital organs in the human body, which are essential to evaluate the risk levels of cardiovascular and cerebrovascular diseases in real-time. Chinese medicine believes that the development of disease follows specific transmission laws, so AI technology will provide strong support for "preventive treatment of diseases" in the future.

5. Tui Na Massage Robot

There have been crucial concepts about the importance of massage therapy in the TCM, e.g., the Yellow Emperor's Classic of Internal Medicine by Ling et al. [28] which has mentioned that "the meridians are not clear, diseases are born in the unkindness, and they are treated by massage," and Luo [29] has stated that "massage method can dredge the hair orifices and can transport the rotation of glory and health." Practically, the main function of Chinese massage therapy is to dredge the meridians, harmonize Qi and blood, and improve immunity. The application of AI in Tui Na massage therapy is in the preliminary stage, and researchers have been continuously working to develop highly intelligent massage equipment or robotics based on Tui Na protocol to improve its efficacy and safety. Based on the passive impedance control technology, Huang et al. [30] and others have developed a four-degree-of-freedom anthropomorphic robotic arm with complete elastic joints programmed with the TCM massage techniques so that it can implement the corresponding prioritization techniques according to the individual symptom, realizing the effectiveness of the combination of AI and traditional therapeutic methods. Intelligent systems for Tui Na massage can provide a wealth of functions, but their high cost and bulky structure make them difficult to apply widely. To overcome these difficulties, Wang et al. [31] have introduced a portable back massage robot that can implement three different massage techniques, namely, percussion, rolling, and kneading, on the human back, and also proposed an effective full-coverage path planning algorithm for better outcomes. Eventually, the proposed effective algorithm can improve the coverage of the massage area and also enhance the massage effects, as demonstrated by the path planning experiments. Notably, the utilization of massage robots is rapidly increasing with higher precision in massage techniques, which makes the physicians available for more critical medical services and brings convenience for rational allocation of medical resources as well. However, the flexibility of massage robots in the treatment of syndrome differentiation still needs to be improved. It can be considered from the dynamic analysis. For example, adding a series-parallel hybrid structure to the design of the Tui Na robot may be useful to achieve the flexibility of pushing, kneading, pressing, and rolling techniques while still having sufficient stiffness and precision. In future investigations, we need to learn and analyze critical aspects from ergonomics to design high-performance massage robots with improved control, sensing, and other essential features [32].

6. Qigong Intelligence

With the continuous improvement of the quality of life, people are increasingly pursuing "green and harmless" treatment methods. Amongst the TCM methods, Qigong therapy has begun to receive attention in recent years.

Qigong requires the right coordination between breathing, body posture, movement, and consciousness as the means to achieve body strength in order to prevent and treat diseases. In the state of Qigong, the body's Qi forms directional movements through the electrical conduction between the meridians and conduction organs, which strengthens the bioenergy of the human body and significantly increases physiological functions.

Modern medical techniques can demonstrate Qigong breathing characteristics by defining disease-related vital breathing patterns through machine learning techniques. Combining Qigong breathing characteristics with unique pathologies can provide AI-guided medical interventions using treatment databases for those pathologies. The daily vitality score index (VSI) [33–35] is collected using AI monitoring to summarize the specific breathing characteristics of Qigong to guide patients to stay healthy. Qigong assessment of respiratory health combined with associated therapies and biomarkers like defining VSI can be useful in establishing tracking patterns for long-term health care. AI summarizes the experimental results of Qigong therapy, suggesting its influences in enhancing cellular activity, boosting immune function, improving central sensitization responses, and delaying organ aging through respiratory regulation, and constantly complements the functions of Qigong when applied to different patients. In addition, AI critically analyzes Qigong's effects in the cellular microenvironment, such as modulation of mechanosensing between subcellular organelles within tissues to achieve therapeutic purposes [36]. Thus, AI provides more possibilities for Qigong to assist clinical treatment and nursing.

7. The Bottleneck of TCM Treatment Intelligence

TCM is an intricate and comprehensive discipline that involves a wide range of topics. The diagnosis and treatment methods of the TCM are based on the physician's knowledge and experience levels in judging the patient's pathological signs and underlying conditions, which have certain subjective elements. The basic theories of the TCM diagnosis and treatment come from abstract theories, such as Ying Yang and five elements, six meridians, and eight principles, which have not been widely recognized by international medical practitioners. Therefore, blending with AI, the scientific and objective nature of the TCM can be enhanced, making it globally applicable and affordable. The development history of the combination of AI with healthcare is only over fifty years, while the intellectualization of the TCM is still in its initial stage. Currently, the quality of the TCM-associated data has not reached the ideal level, and also, the amount of curated data in the system is relatively small, making it difficult to build a standardized and well-correlated model.

As per the essence of the TCM, the treatment plan changes according to the patient's disease symptoms. Therefore, proper application of AI to predict the symptoms is crucial in the diagnosis and treatment process. Since diseases can be diagnosed in different stages of advancements and also there is a one-to-many correlation pattern between diseases and syndromes, how to combine the AI application with therapeutic experiences for objectively and scientifically accurate syndrome prediction in the TCM is an open-ended question and also the major challenge for the development direction of AI-guided TCM in the future. It is believed that by collecting and analyzing data from a large number of samples from different diseases and syndrome types, the establishment of the disease-syndrome model can be achieved toward an intelligent TCM diagnosis and treatment system.

In the process of intelligent development of the TCM treatment, there are many ethical issues that need to be properly resolved, such as the determination of responsible subjects for medical accidents, the impact on the authority of doctors' diagnosis and treatment skills, and the protection of patients' privacy. Therefore, it is extremely necessary to establish and improve the relevant laws and regulations to protect the fundamental rights and interests of both doctors and patients.

The insufficient talent pool of interdisciplinary expertise severely limits the development of AI in the TCM field. In fact, intelligent treatment of the TCM is related to diverse scientific fields, such as Chinese medicine, computer science, statistics, biology, and robotics. Therefore, the formation of a composite talent team covering multiple fields, disciplines, and specialties is the basic requirement to guarantee the successful development of the intelligent TCM system.

Due to the lack of standardized protocols and basic data in the development of the AI-guided TCM system, more diagnostic investigations have been performed than actual treatment methods, with relatively few clinical applications [37, 38]. Presently, the existing AI systems have a single algorithm and lack a shared coding system, resulting in the development of less accurate AI-TCM systems that are not suitable for practical applications [39, 40]. The possibilities for secured and transparent sharing of medical and clinical data using crucial core algorithms of AI will potentially help in the rapid intellectualization of the TCM [41].

8. Outlook

The combination of the TCM treatment methods and AI toolboxes provides a modern data support system for archiving the TCM experiences on diagnosis and treatment methods and their dialectic analyzes, as well as the TCM-based clinical thinking to provide intelligent therapeutic solutions. Notably, this combinatorial approach has gone through the three stages of development, namely, the TCM intelligent assistance, the TCM robotics, and the wisdom of the TCM. At present, it is in the AI-assisted stage, for further development. Therefore, it is necessary to collect, collate, and analyze a large amount of the TCM treatment data by increasing its clinical applications to provide quality data facilitating the research and development of the TCM intelligent projects, which eventually include the development of the all-purpose robotics integrating various therapeutic experiences and technologies of centralized medicine to simulate dialectical thinking. It can prescribe symptomatic medications and also cooperate with precise acupuncture, massage, physiotherapy, and other aspects of treatment to achieve satisfactory patient outcomes. With the application of large numbers of TCM-programmed robots, the complete course of a patient's initial diagnosis, disease transmission, and prognosis can be accurately recorded, including the patient's successive follow-ups to provide long-term and reliable data for in-depth pathological investigations. In the process of realizing the synchronous development of production, teaching, and research, it brings continuous efforts for the intelligent development of TCM.

Data Availability

There are no laboratory data in this study, and the review process and references are corrected and put in the Data Center of Heilongjiang University of Chinese Medicine for 8 years.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication and content of this manuscript.

Authors' Contributions

Chuwen Feng, Shuoyan Zhou, and Yuanyuan Qu contributed equally to this work. Yang Li and Tiansong Yang made critical revision of the manuscript. All authors read and approved the final manuscript.

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Review Article

Discussion on the Rehabilitation of Stroke Hemiplegia Based on Interdisciplinary Combination of Medicine and Engineering

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Interdisciplinary combinations of medicine and engineering are part of the strategic plan of many universities aiming to be world-class institutions. One area in which these interactions have been prominent is rehabilitation of stroke hemiplegia. This article reviews advances in the last five years of stroke hemiplegia rehabilitation via interdisciplinary combination of medicine and engineering. Examples of these technologies include VR, RT, mHealth, BCI, tDCS, rTMS, and TCM rehabilitation. In this article, we will summarize the latest research in these areas and discuss the advantages and disadvantages of each to examine the frontiers of interdisciplinary medicine and engineering advances.

1. Introduction

Stroke is a serious cerebrovascular disease characterized by sudden and acute onset and rapid neurological deficits, which is the world's leading cause of disability and the second leading cause of death [1], leaving 80% of patients having varying degrees of lifetime neurological deficits [2]. As the global aging problem is getting worse, the positive correlation between stroke and age means that the incidence of stroke will only continue to rise. Stroke incidence is also trending toward even younger patients due to factors such as irregular work life and infrequent rest, a growing sense of pressure and anxiety, poor eating habits, and many other reasons. Hemiplegia is one of the most common symptoms of stroke and significantly affects the patient's quality of life by reducing their ability to perform activities of daily living. While the rehabilitation of hemiplegic stroke patients has commanded considerable attention in society and medicine, a severe shortage of rehabilitation therapists leads to inconsistent traditional rehabilitation training results. Thus, new treatments borne out of interdisciplinary medicine and engineering methods offer the potential to provide superior care for hemiplegic stroke patients. Such methods can not only promote the recovery of the patient by stimulating nerve remodeling, but also reduce physician workload. As shown in Figure 1, we will describe advances in the interdisciplinary combination of medicine and engineering for stroke hemiplegia rehabilitation through four primary domains: artificial intelligence, brain-computer interface, noninvasive brain stimulation, and traditional Chinese medicine.

2. Artificial Intelligence (AI)

2.1. Virtual Reality (VR). Virtual reality (VR) combines the VR technology characteristics of autonomy, interactivity, and presence with rehabilitation training, to provide novel methods for stroke patients to undergo neurorehabilitation

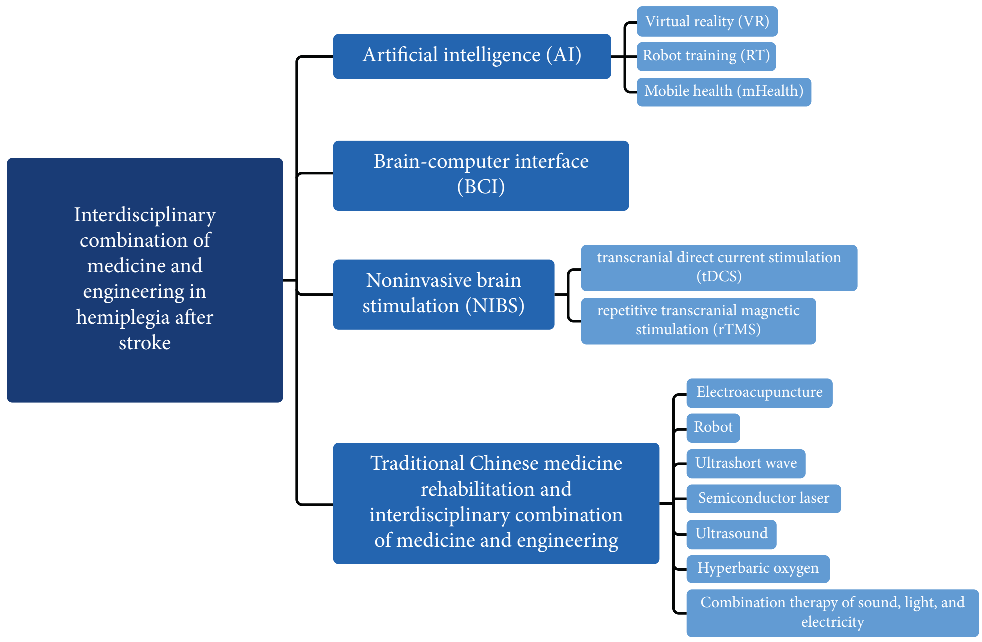

Figure 1: Application of interdisciplinary medicine and engineering approaches and technologies in the field of stroke hemiplegia rehabilitation.

in virtual environments [3]. VR is either (1) immersive, in which participants act within a computer-generated simulation world, often as an avatar, or (2) nonimmersive VR, which uses an environment that includes a 3D graphics game system. Users can use a keyboard, mouse, or other game interface devices to interact with and navigate within the virtual environment on-screen [4].

A study of 10 stroke patients found that, by wearing a head-mounted display, immersive VR mirror therapy could treat poststroke upper limb paresis [5]. Studies have also been done using VR training to improve lower limb function following a stoke; however, these studies are more infrequent [6]. Immersive VR appears to have greater effects on patient recovery compared to nonimmersive VR [7, 8]. Another study showed that providing patients with unilateral or bilateral limb mirror exercises in a fully immersive virtual environment can activate mirror neurons in damaged areas of the brain, enhance cortical reorganization, and improve motor function [9]. However, other reports have noted there is no obvious correlation between the level of immersion and hemiplegia recovery [10].

Some studies have suggested that VR has more significant effects than conventional therapy in improvement of gait speed, stride frequency, and step length [11], and can improve dynamic balance control, which could prevent patients from falling [12]. However, a study reported that VR and interactive video games are not better than traditional therapies in improving upper limb function [13]. Thus, a nuanced answer in the long-standing debate of the superiority of VR or conventional therapy is that the concept of VR is too general and broad. For example, some methods of VR are simply to improve the fun of rehabilitative exercise to promote patient adherence. In general, head-to-head comparisons between VR and conventional therapy can only be made when VR incorporates the principles of neurorehabilitation [14], which should be the subject of future research efforts.

Though promising, VR technology does have room for further development as VR can induce eye fatigue and physical fatigue during treatment, commonly manifesting as motion sickness. Motion sickness occurs when the screen display and the user's visual response are delayed [15]. Some studies claim, within the virtual environment, patients with hemiplegia use less wrist extension and more elbow extension at the end of the placement phase during arrival, grasping, and performing VR tasks [15]. VR using head-mounted displays is also slower than that in the real environment, and the spatiotemporal kinematics between VR and the real environment is also different [16]. The advantages and disadvantages of VR are summarized in Table 1.

2.2. Robot Training (RT). Rehabilitation robotics have expanded in recent years as the result of extensive communication and interaction between clinicians and engineers, leading to the development of new technologies that stimulate [17]. Rehabilitation robots are different from traditional rehabilitation equipment, as they have a logical control system that can automatically complete a series of complex operations to aid in rehabilitation treatment [18]. Robot systems in the rehabilitation field include exoskeleton and end-effector type robots [19]. Advanced robotic systems can also provide highly repetitive, reproducible, and interactive training forms. It is also possible to use technology developed to evaluate sports performance objectively (e.g., biomechanical data such as speed and strength) in the analysis and evaluation of stroke patient recovery [20].

Table 1: Virtual reality advantages and disadvantages.

Virtual reality	
Advantages	Low labor cost, high safety, improved training fun, and increased patient adherence [3, 4]
Disadvantages	(1) Vertigo [15] (2) Varying head-mounted display weight and comfort [15] (3) Eye fatigue [15] (4) Difference in the efficacy of immersion vs. nonimmersion therapy [10] (5) Limited research on efficacy in lower limbs [13] (6) Research on VR with neurorehabilitation principles should be increased [14]

One study included patients with subacute stroke that were given three weeks of intensive robot training. At the conclusion of the study, their athletic and living ability significantly improved [21]. Another reports that chronic stroke hemiplegia patients receiving three months of robotic training had improvements in proprioceptive control, reactive balance, and posture control [22]. However, a systematic review and meta-analysis found that although RT has the benefit of low labor cost, when the same amount of RT is employed as conventional treatment, RT alone is not better than conventional treatment [23]. Is there a bias in efficiency studies because of one type of robot? A systematic review and meta-analysis study comparing six types of 28 different robotic devices showed that no one type of robotic device is better or worse than other robotic devices [24]. Thus, while current research shows that there is a significant improvement before and after RT treatment, there is no obvious advantage compared with the same amount of conventional treatment and when RT is used as an auxiliary method of conventional treatment, the clinical treatment effect is strongest when the two are combined.

The current paradigm is that many repetitions of rehabilitation actions are effective for promoting recovery. However, traditional rehabilitation therapists have limited energy and the number of repetitions they can manually perform is too small to induce neuroplasticity. Thus, robot-based rehabilitation training may lead to higher exercise repetition intensity, which could promote neuroplasticity. However, some robots, such as Robot-Assisted Step Training (RAST) [25], provide active intervention that does not allow for movement errors or allow patients to take corrective measures. This training can only involve mechanical repetitive training actions, which often reduces the patient's initiative to participate, due to lack of engagement. Thus, researchers have put forward the concept of "assist-as-needed" [25] which refers to helping patients with rehabilitation exercises with the least assistance, so as not to reduce patient spontaneity and initiative. In contrast to this model, a single-blind randomized controlled trial study showed that passive intervention robots are more effective in the rehabilitation of patients with hemiplegia after stroke, and the cost and complexity of passive intervention robots are lower than those of active intervention robots [26].

Some recent research has also studied the portability and comfort of robots. For example, a biofeedback wearable robot based on human-computer interaction, compared to EMG feedback, can better improve patient compliance and can help accelerate the recovery of ankle-foot deformity after stroke [27]. Another study of wearable robots showed that the step symmetry of all stroke patients was significantly improved after training [28]. ReWalk ReStore™ is a soft robotic exosuit that is designed to assist stroke patients in walking through actively assisting the ankle joint [29]. The data recorded by wearable sensors can be used to build models and reduce the high cost and time-consuming efforts of RCT verification. This may lead to the development of robots for specific types of patients in a faster and more targeted manner [30]. The advantages and disadvantages of RT are summarized in Table 2.

2.3. mHealth. Rehabilitation of stroke hemiplegia is a long process, and the rehabilitation clinic resources are limited. When discharged from the hospital, hemiplegic patients are usually provided with a written family exercise plan to guide their recovery in the chronic stage of stroke. However, these plans rely on the patient's consciousness, and are unsupervised, which can limit efficacy. To address this, mobile health (mHealth) can provide remote monitoring and remote consultation [31]. mHealth can also provide people living in remote and impoverished areas with access to equitable rehabilitation services [32].

One mHealth example is smart shoe technology based on the Personalized Self-Management Rehabilitation System (PSMrS), which monitors the patient's movement through inductive insoles and projects sensor data on screen to provide feedback to the patient that can be assessed and monitored at home [33]. Another technology is mRehab, a mobile medical technology that combines smartphones and 3D printing and can better support stroke patients with hemiplegia attempting upper limb rehabilitation programs at home [34]. There have also been reports of new technologies that combine egocentric cameras and computer vision algorithms to allow stroke patients with hemiplegia to measure and evaluate hand function at home [35]. Other examples of mHealth include real-time sensor data combined with decision-making algorithms. For example, 70% of users of a music-based digital therapy instrument that helps perform a personalized rhythmic exercise training program to train walking speed after stroke said that they use the device at home most of the time [36]. Similar devices also exist that continuously acquire data without interference so that the patient's motor function can be evaluated in daily life [37]. The ability for patients to perform exercise assessments without a therapist makes assessments more convenient for patients and reduces the cost of medical treatment [38]. The advantages, disadvantages, and technical requirements of mHealth are summarized in Table 3.

Table 2: Robot therapy advantages and disadvantages.

Robotic therapy	
Advantages	Low labor cost, no trauma, no side effects, simple operation, and high conversion rate of economic benefits [18–20]
Disadvantages	(1) Generally large in size, poor in portability, and lack flexibility [27, 28] (2) Low comfort [29] (3) Personalized RT plans are needed for specific populations (e.g., subacute and chronic phases) [30] (4) Robot interfaces can be boring and fatigue-prone, necessitating development of a more friendly human-machine interface and with interesting games [30] (5) Robot mechanical structure and control systems lack real-time and precise control of the angle and speed of the patient's joints [25] (6) Not optimized for slower responding elderly patients [30]

Table 3: Mobile health advantages, disadvantages, and technical requirements.

Mobile health	
Advantages	Improve the efficiency of patients' self-rehabilitation exercises, provide services to people in remote areas, and reduce medical costs [31]
Disadvantages	(1) Sampling at a low rate may cause information loss [37] (2) Noise during exercise can affect data sampling [37] (3) Problems with the battery life of the device [38] (4) Regular maintenance and cleaning issues [38] (5) Putting on and taking off devices when used on disabled patients [34]
Technical requirements	(1) The patient can operate as much independently as possible [38] (2) Technical safety must be guaranteed [38]

3. Brain-Computer Interface (BCI)

Brain-computer interface (BCI) is a direct connection path established between the human brain and external devices. This technology translates the neurophysiological signals in the brain into control signals that can operate external devices or computers to assist in performing different tasks [39]. The accuracy of the cortical signals obtained by noninvasive BCI systems is not as high as the signals from invasive BCI [40], but portability, safety, comfort, and low cost make noninvasive BCI the first choice for obtaining relevant brain electrical signals and electroencephalogram (EGG) [41]. These devices include wireless EEG which offers reduced noise and signal artifacts that can be generated by the movement of wired EEG devices [42].

Many clinical studies have shown that BCI training is effective in the rehabilitation of hemiplegia after stroke [43–45]. The combination of BCI and functional electrical stimulation (FES) can also lead to superior clinical outcomes, as FES can enhance the patient's motor awareness and corticospinal excitability during exercise training, which enhances the closure of the sensorimotor circuit in BCI training [46]. Other studies have also found that the combination of BCI and tDCS training in chronic stroke patients enhances the integrity of white matter structures in the brain, increases excitability of the cortex on the same side of the lesion, and improves cerebral blood flow of the parietal and occipital lobes [47]. Despite significant short-term improvement of upper limb motor function after stroke, BCI has not been shown to produce long-term effects. SMR, the target of EEG, has been recently shown to have great potential for improving patients' exercise ability through neurofeedback procedures based on SMR-BCI. In a study that used 20 sessions of SMR-BCI neurofeedback training, patients showed significant upper limb motor recovery which was observable on functional magnetic resonance imaging (fMRI) as an increase in hemisphere activation on the ipsilateral side of the stroke lesion [48]. Quantitative electroencephalogram can also be used for clinical prognosis and monitoring after stroke in acute/subacute stages and can provide a reference value during chronic recovery stages of rehabilitation [49].

BCI via wearable and wireless EEG headsets can record EEG signals in different environments, making EEG-BCI more flexible, yet the recording quality of current headset technology usually declines after about an hour [50, 51]. Dry EEG sensors have also been developed to replace traditional wet sensors and do not require humidifying electrodes or applying gel on the skin. Dry electrodes have technical limitations however, in that they can cause significant scalp discomfort and are very sensitive to muscle and movement artifacts [52, 53]. BCI-based forehead EEGs have also been developed to assess sleep quality and can also be used as a depression treatment screening system, providing new possibilities for the treatment and evaluation of stroke patient sleep and depression risk [54]. Future efforts to improve BCI for neurorehabilitation include the development of "flexible electronics" [55] that can provide a flexible hardware platform for signal amplification to achieve closed-loop interaction, in addition to precise sensing functions. The advantages and disadvantages of BCI are summarized in Table 4.

4. Noninvasive Brain Stimulation (NIBS)

4.1. Transcranial Direct Current Stimulation (tDCS). Transcranial direct current stimulation (tDCS) is a form of noninvasive brain stimulation (NIBS). Under physiological

Table 4: Brain-computer interface advantages and disadvantages.

Brain-computer interface	
Advantages	Invasive BCI: high accuracy [40] Noninvasive BCI: portability, safety, comfort, and low cost [41]
Disadvantages	(1) Side effects: short-term nausea, fatigue, and headache [43–45] (2) Small studies, limited research [55] (3) No long-term effects [48] (4) Lack of comparison between BCI and traditional therapies [48] (5) Unknown which stage of poststroke hemiplegia is best for BCI training [49] (6) Limited research on efficacy in lower limbs [43–45]

conditions, competition between cerebral hemispheres maintains the balance of bilateral cortical excitability. After a stroke, the balance between the hemispheres is disrupted, the excitability of the affected hemisphere decreases, and the excitability of the unaffected hemisphere increases [56]. In tDCS, an anode electrode (+) is usually placed on the affected brain area to increase excitability, whereas the cathode electrode (−) is placed on an unaffected brain area to inhibit excitability [57]. tDCS regulates the resting membrane potential and changes the spontaneous discharge rate through the use of low-amplitude direct currents applied by sponge surface electrodes soaked in salt water [58] to induce neuroplasticity [59].

tDCS is widely used clinically and has significant effects on the recovery of gait speed and gait quality [60]. Studies have found that tDCS can significantly improve the upper limb function of chronic stroke patients and can have significant effects on the lower limbs in patients with subacute stroke [61]. There are three main clinical applications of tDCS which include anode (+) stimulation, cathode (−) stimulation, and bipolar (+) (−) simultaneous stimulation. A network meta-analysis involving 754 stroke patients with hemiplegia found that cathodic (−) tDCS can improve the activities of daily living in patients with hemiplegia after stroke [62]. Preclinical animal studies have also shown that the limb strength and gait of animals treated with cathodic (−) tDCS lead to complete recovery, but animals treated with the anode (+) tDCS only recovered their gait and not limb strength [63]. Cathodic (−) tDCS has also been shown to reduce edema, inflammation, cell apoptosis, and cortical glutamate, creatine, and taurine levels. Cathodic (−) tDCS also preserves cell structure within the cerebral cortex which can lead to reduction in infarct volume and better recovery of function [64]. Other theories of cerebral interactions during the recovery from exercise suggest that the cerebral hemispheres work in cooperation rather than competition. Compared to unipolar stimulation, bipolar stimulation (+) (−) can produce greater performance improvement [65] and future research should focus on bipolar simultaneous stimulation.

The study found that stimulation showed more significant changes in interval stimulation after stroke (such as day 3, day 7, and day 14) compared to daily tDCS. The results showed that the density of cortical dendritic spines increased significantly and the expression of pannexin-1 mRNA involved in hypoxia depolarization decreased [66]. Current density is the main determinant of the efficacy of tDCS, and it is generally believed that the greater the current density is, the better the effect will be, which can activate neurotrophic factors and increase calcium current [67]. However, recent studies have shown that, in anodic tDCS, the excitability change caused by 0.013 mA/cm2 current density is significantly greater than that caused by 0.029 mA/cm2 current density and is sufficient to activate calcium channels and increase intracellular calcium content. Appropriate current density is important because the higher the current density, the deeper the penetrated electric field, which is likely to affect the excitability of undamaged neurons. If the electrode size is too large, it will not only stimulate the target area, but also affect the adjacent cortex [59]. Participants in another trial reported that they had discomfort such as itching and burning during treatment [68]. Traditionally, tDCS uses two common large electrodes for treatment; however, the use of multiple small electrodes may help optimize the applied current, thereby achieving effective targeted stimulation while ensuring the safety of stimulation. In this way, personalized stimulation therapy can be customized for different patients [69]. The advantages and disadvantages of tDCS are summarized in Table 5.

4.2. Repeated Transcranial Magnetic Stimulation (rTMS). rTMS is another type of noninvasive brain stimulation (NIBS), which modulates the excitability of neurons by passing current through an insulated coil. The adjustment of excitability depends on the rTMS parameters. High-frequency stimulation can have excitatory effects within the stroke-damaged hemisphere, and low-frequency stimulation with inhibitory effects is used for the undamaged hemisphere [70]. High-frequency rTMS acts on the brain tissue through a pulsed magnetic field that promotes nerve cell depolarization and can stimulate the neurons of the cerebral cortex to speed up the reconstruction of neural pathways, thereby improving nerve function [71]. Low-frequency rTMS uses pulsed magnetic fields to activate inhibitory circuits in the cortex to inhibit brain nerve activity [72].

rTMS can delay or prevent the death of hippocampal neurons in adult rats with cerebral ischemia. The specific preservation of neurons depends on the stimulation mode and the time interval between ischemia and stimulation. Maximum neuronal protection can be achieved by applying high-frequency rTMS (at least 128 seconds) in the first 48

Table 5: Transcranial direct current stimulation advantages and disadvantages.

Transcranial direct current stimulation	
Advantages	Relatively cheap, easy to manage, and carry [56–58]
Disadvantages	(1) Side effects such as pain, itching, and burning sensation [68] (2) Optimal current density is unknown [59] (3) Optimal stimulation parameters (anode/cathode/bipolar) are unknown [62–65] (4) Optimal treatment duration is unknown [66] (5) Future research should focus on designing more personalized tDCS stimulation programs for patients [69]

hours of ischemia occurring [73]. Ischemic lesions can also cause a decrease in the expression of microtubule-associated protein 2 and mitochondrial axon transport, which leads to a decrease in ATP utilization and, ultimately, neuronal death. In rats treated with high-frequency rTMS, the expression of microtubule-associated protein 2 and ATP content in the diseased hemisphere increased significantly, suggesting that neuron repair was in progress [74]. Moreover, the expression of c-Fos and brain-derived neurotrophic factor in the cortex of rats treated with rTMS also increased significantly and promoted stroke recovery [75]. Other studies have shown that the application of 10 Hz rTMS treatment to the diseased hemisphere for 7 days significantly increases the proliferation of adult neural stem cells in the ventricle on the side of the lesion [76].

Although rTMS has been widely used to improve upper limb movement in stroke patients with hemiplegia, a systematic review and meta-analysis of 199 patients showed that current literature is insufficient to support the conclusion that rTMS combined with upper limb training is more effective than upper limb training alone [77]. The 2009 rTMS Clinical Guidelines indicate that 10 courses of rTMS are optimal; however, a 2017 study found that 5 courses of rTMS treatment are best for improving stroke-induced dyspraxia. This study also found that more than 5 courses of rTMS treatment did not have a better effect on the recovery of motor function, especially after more than 10 courses of treatment, in which case the therapeutic effect of rTMS actually decreased [78].

Theta burst stimulation (TBS) is a newly developed form of rTMS that mimics the firing patterns of hippocampal pyramidal cells during wakefulness in rodents exposed to new environments, producing low-intensity bursts of stimulation to coordinate cortical excitability [79]. Intermittent theta burst stimulation (iTBS) has been shown to enhance cortical excitability, while continuous theta burst stimulation (cTBS) inhibits cortical excitability [80]. iTBS lasting for 10 days can also promote the development of nerves in the ipsilateral inferior ventricle and increase outgrowth of nerve progenitor cells [81], in addition to enhancing neuron excitability and improving motor ability. Although cTBS inhibits excitability in the unaffected hemisphere, it does not improve hand motor function. Thus, iTBS appears to be more beneficial for patients' limb recovery than cTBS. In addition, TBS increases the risk of epileptic seizures [78]. The advantages and disadvantages of rTMS are summarized in Table 6.

5. Traditional Chinese Medicine Rehabilitation and Interdisciplinary Combination of Medicine and Engineering

Traditional Chinese medicine (TCM) is a treasure of the Chinese nation and when combined with modern science and technology can result in truly optimal integrations of medicine and engineering to advance TCM rehabilitation technology. TCM treatment of stroke hemiplegia typically includes acupuncture, massage, and rehabilitation training, supplemented by drug, psychological, physical, and exercise therapy, to promote the recovery of limb function. TCM first began taking advantage of advances in medicine and engineering through combination of acupuncture and electricity in the 1950s when Zhu Longyu established electroacupuncture therapy [82]. Acupuncture can improve the excitability of residual nerve cells, promote neuroplasticity in the damaged area, and reduce muscle tension. Electroacupuncture is mainly used to stimulate muscle movement by infusing low-frequency current stimulation on the skeletal muscle through needles, to achieve the purpose of enhancing the effect of acupuncture [83]. Electroacupuncture is currently the most widely used TCM for the treatment of poststroke hemiplegia. Newer technologies that also incorporate TCM include combinations of robotics, ultrashort wave, semiconductor lasers, ultrasound, and hyperbaric oxygen. Zhang [84] used acupuncture and a Lokohelp robot to treat patients with acute ischemic stroke hemiplegia, which significantly improved the patient's neurological deficits and improved the patient's walking ability, balance function, motor function, and activities of daily living. Ultrashort wave therapy uses the microthermal effect of electromagnetic fields to not eliminate only inflammatory cells, while simultaneously promoting edema absorption and accelerate microcirculation. Ultrashort wave therapy can also reduce sympathetic nerve tension, reduce vasospasm, establish collateral circulation, and nourish nerve tissue [85]. Li and Lai [86] showed that rehabilitation training combined with ultrashort wave therapy had significant effects in patients with hemiplegia after stroke stage I shoulder-hand syndrome. The mechanism of the semiconductor lasers is similar to that of the ultrashort wave, except that it uses light energy to reduce swelling, inflammation, and analgesia. Zhu [87] has achieved good clinical effects by using a semiconductor laser with electroacupuncture and rehabilitation training. Ultrasound uses waves that can produce physical, chemical, thermal, and mechanical effects, as well as cause tissue cytoplasm to flow and rotate. This can

Table 6: Repeated transcranial magnetic stimulation advantages and disadvantages.

Repeated transcranial magnetic stimulation	
Advantages	Relatively cheap, easy to manage and carry [70–72]
Disadvantages	(1) The effect of rTMS in different periods poststroke is unknown [73] (2) Lack of standardization with unknown optimal course of treatment [78] (3) The optimal stimulation parameters of rTMS need to be further determined [76] (4) At present, a lot of evidence does not support the individual efficacy of rTMS, and rTMS technology needs to be further optimized [77]

change the PH value in the tissue, improve the permeability of the biofilm, and accelerate the blood circulation and metabolism of the tissue [88]. Xu et al. [89] have also achieved excellent results in the treatment of hemiplegic shoulder pain after stroke using ultrasound introduction combined with rehabilitation training. Acupuncture combined with hyperbaric oxygen can have a synergistic effect in improving the oxygen supply status to the brain. This method can improve brain tissue energy metabolism, restoring the aerobic metabolism of nerve cells in the ischemic penumbra area, and scavenging oxygen free radicals. Hao [90] used Xingnao Kaiqiao acupuncture combined with hyperbaric oxygen to treat stroke hemiplegia and achieved significant clinical effects. New techniques combining sound, light, and electricity also serve as comprehensive treatments, which aid in recovery of peripheral and central nerves, effectively avoiding the limitations in space and time of conventional treatment with three kinds of equipment [91]. The advantages and disadvantages of TCM rehabilitation are summarized in Table 7.

6. Discussion

With the rapid development of science and technology, artificial intelligence, brain-computer interface, and other technologies have been widely used in clinical practice. Interdisciplinary combination of medicine and engineering is an inevitable trend in the development of modern medicine. However, as summarized above, there are some areas to be improved regarding appropriate patient selection and technical optimization. A major problem that exists is that most of the current interdisciplinary combination of medicine and engineering methods cannot prove that they are better than conventional therapy when used alone, and require further technical optimization. Additionally, in some studies, patients in the subacute phase after stroke were included in the comparison of treatment methods, but these data were not convincing because spontaneous recovery in the subacute phase would interfere with experimental results. There are also unique differences among stroke patients with hemiplegia, such as those suffering from ischemic or hemorrhagic stroke or those in the subacute or recovery phases. A limitation of some studies is that they do not specify the category of patients in the study. Many interdisciplinary combinations of medicine and engineering treatment methods also lack standardized programs for intervention measures, stimulation parameters, and treatment course standards, which likely contribute to a lack of mechanistic insights regarding these methods. The interdisciplinary combination of medicine and engineering in the field of TCM rehabilitation has great potential, but the foundation is relatively weak, and further development and research are needed.

In addition to helping doctors treat patients and promote their recovery, interdisciplinary combination of medicine and engineering has also been initially used to predict the incidence and prognosis of stroke hemiplegia. Chen and Song [93] established a stroke recurrence prediction model based on big data to assess the risk of stroke recurrence and achieved a prediction accuracy of 83%. This study found that the top 9 factors affecting recurrence are age, hypertension, triglyceride, coronary heart disease, family history of hypertension, body mass index, total cholesterol, homocysteine, and high-density lipoprotein. Liang et al. [94] also used big data to establish a stroke platform based on the new model of "Internet Plus Disabled Community Rehabilitation," providing a standardized model for describing the rehabilitation of stroke patients and at the same time, providing a platform for effective information exchange regarding rehabilitation institutions. One of the most dangerous complications of long-term oral anticoagulant therapy (OAT) is associated with intracerebral hemorrhage (OAT-ICH). The allele $\varepsilon 2/\varepsilon 4$ of apolipoprotein E (APOE) is strongly associated with recurrence of OAT-ICH. Biffi et al. [95] used neuroimaging to detect MRI markers of APOE $\varepsilon 2/\varepsilon 4$ variants to predict OAT-ICH recurrence. Liew et al. [96] also used the combination of neuroimaging and big data to establish the ENIGMA Stroke Recovery Working Group to predict the recovery of stroke patients.

Interdisciplinary combination of medicine and engineering refers to integration and collaborative innovation of medicine and engineering centering on existing medical needs. This allows the most advanced technological means of engineering to help solve clinical needs, and aid doctors in quick and accurate diagnoses, which promotes rapid patient recovery [92]. However, there are still many bottlenecks in the development of optimal interdisciplinary combination of medicine and engineering. For example, substantial integration is not widespread and current efforts are primarily concentrated within specific disciplines, producing many "one-to-one" and not "one-to-many" or "many-to-many" interdisciplinary models. There is also a critical lack of highly educated talents with medical and engineering backgrounds. Science and engineering students do not sufficiently understand clinical medicine and medical students do not have relevant knowledge of science and engineering, which leads

Table 7: The advantages and disadvantages of interdisciplinary combination of medicine and engineering in TCM rehabilitation.

Traditional Chinese medicine rehabilitation and interdisciplinary combination of medicine and engineering	
Advantages	Combination therapy has better clinical effects than single therapy [84–91]
Disadvantages	(1) Late start, weak foundation, and lack of hardware measures [92] (2) Lack of high-innovation teams and compound leading talents [92] (3) Lack of quantification, standardization, and standardization [92]

to the current situation of knowledge separation and difficult integration. The industry-university-research chain is also not perfect as hospitals, enterprises, and schools at times lack effective communication and separate projects that are not openly discussed limit the ability for widespread research advancement. Insufficient policy and financial support have also limited interdisciplinary combination of medicine and engineering.

To break through the bottleneck of development, in addition to the special support of policies and funds, it is suggested to promote the interdisciplinary research of medicine and biology, physics, material science, computer science, and other disciplines, to form many cross-disciplines with the characteristics of interdisciplinary combination of medicine and engineering. However, the most important thing for cultivating high-level interdisciplinary combination of medicine and engineering talent is the promotion cross-disciplinary thinking and innovation for trainees who are proficient in medical and engineering knowledge and can actively find problems encountered in clinical practice and solve them with engineering methods.

Data Availability

No data were used to support this study as this is a review article.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of the paper.

Authors' Contributions

Xiaowei Sun, Ke Xu, Yinghua Chen, and Tiansong Yang contributed equally to this work.

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Research Article

Platelet Distribution Width and Mortality in Hemodialysis Patients

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Objectives. The association between platelet distribution width (PDW) and mortality in hemodialysis (HD) patients has received little attention. *Methods*. We retrospectively enrolled HD patients in a single center from January 1, 2008, to December 30, 2011. The primary and secondary endpoints were all-cause and cardiovascular mortality, respectively. The association between PDW and mortality was estimated by Cox regression model. *Results*. Of 496 patients, the mean age was 52.5 ± 16.6 years, and the Charlson comorbidity index was 4.39 ± 1.71. During the follow-up period of 48.8 ± 6.7 months, 145 patients (29.2%) died, including 74 (14.9%) cardiovascular deaths. 258 (52.0%) with PDW < 16.31% were in the low group and 238 (48.0%) in those with PDW ≥ 16.31% according to cut-off for all-cause mortality by receiving-operator characteristics. After adjusting for confounding factors, high PDW values were independently associated with higher risk of all-cause (hazards ratio (HR) = 1.49, 95% confidence interval (CI) 1.15–6.82) and cardiovascular deaths (HR = 2.26, 95% CI 1.44–3.63) in HD patients. When comparing with quartile 1 of PDW, quartile 4 of PDW was independently associated with a higher risk of all-cause (HR = 1.59, 95% CI 1.18–5.30) and cardiovascular deaths (HR = 2.71, 95% CI 1.49–3.76) in HD patients. *Conclusions*. Baseline PDW was independently associated with all-cause and cardiovascular mortality in HD patients.

1. Introduction

According to the 2015 annual data report of kidney disease surveillance network in China, hemodialysis, which is about 402.18 per million in prevalence rate and 553,000 patients when quantified, is the primary renal replacement therapy for end-stage renal disease (ESRD) patients [1]. Patients on maintenance hemodialysis (HD) exhibit a high mortality, mainly due to cardiovascular events [2]. Among patients with ESRD, high concentrations of uremic toxins, chronic inflammation state, and broken hemostasis impaired platelet activation, including adhesiveness, aggregation, and release function, lead to the worse prognosis because of both bleeding or thrombosis events [3]. Besides extrinsic anti-coagulation, blood-membrane reaction during hemodialysis may aggravate and amplified this process [4]. An increasing body of evidence suggests that platelet distribution width (PDW), an indicator representing the heterogeneity of platelet size, is a potent marker of platelet activity [5–8]. Several studies show that higher PDW levels are associated with risk factors of cardiovascular disease such as hyperuricemia, diabetes, and metabolic syndrome [9–11]. Studies also show that a lower PDW was related to a poor outcome in acute ischemic stroke patients on intravenous thrombolysis, mild cognitive impairment, and Alzheimer's disease [12, 13].

A previous study found that the mean values of PDW in HD patients were higher than those of healthy volunteers. [14] However, the association between PDW values and the prognosis of HD patients has received little attention. Therefore, we aimed to evaluate the association between PDW values and mortality in HD patients.

2. Methods

2.1. Study Population. We performed a retrospective cohort study of HD patients (dialysis vintage was ≥ three months) between January 1, 2008, and December 30, 2011, in the blood purification center of the National Clinical Research Center of Kidney Disease in Jinglin Hospital. We excluded patients according to the following criteria: infections that needed antibiotic therapy, hematological diseases, immunosuppressant drugs or steroids therapy, antiplatelet therapy, or carcinomas. This study was conducted according to the principles expressed in the Declaration of Helsinki. The Ethics Committees of Jinglin Hospital approved the protocol of this study and waived the need for written informed consent because the data were analyzed anonymously.

Baseline variables included age, sex, Charlson comorbidity index (CCI), dialysis vintage, dry weight, body mass index (BMI), Kt/V, dialysis access, access thrombosis, and blood pressure. Laboratory indexes, including creatinine, albumin, high-sensitive C-reactive protein (hs-CRP), hemoglobin, platelet count, mean platelet volume (MPV), and PDW, were obtained from the first month of patients' enrollment.

The primary endpoint was all-cause death, and the secondary endpoint was cardiovascular death. Death certification was obtained from the mortality records of our center. Cardiovascular death was judged when death was caused by myocardial infarction, sudden cardiac death, heart failure, arrhythmia, cardiogenic shock, and stroke [15]. The comorbidity score was determined according to the CCI, which is one of the most commonly used comorbidity models. Dry weight was defined as the lowest weight a patient can tolerate without the presence of symptoms or hypotension [16]. Body mass index (BMI) before dialysis was calculated by dividing the dry weight in kilograms by height in meters squared. Kt/V was the clearance of urea multiplied by dialysis duration and normalized for urea distribution volume [17]. Access thrombosis defined as access (autologous arteriovenous fistula or catheter) continued anomaly due to clot, which could be detected by any physical examination, blood flow measurement, or static venous pressure.

2.2. Statistical Analysis. Receiving-operator characteristics (ROC) curves were applied to find a PDW cut-off value for predicting all-cause mortality. Participants were divided into two groups according to the PDW cut-off value of ROC. The results are presented as frequency and percentage for categorical variables, the mean and standard deviation (SD) for the continuous variables of the normal distribution, and the median and interquartile range for the nonnormal distribution parameters. Comparison between two groups proceeded through chi-square tests for categorical variables, unpaired *t-test* for continuous variables of the normal distribution, and nonparametric test for nonnormal distribution parameters. Logistic regression analyses were conducted to evaluate the association between baseline variables and high PDW (PDW ≥ 16.31%). Variables with $P < 0.05$ in the univariate analysis were included in a multivariate-adjusted model. Cumulative survival was estimated by Kaplan–Meier curves, and the difference between survival curves was compared through the log-rank test. The association between the PDW values and all-cause and cardiovascular mortality was estimated by the multivariable-adjusted Cox regression analysis. Unadjusted associations were first examined, followed by adjustments for age, sex, and CCI. Next, BMI, creatinine, albumin, hs-CRP, and MVP were added to examine whether the association of the PDW with all-cause and cardiovascular mortality was independent of confounding factors. Furthermore, patients with continuous PDW were classified into quartiles: quartile 1 < 10.53, quartile 2 = 10.53–14.67, quartile 3 = 14.68–18.86, and quartile 4 > 18.86. The association of the quartiles of PDW and all-cause and CVD mortality was further analyzed with the Cox regression models. The results of the Cox analysis were presented as the hazard ratio (HR) and the 95% CI. Data were analyzed by SPSS version 21.0 for Windows. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline Characteristics. A total of 749 patients received HD in this blood purification center. 215 of them received less than three months of HD. Thirty-eight patients were excluded due to different reasons: 10 patients received antibiotics because of infections, three had hematological diseases, eight received immunosuppressant drugs or steroids, six received antiplatelet therapy, and 10 had malignant carcinomas. The remaining 496 patients were included in the analysis (Figure 1).

The mean values of PDW were 14.37 ± 1.63%. According to the ROC curve analysis, a PDW cut-off value of 16.31% was obtained (area under the curve = 0.761, 95% CI = 0.690–0.831, $P = 0.037$), which had 85% sensitivity and 77% specificity for differentiating the patients with a high risk of all-cause mortality. Patients were divided into two groups (PDW < 16.31% and PDW ≥ 16.31%). The baseline demographic characteristics and variables are summarized in Table 1.

The mean age was 52.5 ± 16.6 years, and 59.1% were male. Patients with higher PDW were likely to be male ($P < 0.001$) and had higher BMI ($P = 0.049$), hs-CRP ($P < 0.001$), creatinine ($P = 0.005$), and MPV ($P = 0.022$) and had lower albumin values ($P = 0.033$).

3.2. Association between Baseline Variables and High PDW Using Logistic Analysis. The prevalence of high PDW (PDW ≥ 16.31%) was 47.9% in the cohort study. Univariate logistic analysis found that age ($P < 0.001$), female sex ($P < 0.001$), CCI ($P < 0.001$), and albumin ($P = 0.019$) were associated with high PDW. Multivariate logistic analysis showed that age ($P < 0.001$) and CCI ($P < 0.001$) were independently associated with the high PDW.

3.3. Association between PDW and Mortality. A total of 16 patients had transferred to other hospitals, and six patients had received renal transplantations by the end of the study.

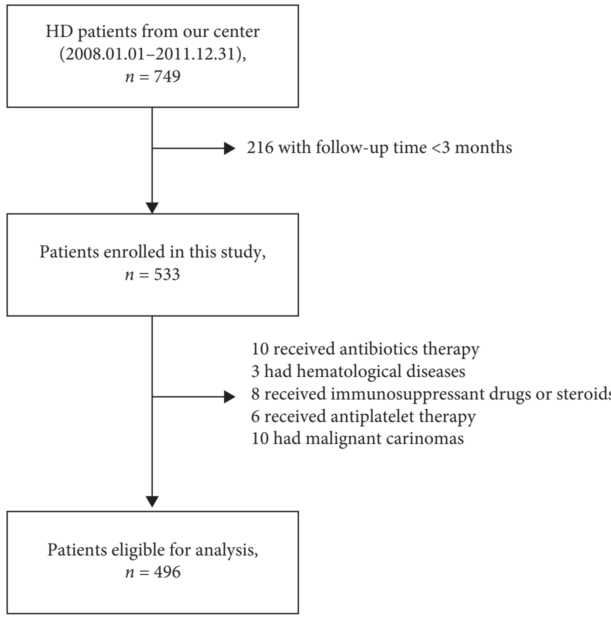

Figure 1: Flow chart showing the process of patients' enrollment.

Table 1: Baseline characteristics and laboratory parameters stratified by PDW.

	Cohort, $n = 496$	PDW < 16.31%, $n = 258$	PDW ≥ 16.31%, $n = 238$	P value
Age (years)	52.5 ± 16.6	53.0 ± 10.6	52.4 ± 17.0	0.773
Male, n (%)	293 (59.1%)	94 (36.4%)	199 (83.6%)	<0.001
CCI	4.39 ± 1.71	4.28 ± 1.69	4.50 ± 1.94	0.106
Dialysis vintage (months)	85.8 (71.2, 110.3)	85.0 (70.9, 110.3)	86.1 (65.1, 99.8)	0.364
Dry weight (kg)	60.4 ± 11.1	57.6 ± 11.9	60.6 ± 13.7	0.150
BMI (kg/m^2)	23.6 ± 5.0	21.5 ± 4.2	24.5 ± 5.3	0.049
Kt/V	1.43 (1.26, 1.64)	1.48 (1.28, 1.66)	1.36 (1.27, 1.52)	0.362
Access thrombosis, n (%)	115 (23.2%)	62 (24.0%)	53 (22.3%)	0.762
Access, n (fistula/catheter)	480/16	252/6	228/10	0.641
Systolic (mmHg)	134 ± 21	134 ± 16	140 ± 22	0.543
Diastolic (mmHg)	80 ± 15	79 ± 13	83 ± 15	0.414
Creatinine (mg/dL)	8.2 (7.5, 9.8)	6.9 (4.1, 8.3)	9.0 (8.0, 10.8)	0.005
Albumin (g/L)	43.4 ± 4.3	42.9 ± 3.3	37.0 ± 5.8	0.003
Hs-CRP (ug/mL)	2.5 (0.7, 5.3)	2.0 (0.9, 4.1)	5.8 (1.4, 7.9)	<0.001
Hemoglobin (g/L)	107.1 ± 23.8	108.6 ± 19.2	102.2 ± 24.7	0.571
Platelet counts (x 10^9/L)	150 ± 73.0	152 ± 66.4	144.2 ± 76.4	0.066
MPV (fL)	9.3 ± 5.3	9.2 ± 3.2	10.0 ± 7.7	0.022

PDW, platelet distribution width; CCI, Charlson comorbidity index; BMI, body mass index; hs-CRP, high-sensitive C-reactive protein; MPV, mean platelet volume.

No patients were lost to follow-up. There were 145 patients (29.2%) died, including 74 (51.0%) cardiovascular deaths. All-cause mortality and cardiovascular mortality in patients with higher levels of PDW were 36.6% and 19.3% and 22.5% and 10.9% in patients with lower levels of PDW. Kaplan–Meier analysis showed that cumulative all-cause mortality and cardiovascular mortality in the PDW ≥ 16.31% group were significantly higher than those in the PDW < 16.31% group (log-rank test: $P = 0.006$ and $P = 0.0001$, respectively, Figure 2).

Crude analysis showed that PDW ≥ 16.31% (PDW < 16.31% as a reference) was associated with higher risks of all-cause and cardiovascular deaths (HR = 1.53, 95% CI 1.33–5.92, $P = 0.001$, and HR = 2.51, 95% CI 1.53–3.59, $P = 0.002$, Table 2, Model 1). Multivariable analysis showed that PDW ≥ 16.31% was independently associated with higher risks of all-cause and cardiovascular deaths (HR = 1.49, 95% CI 1.15–6.82, $P = 0.007$, and HR = 2.26, 95% CI 1.44–3.63, $P = 0.011$, Table 2, Model 3).

Besides, patients with PDW quartile 4 had 1.59 and 2.71 times of all-cause and CVD mortality as compared with those with PDW quartile 1, respectively, when adjusting for confounding factors.

4. Discussion

In this retrospective cohort of HD patients, we observed that higher PDW levels were independently associated with a

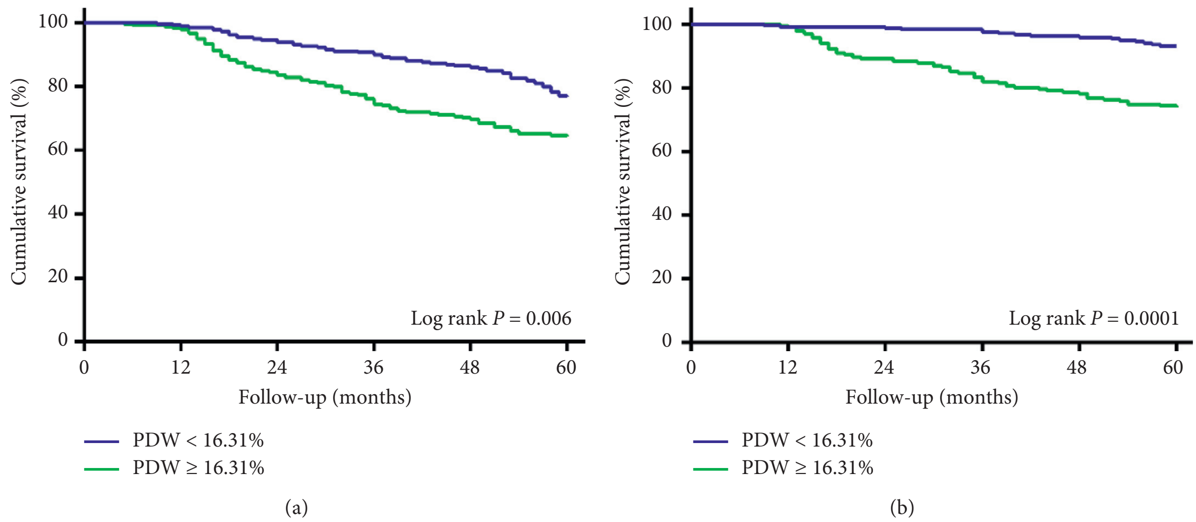

Figure 2: Cumulative all-cause and cardiovascular mortality in the PDW ≥ 16.31% or PDW < 16.31% groups. CVD, cardiovascular disease; PDW, platelet distribution width. (a) All-cause mortality. (b) CVD mortality.

Table 2: Association between PDW and all-cause and cardiovascular mortality using Cox regression models.

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95%CI)	*P*
All-cause mortality						
PDW < 16.31%			Reference			
PDW ≥ 16.31%	1.53 (1.33–5.92)	0.001	1.50 (1.21–5.11)	0.003	1.49 (1.15–6.82)	0.007
Quartiles of PDW						
Quartile 1			Reference			
Quartile 2	1.21 (1.06–5.36)	0.037	1.19 (1.05–5.41)	0.0041	1.15 (1.04–5.84)	0.045
Quartile 3	1.42 (1.09–5.17)	0.021	1.38 (1.07–5.28)	0.024	1.31 (1.06–5.53)	0.029
Quartile 4	1.69 (1.18–4.85)	<0.001	1.64 (1.21–5.02)	<0.001	1.59 (1.18–5.30)	0.001
P for trend	<0.001		<0.001		<0.001	
CVD mortality						
PDW < 16.31%			Reference			
PDW ≥ 16.31%	2.51 (1.53–3.59)	0.002	2.46 (1.62–4.01)	0.008	2.26 (1.44–3.63)	0.011
Quartiles of PDW						
Quartile 1			Reference			
Quartile 2	2.02 (1.41–3.82)	0.003	1.96 (1.37–3.97)	0.006	1.87 (1.30–4.05)	0.012
Quartile 3	2.39 (1.43–3.53)	0.001	2.31 (1.40–3.61)	0.002	2.27 (1.34–3.79)	0.003
Quartile 4	2.94 (1.59–3.58)	<0.001	2.86 (1.53–3.67)	<0.001	2.71 (1.49–3.76)	<0.001
P for trend	<0.001		<0.001		<0.001	

Model 1: crude analysis. Model 2: adjustment for age, sex, and CCI. Model 3: adjustment for model 2 and BMI, creatinine, albumin, hs-CRP, and MPV. PDW, platelet distribution width; CCI, Charlson comorbidity index; BMI, body mass index; hs-CRP, high-sensitive C-reactive protein; MPV, mean platelet volume.

high risk of all-cause and cardiovascular deaths. In addition, we further found that there was a dose-dependent relationship between PDW at baseline and mortality in HD patients.

Platelets play a crucial role in maintaining vascular integrity, and hemostasis and activated platelet also aggregate at the site of atherosclerotic plaque rupture, stimulate thrombus formation, and promote atherothrombotic disease. Besides, platelets also take part in sterile inflammation and response to pathogens [18]. Given that dialysis patients are known to be chronically inflamed, platelet dysfunction is common in HD patients. Atherosclerosis is an inflammatory condition, and it seems that the abnormalities in platelets contribute to the access events and cardiovascular events of these HD patients [19, 20]. In our patients, 23.2% of patients had vascular access thrombosis, and 14.9% died from cardiovascular events, which accounted for 51.0% of all-cause mortality. This result is similar to previous research that cardiovascular disease accounts for 40% to 50% of deaths in patients with ESRD, which suggested that platelet activity may be related to the prognosis of HD patients [21].

Platelet counts, MPV, and PDW are indexes obtained quickly, and conveniently, the counts of platelets reflected the number of platelets, which are highly susceptible to the external environment like the usage of drugs. The MPV reflects the volume of platelets and the production of new platelets from bone marrow [22]. Recent evidence also showed that abnormal MPV is linked to diabetes, cardiovascular disease, and autoimmune disorders, as well as PDW [23, 24]. However, the MPV reference values are varied among different laboratories [22, 25]. Furthermore, MPV presents noticeable differences among different sexes, ages, and populations, as well as platelet counts, which may be due to genetic variations [26]. PDW is just an index reflecting the variation of platelet sizes independent of platelet counts and MPV [27]. It has been shown that a higher value of PDW presence a higher production of larger reticulated platelets, which have larger and more metabolical activity [28, 29]. Thus, PDW can be recognized as a sign of inflammation and coagulation disease. A PDW cut-off value of 16.45% (AUC = 0.870) could predict persistent organ failure in acute pancreatitis [30]. In addition, PDW ≥ 13.65% for predicting systemic lupus erythematosus (SLE) active stage and PDW ≥ 11.85% for SLE diagnosis was taken to grouping, which reported that PDW was positively correlated with SLE disease activity index and erythrocyte sedimentation rate, and the two indexes are commonly used in inflammatory diseases [31]. A cohort of 254 patients with intermediate (50%–70%) carotid artery stenosis were observed that PDW ≥ 14.3% were independent predictors of developing symptomatic carotid artery stenosis [6]. According to PDW values, patients classified into quartiles were applied in patients undergoing percutaneous coronary interventions [32]. In this study, the mean PDW values were 13.4 ± 2.5% and independently associated with a high risk of major adverse cardiovascular events. A large cohort of 31751 Chinese middle-aged and older people from the Dongfeng-Tongji cohort study showed that lower PDW values (PDW < 13.2%) were significantly related to lower risk of cardiovascular diseases compared with participants with 13.2% ≤ PDW ≤ 18.1%, after a median follow-up of 5.9 years [33]. Another study reported that PDW showed a significant increase from the first to the third trimester of pregnancy [8]. However, it was worth noting that a large sample size of 1882 patients undergoing coronary angiography found PDW was not related to the extent of coronary artery disease and carotid intima-media thickness. [28] Thus, the association between PDW and cardiovascular disease remained inconsistent, and the definition of high PDW was also inconsistent. Besides, the association between PDW and mortality remained unclear. In the present study, the mean values of PDW in the present study were 14.37 ± 1.63%, which were inconsistent with those in the previous studies. A previous study reported that PDW values of HD patients were higher than healthy people [14]. High PDW in our findings was defined according to the population with difference disease based on previous studies in this area. We found that older age and higher CCI were independently associated with the high PDW in HD patients in our study. To evaluate the association between PDW and all-cause and cardiovascular mortality, we divided eligible HD patients into the high PDW group and low PDW group according to the cut-off of a PDW value of 16.31%, which was analyzed by ROC curve (AUC = 0.661, sensitivity: 90%, and specificity: 47%). We found that higher PDW values may be an independent predictor for all-cause and cardiovascular mortality in HD patients, even after adjusting for confounding factors. Thus, as a common, readily available, and inexpensive biomarker, PDW could be a promising predictor to identify HD patients at high risk for all-cause and cardiovascular mortality. Further study should be conducted to evaluate whether the prognosis of HD patients may be improved by the management of PDW.

Several limitations should be mentioned in the present study. First, a retrospective study allows us to establish associations but not causal relationships. It was impossible for us to adjust all factors for all-cause and cardiovascular mortality, and the effect of residual confounding cannot be eliminated completely. Nonetheless, we adjusted for significant risk factors for all-cause and cardiovascular mortality. Second, all patients were from a single center in Nanjing, and the sample size is small, which means our study may lack generalization to other centers or other regions. Third, we only evaluated baseline variables rather than changes over time in all-cause and cardiovascular mortality. Finally, because HD patients were all Chinese in the present study, the results may not apply to other ethnic HD patients.

In conclusion, we found that PDW at baseline was independently associated with all-cause and cardiovascular deaths in HD patients. As a common, readily available, and inexpensive biomarker, PDW could be a promising parameter to identify HD patients at high risk for all-cause and cardiovascular mortality.

Data Availability

Readers can access the data underlying the findings of the study by contacting the corresponding author.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

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Review Article

A Review on Different Kinds of Artificial Intelligence Solutions in TCM Syndrome Differentiation Application

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In 1979, the first computer program for TCM diagnosis was launched, although this time was about 30 years after artificial intelligence (AI) came into being and began to be widely used. However, an endless stream of artificial intelligence methods was applied in the field of Chinese medicine research, expert system, artificial neural network, data mining, and multivariate analysis; not limited to what was mentioned, this study tried to make a review on application of AI to TCM syndrome differentiation, while summarizing the artificial intelligence application of TCM syndrome differentiation in the current context. It also provides a theoretical background for the upcoming fully automated research on TCM syndrome differentiation and diagnosis robot.

1. Introduction

TCM diagnostics is one of the basic theories of TCM (Traditional Chinese Medicine), aimed at examining the clinical manifestations of symptoms in patients, so as to make a definite syndrome diagnosis and analyze the progression of diseases [1]. TCM diagnosis has two important characteristics. One is the concept of holism; i.e., the human body is an organic whole, where all the organs and tissues are inextricably linked with one another. Local changes within the human body reflect its constitutional conditions, while internal changes are manifested outwardly. During the process of clinical diagnosis and treatment, a traditional Chinese physician infers a pathological change in the human body based on the patient's experience and his own observation. The other is syndrome differentiation and treatment, which is the essence of TCM and the basis and prerequisite of all TCM-related clinical activities. Syndrome differentiation is the core of TCM diagnosis and is characterized by differentiation of disease and differentiation of syndrome, of which differentiation of disease comes prior to differentiation of syndrome [2, 3]. Only correct differentiation of the various syndromes is able to ensure reasonable treatment of diseases [4].

The physician's own knowledge of the TCM theory and accumulated clinical experience is relied upon to make a TCM diagnosis using the four diagnostic methods and differentiation methods, according to the patients' clinical symptoms [1]. Subjective factors play a decisive role in TCM diagnosis. This unique diagnostic mode promotes the open and divergent development of TCM; however, it has become a bottleneck to its development. The accuracy of diagnostic results is too dependent on the traditional Chinese physicians' ability and experience, owing to the difference in personal competence among traditional Chinese physicians; therefore, the therapeutic effect of TCM is inevitably uncertain [4].

In the 1950s, artificial intelligence (AI) came into being and began to be widely used in various disciplines [5]. In 1979, the first computer program for TCM diagnosis was launched, initiating the development of an intelligent TCM diagnostic system. In the 1980s, rule-based decision inference was widely used in expert systems, significantly characterizing the intellectualization of TCM diagnosis during this period. On the one hand, a knowledge tree was built to make inferences by judging the credibility of nodes, while a backtracking mechanism was used to achieve optimization (or knowledge was absorbed inversely according to the production rule); on the other hand, the matrix and array were taken as forms of knowledge expression, while extremum searching was used to build a heuristic inference engine. Moreover, multiple inference techniques started being combined in strict accordance with TCM holistic thinking [6]. In 1989, Prof. Qin, a bioengineer at the Capital Medical University, published *An Introduction to the Computer Simulation and Expert System of TCM*, where representative TCM expert systems are classified and summarized from the perspective of thinking models and techniques. A clue as to the replacement of expert systems with intelligent syndrome differentiation was discovered at that time. However, the studies conducted during this period of time were severely restricted by the concept of these early expert systems, e.g., it is difficult to acquire knowledge, and studies must depend on complete expert knowledge; the combination of diseases syndromes and symptoms is not yet universal, and the self-learning ability of the systems and complexity and specificity of diseases was ignored. Excessive energy was used to study and arrange expert knowledge and inference rules, while there was not sufficient attention to the diversity and uncertainty of applications in clinical practice. In the 1990s, mathematical inference, analysis, and statistical methods were put into use, promoting the development of diagnostic inferences in TCM; however, the linear inference mode could not cope with highly nonlinear characteristics of TCM syndromes [7]. In recent years, a series of methods have been put forward for dealing with nonlinear technical problems, such as soft computing and data mining. For example, Gan applied the fuzzy mathematics theory to TCM diagnosis [8]; Zhang Qin et al. made a combined use of the cluster analysis and fuzzy theory to extract a number of syndrome principles concerning hepatopathy in TCM clinical practice, presenting a method for syndrome identification [9]; Qin and Mao applied an improved neural network model based on a rough set to the typical diagnosis of rheumatoid diseases, greatly increasing the accuracy of diagnosis [10]; advanced smart technology was applied to TCM syndrome differentiation, breaking through the expert system, improving the flexibility and practicability of the diagnostic system, lifting the attachment of the rules and differentiation system to complete knowledge and linear programming, finally enhancing the independence of the system and its ability to solve nonlinear problems. The diagnosis model built on the basis of smart technology greatly reduced the influence of various subjective factors on the development of TCM syndrome differentiation, dramatically promoting the intellectualization of TCM syndrome differentiation [5, 6].

Intelligent diagnosis of TCM has grown out of a computer-based combination of AI technology and the TCM diagnosis theory. The emergence and development of each smart technology features its own unique knowledge background and research direction. As such, each must have advantages and disadvantages in practical applications.

2. Expert System (ES)

The ES was the embryonic form of AI and laid a foundation for the generation and development of AI, promoting the transformation of intellectualization from a textual theory into a practical application, bringing about a breakthrough in replacing mechanical logical inference with the use of expert knowledge to solve complex problems. Its advantages are as follows: it could handle complex system problems difficult to express and statistically analyze in a mathematical model; and the expression of knowledge was readable and easy to understand. Its disadvantages are as follows: it had difficulty in acquiring tacit knowledge and could not give a clear instruction description of uncertain problems; the ES did not have the ability to learn independently, while its development depended on a complete knowledge base; the knowledge was so subjective that an inaccurate conclusion might be drawn for some problems, and the conflict between different expert knowledge could not be solved; because the knowledge came from a limited scope and field, it could not play a part once a problem was beyond said scope or field; moreover, as there was more and more knowledge in the ES, the size of the knowledge base would be enlarged infinitely, thus reducing the efficiency of inferences. The serial treatment method had great difficulty in solving parallel problems. The ES of TCM syndrome differentiation could help to make a logical inference about TCM syndrome differentiation based on TCM experts' rich clinical experience and knowledge under a fully transparent inference rule [11, 12]. However, when used in a complex clinical medical diagnosis environment, the ES called for the solving of difficult technical problems, such as bottle-necked knowledge acquisition, the lack of memory and self-learning ability, and the nonrobustness of the system, limited to rules as it is. All these problems made it difficult for the ES to be suitable for the inference and calculation of heterogeneous, high-dimensional, and fuzzy clinical TCM data [9]; see Figure 1.

3. Artificial Neural Network (ANN)

ANN is another important research field of AI. Different from the rule-based ES, ANN is a physiological bionic operation model that works by simulating the activity of the cerebral neural network. It is a nonlinear and self-adaptive dynamic system formed from the adjusted connection between nodes (neurons) [13, 14]. The basic unit of its structure is the neuron (i.e., the information node). Each neuron is composed of three parts: cell body, dendrites, and axons. The connection points between independent neurons are synapses [15]. The neurons transmit and process the information resources in the

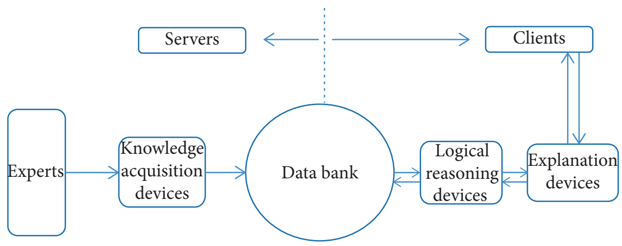

Figure 1: Expert system schematic.

network through weighted interconnection [16]. A neuron can convert the information from other neurons connected to it into a self-input activation function to calculate the corresponding output information, and then send the information to other neurons. The neural network and its simplified structure are shown in Figure 2 [17]. There are many types of ANN models, such as Rosenblatt's perceptron model and BP network machine algorithm, Widrow's ADALINE model and MADALINE model, Grossberg's ART model, Kohonen's SOM model, Hinton's Boltzmann machine, Hopfield's Hopfield network, and Rumelhart's PDP model; see Figure 2.

The ANN has multiple advantages in simulating the activity of the human brain, including parallelism, nonlinearity, and nonconvexity. It is fairly able to handle practical application problems characterized by a complex information environment and fuzzy or unclear knowledge and rules. With its self-organizing ability, adaptive ability, and strong self-learning ability, it can adjust and change its own connection weight under constantly changing external information. The state of the neurons and the connection between them determine the holistic system activity. However, the ANN also has many shortcomings: Its "black box" mode makes the neural network unable to explain the knowledge and the entire inference process; the learning of the neural network requires a lot of samples, thus prolonging the training duration. Moreover, local minimum and overfitting are hard to avoid [18]. According to the above description and analysis of the characteristics of the neural network, it is not difficult to find that many of its characteristics are very similar to the highly fuzzy and nonlinear knowledge structure of TCM, as well as the logical inference of TCM syndrome differentiation. By independently learning clinical information resources, it is able to discover the complex connection between the symptom and syndrome without relying on the formalized description and clear rules and mechanisms of the mathematical model. This fully displays the flexibility and adaptive ability of the network. Therefore, the ANN is a good tool and method in the process of intelligent TCM syndrome differentiation [16]. However, the susceptibility of the ANN to local minimum and overfitting affects the accuracy and reliability of clinical diagnosis, making it impossible to realize rule integration and clinical practice guidance. To adapt to the characteristics and requirements of TCM syndrome differentiation, it can be combined with other intelligent technologies and methods to reduce the impact of its own deficiencies on syndrome differentiation.

4. Data Mining (DM)

DM, also called Knowledge Discovery in Database (KDD), is a smart technology that is used to extract relevant laws and rules from massive data by analyzing various data [19]. The basic process of DM is shown in Figure 3.

DM technology, which is completely free from the pyramidal cascading research model, focuses on researching the knowledge contained in real data; as such, the laws revealed are objective and reliable. From the perspective of information science and technology [20], the research of intelligent TCM syndrome differentiation is a process from data to discovery, involving data acquisition, data management, data analysis, and simulation, as shown in Figure 3 [21, 22]. DM technology is also a feasible method suitable for intelligent TCM syndrome differentiation. Through DM, syndromes can be differentiated objectively and quantitatively. This indicates that it is a good mode of research on the laws of TCM syndrome differentiation [23]; see Figure 3.

From the perspective of laws and knowledge acquisition, almost all DM techniques are related to machine learning [11, 24]. Unlike the traditional methods such as cluster analysis and regression analysis, which are performed in order to obtain quantitative data features from data, the decision tree, association analysis, and Bayesian learning help to acquire object-oriented knowledge [25, 26].

The decision tree is a tree structure which solves the problem of syndrome differentiation and classification in TCM. As shown by the essential elements of the decision tree in Figure 4, with a simple structure and high classification efficiency, it can process and analyze a large amount of data concerning nonlinear relationships to reveal relevant attributes and rules, which are mostly used for research on syndrome classification [27, 28]. ID3, C4.5, SLIQ, and SPRINT, etc. are all typical algorithms in the decision tree [19]; see Figure 4.

Association analysis is a process of obtaining effective knowledge with specific minimum support and minimum confidence. The association rules reflect the dependency and association among different categories of things, as shown by the diagram of association analysis rules in Figure 5. These two methods have also been widely used in practice; see Figure 5.

Wang and Ma studied the diagnosis of hepatopathy after its periodic occurrence in TCM clinical practice, optimizing and improving the decision tree algorithm, discovering a law by which the pathogenetic condition could be diagnosed periodically, thus differentiating compensated cirrhosis from decompensated cirrhosis clearly and quantitatively [28]. Yao et al. made some preliminary studies on the compound compatibility of Chinese herbal drugs based on pharmacology and toxicology using the association analysis technology and verified the results in hundreds of TCM cases treated [29]. Li et al. discovered the application of frequent item sets in pharmacology and drug efficacy through DM, extracting the association rules regarding drug interactions based on the data about many years of clinical cases with infectious hepatopathy [30]. The advantages of the decision tree and association analysis are obvious [31, 32].

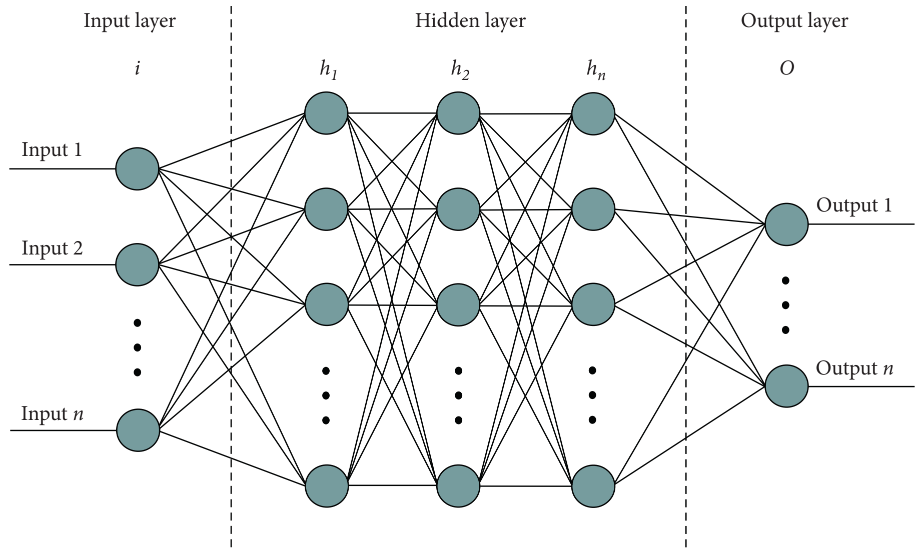

Figure 2: Artificial neural network architecture [17].

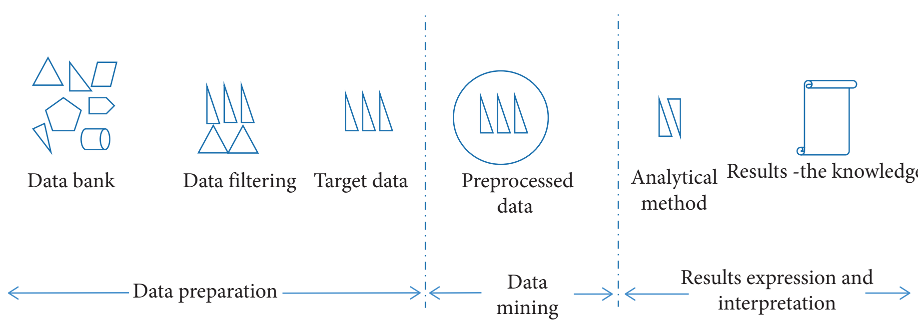

Figure 3: Data mining process.

Their strong generalization ability makes it easier to extract rules. Moreover, the rules extracted are usually easy to explain and understand; other important attributes can be extracted if the rules extracted are further learned; furthermore, the computational complexity can absolutely be estimated and predicted. However, the decision tree and association analysis are instable, so the difference in results obtained from training samples and test samples should not be underestimated; if some data items are missing, the classification effect will be directly affected; the database is scanned and sorted too frequently in the process of rule extraction, producing a large number of intermediate results, which affects the processing speed of larger training samples.

DM is suitable for solving and revealing the hidden connections within data and the acquisition of effective knowledge. However, in the process of building an intelligent system of TCM syndrome differentiation, the extensive and simple application of DM technology is obviously unable to cope with high fuzziness, high dimensionality, nonlinearity, and uncertainty when they are interwoven together. In TCM clinical practice, various signs, which are related to symptoms and syndromes, are independent and interdependent on one another. This diversity and complexity determine a specific knowledge structure system, making it difficult to set a model expression expectation in line with its features effectively and accurately through DM [33, 34].

5. Multivariate Analysis

Multivariate analysis, also called multifactor analysis, is a common statistical method. It is mainly used to study the relationship among several interdependent factors and the relationship among the samples with such characteristics [35]. In TCM syndrome differentiation, such dependency-based multivariate analyses can be roughly divided into two types: the first type is characterized by dependency among various factors. The relevant processing methods include principal component analysis (PCA), factor analysis, cluster analysis, etc. Its goal is to obtain the corresponding symptom dataset and explain it. The main process of cluster analysis is shown in Figure 6.

However, it dilutes the implicitness and ambiguity of the internal relation between “symptom” and “syndrome” [36]. The high-dimensional complexity, i.e., they are not only intertwined with each other, but also separated from each other, makes it difficult for this type of method to reveal the

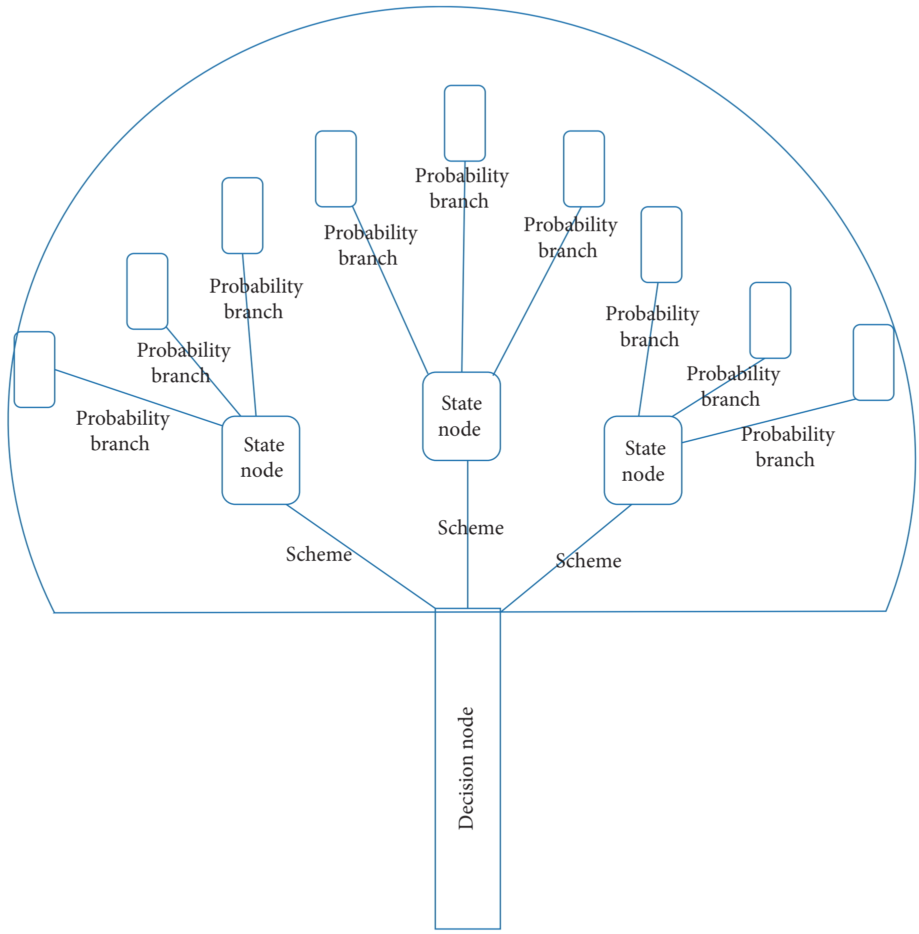

Figure 4: Decision tree element composition diagram.

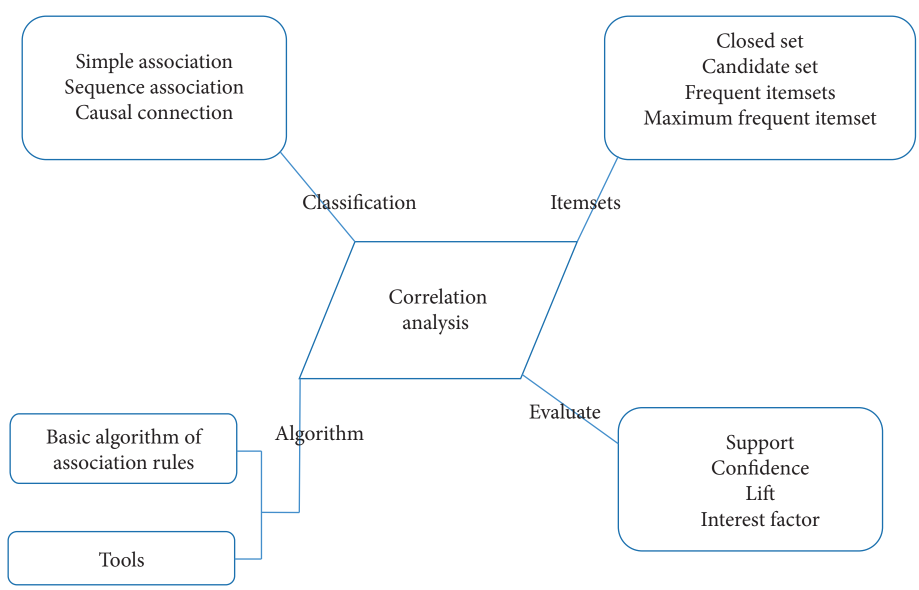

Figure 5: Rules schematic correlation analysis.

clear structure of the TCM clinical data. For example, most patients may have multiple secondary symptoms, and a single symptom may have specific clinical manifestations in different syndromes. In other words, an individual patient and his/her symptoms are very likely to be clustered into multiple categories. However, according to the one-to-one

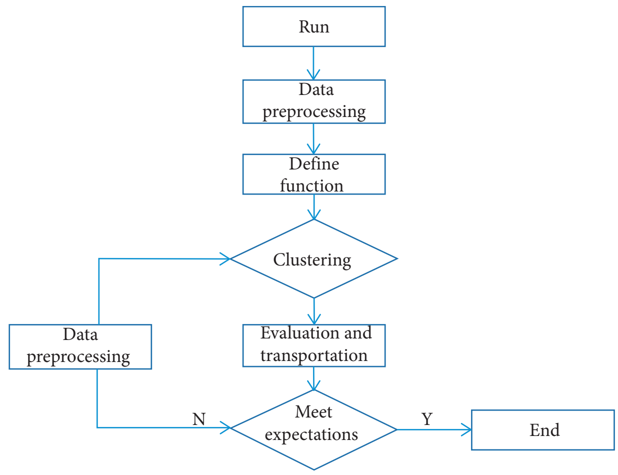

Figure 6: Cluster analysis process.

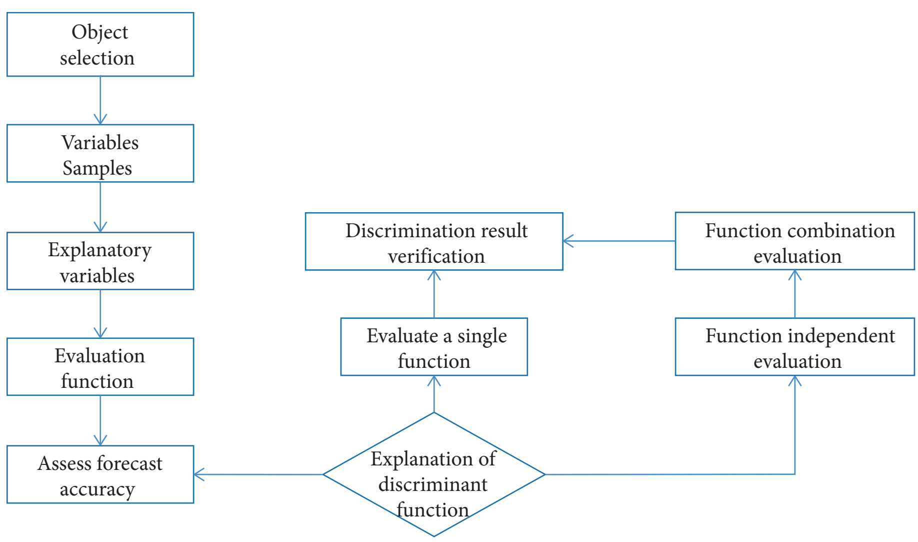

Figure 7: Discriminatory analysis process.

classification of cluster analysis, it is obviously preposterous that a certain symptom or individual is put under a single category. Thus, it has extreme limitations and ambiguity in use, and so, it can only be used as a supplementary means; the other is the dependency between antecedents and consequences; i.e., syndromes (consequences) are dependent on symptoms (antecedents). Multiple linear regression analysis, discriminatory analysis, and logistic regression are the main methods; see Figure 7.

The process of discriminatory analysis is shown in Figure 7. By building a functional relationship and diagnostic inference model that simulates the process of TCM diagnosis, this type of method can reveal the internal hidden relationship between them according to their mathematical relationship. However, there is not just a simple one-to-one relationship between TCM syndrome and symptom, so it is indeed difficult for a single relational function to accurately describe such multidimensional and multilayered relationships. Moreover, it is hard to provide a simple and effective method for rule differentiation, so it has no guiding significance for TCM clinical diagnosis [36]. By combining the TCM theory with clinical practice, we can easily see that the multivariate statistical analysis' ability to express the relationship between complex, multidimensional objects is not suitable for intelligent TCM syndrome differentiation [37].

In addition, AI also contains many other intelligent technologies, such as rough sets, support vector machines, grey theory, and agent, all of which have been widely used in practice [7]. During the intellectualization of the TCM syndrome differentiation system, the fuzzy theory can be used to appropriately deal with the high ambiguity of knowledge structure; the emerging intelligent methods and their improved technologies provide a broader platform for the optimization of diagnostic procedures; the combination of multiple methods and strategies can make up for the shortcomings brought about by the independent application of a certain technology, thus strengthening the system's ability to solve problems [37].

Research on intelligent TCM diagnosis is an inexorable trend in the information age. However, during a hard work of literatures reading, we found that there was a separation of TCM AI relevant research trends in and outside China; as we listed in the reference parts, most TCM AI relevant studies were in China, and published in Chinese; this gap made a big difficult language problem to push AI TCM relevant study forward. It seems only one way by reporting more with international general scientific research language. Meanwhile, the modernization of TCM is of far-reaching significance, combining emerging intelligent techniques with traditional TCM diagnosis to develop AI-based TCM syndrome differentiation technology with the aim of eventually building an intelligent diagnostic system. This is also of great practical significance in improving traditional Chinese physicians' diagnostic capability while further enhancing their training. The application of smart technology in TCM plays a role in promoting the research of the laws of TCM syndrome differentiation, thereby changing the completely arbitrary diagnostic approach, enriching the content and method of TCM studies.

Data Availability

The data are stored in Guangzhou Medical University Data Center, which is the responsibility of the first author and corresponding author, and will be made public three years later. The data will be stored for 10 years.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Development and Application of Artificial Intelligence in Auxiliary TCM Diagnosis

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As an emerging comprehensive discipline, artificial intelligence (AI) has been widely applied in various fields, including traditional Chinese medicine (TCM), a treasure of the Chinese nation. Realizing the organic combination of AI and TCM can promote the inheritance and development of TCM. The paper summarizes the development and application of AI in auxiliary TCM diagnosis, analyzes the bottleneck of artificial intelligence in the field of auxiliary TCM diagnosis at present, and proposes a possible future direction of its development.

1. Introduction

AI is the main force of the fourth scientific and technological revolution [1], which is dedicated to embodying human intelligence through computational methods. It is widely used in various fields and currently mainly possesses functions such as voice and image recognition, logical reasoning ability, and emotion recognition [1, 2]. Traditional Chinese medicine (TCM) is the product of the successful combination of ancient Chinese macroscience and the medical practice of that time [3]. After thousands of years of accumulation and precipitation, a unique diagnosis and treatment system has been gradually formed, and its therapeutic effect has been widely recognized. According to TCM theory, the physiological and pathological changes of the human body's viscera and bowels, yin and yang, and qi and blood can be reflected on the outside, such as the face, tongue, pulse, and voice. Through "inspection, listening and smelling examination, inquiry, and palpation" to grasp the basic situation of the patient, the information of the four examinations is integrated to achieve the correlation of all four examinations, to realize the purpose of diagnosing diseases and symptoms. As the basis of syndrome differentiation and treatment, the four examinations are easily influenced by objective conditions such as environment and light source, as well as the subjective judgment of doctors, and lack objective and quantitative indicators. Through the combination of AI and TCM diagnosis, a large amount of TCM diagnostic information can be collected, organized, and analyzed, thus providing the possibility of establishing disease-pattern models, and promoting the objective and scientific development of TCM diagnosis.

AI with machine learning and deep learning as the mainstream ushered in a new upsurge [4]. In the 1970s, AI was applied in the field of TCM diagnosis [5], which provided a rare opportunity for the development of objective and modernized TCM diagnosis, but the problems of logical reasoning and objective quantification were not well solved and its development speed was slow [6]. In recent years, thanks to the rapid development of microsensors [7], computer image analysis, speech recognition technology [8], and deep learning [9, 10], the programmatic innovation of TCM has been accelerated and a milestone progress has been made in the standardization and normalization of TCM diagnosis [11]. The purpose of this paper is to review the application and development of AI in assisting TCM diagnosis and to analyze the current development bottlenecks and future development directions of AI-assisted TCM diagnosis.

2. Application of AI in the Field of Medicine

The advent of computers in the 1940s prompted people to explore the use of computers to replace or extend part of human mental work [4]. The concept of artificial neural networks was first introduced by Donald Hebb in 1949 [12], marking the nascent stage of AI. The term artificial intelligence was first coined by McCarthy in 1955 when AI was defined as the science and engineering of making intelligent machines [13]. Over the years, the term has been overused to include various computerized automated systems, logic programming, probabilistic algorithms, and remotely controlled robots [13]. It is worth mentioning that convolutional neural networks (CNN), an important part of deep learning (DL), have extensive application in various subfields of medical image analysis, including classification, detection, and segmentation. For example, the TCM facial diagnostic detector and tongue manifestation analysis system mentioned below both benefit from the development of machine learning and neural networks, while machine learning-based speech recognition technology plays an important role in listening examination.

In the 1970s and 1980s, Stanford University's Experimental Computer Research Program in Medicine was established [14], and medical expert systems were broadly used in clinical diagnosis [15], laying the foundation for the development of AI in the medical field. Nowadays, AI is widely used in modern medicine for both clinical diagnosis of common diseases [16] and image-assisted diagnosis [17, 18]. Hirasawa et al. [19] designed a CNN system capable of automatically identifying gastric cancer from a large number of endoscopic images, which is promising in aiding the diagnosis of gastric cancer. Numerous studies have shown that DL systems have a powerful ability to diagnose diabetic retinopathy [20]. And some achievements have been made in the application of auxiliary surgery [21], the most representative being the da Vinci surgical robot [22]. Multiple pieces of evidence support that AI and big data classifiers play a vital role in the field of organ transplantation [23]. A group of researchers have proposed a facial analysis framework for genetic syndrome classification, called DeepGestalt, which uses computer vision and DL techniques to quantify the similarity of hundreds of symptoms. The accuracy of the test of identifying correct symptoms on 502 different images was 91%, which was better than that of clinicians. DeepGestalt has potential application value in the phenotypic evaluation of clinical genetics and gene testing [24]. The application of artificial intelligence nursing providers (AICP) in the field of mental health care and treatment is also an embodiment of the development of AI virtual technology [25].

The combination of TCM and AI began in the 1970s, with the birth of the first international expert system of TCM, which was named "TCM Guan Youbo Hepatitis Diagnostic and Treatment Procedures," as a landmark event. In the decade since, AI has also made progress in TCM disease diagnosis, assisting in standardizing TCM diagnostic models [26]. Recently, Zhang et al. [27] proposed an AI-based TCM auxiliary diagnosis system, which can diagnose 187 common TCM diseases and related syndromes. The prediction accuracy of the top 3 and the top 5 disease types were 80.5%, 91.6%, and 94.2%, respectively, indicating that they had precise diagnostic accuracy. Besides, AI has an active impact on the development and quality monitoring of new Chinese medicines, the construction of Chinese medicinal prescription models, and acupuncture point combination [28, 29]. Yao et al. [30] proposed an ontology-based artificial intelligence model for medicine side-effect prediction, and these predictions were validated with neural network structures, but the model is highly dependent on sufficient clinical data, and more in-depth exploration to improve the accuracy of the predictions is necessary in the future.

3. Application of AI in Auxiliary TCM Diagnosis

3.1. Inspection. As the first of the four TCM examinations, inspection has the characteristics of intuitiveness and simplicity and plays an important role in the TCM diagnosis. Through inspection, the physician observes the patient's general or local appearance and morphology, thus achieving the goal of determining the patient's disease state. The contents of TCM inspection are numerous, with particular emphasis on facial and tongue diagnosis in clinical practice.

3.1.1. Facial Diagnosis. Changes in facial color and luster can reflect the glory and decline of qi and blood of the corresponding viscera and bowels and meridians. AI plays a key role in the recognition and extraction of facial information, so it has been used to study the differences and correlations of facial information between different diseases as well as between different patterns of the same disease. Dong [31] applied a TCM face digital detector to collect and analyze the facial color characteristics of patients with coronary heart disease, chronic renal failure, and chronic hepatitis B. The results showed that there were significant differences in the facial color index between the three diseases, indicating that there is a pattern of changes in the facial color and its parameters in different visceral diseases. Liu et al. [32] used a TCM face detection instrument to collect facial features of 60 patients with chronic nephritis, to study the facial features of patients with damp-heat type chronic nephritis and to analyze the relationship between the facial features of nephritis patients and changes in renal function. It was found that there were differences in facial color parameters between different types of patients, and there was a correlation between facial color parameters and renal function testing indicators. Guo et al. [33] applied the TCM face detection instrument to carry out a study on the correlation between different stages of chronic renal failure and the changes in face information and found that the face color index of patients in the decompensated stage of renal function and the uremia stage decreased significantly, which confirmed that there is a certain correlation between the disease stages of chronic renal failure and the face color parameters.

3.1.2. Tongue Diagnosis. The tongue and internal viscera and bowels are connected by meridians. Exuberance and debilitation of the healthy qi or pathogenic qi and the changes of qi, blood, fluid, and humor can be obtained by observing the tongue manifestation. Tongue diagnosis mainly includes looking at the tongue body and tongue fur. The tongue body mainly reflects the patient's exuberance and debilitation of qi and blood and strength and weakness of the viscera and bowels. The location and nature of the disease can all be reflected by tongue fur. To integrate the collection, processing, and analysis of tongue manifestation into a whole procedure and make TCM tongue diagnosis tend to be more intelligent, the development and application of tongue manifestation analyzer and "TCM tongue diagnosis automatic identification system" have been set off.

As early as the 1990s, the "TCM tongue diagnosis automatic identification system" established by Tsinghua University and Xiyuan Hospital of China Academy of Traditional Chinese Medicine realized the quantitative analysis of tongue body and tongue fur. In an experiment using this system to observe the tongue body of patients with blood stasis, the analysis result was 86.34% consistent with the visual observation [34]. At the beginning of the 21st century, Jiang et al. [35] designed a computerized tongue diagnosis system of TCM to analyze the characteristics of the tongue using fuzzy theory, which can initially read the amount of tongue fur, the bias in the distribution of the tongue fur, and the thickness of the tongue fur. Cui et al. [36] applied the "TCM tongue diagnosis expert system" to quantitatively study the tongue manifestation of patients with stroke disease, and the results were consistent with the characteristics of the mechanism of disease changes in the acute and recovery phases of stroke disease. Zhang et al. [37] designed a Bayesian network-based tongue diagnosis auxiliary system, and the accuracy of which was higher than 75% in identifying tongue manifestation of healthy individuals, patients with pulmonary heart disease, appendicitis, gastritis, pancreatitis, and bronchitis. Lo et al. [38] extracted nine tongue manifestation features such as tongue color and tongue body using an automatic tongue diagnosis system and further divided the extracted features by region to achieve screening for early breast cancer. Han et al. [39] used a tongue diagnosis information acquisition system to collect tongue manifestation from colorectal cancer patients and healthy individuals and analyzed the thickness of their tongue fur. The study showed that the tongue fur of colorectal cancer patients was significantly thicker than that of healthy people, which provided a basis for tongue diagnosis as an early screening tool for colorectal cancer.

Tongue manifestation analyzer can be adjusted according to the patients' tongue diagnostic environment and tongue spitting posture, and it can acquire the tongue in a multidimensional manner, analyze the tongue manifestation completely, evaluate the tongue accurately, and finally store data and imaging [40]. In recent years, many scholars have used tongue analyzers to study the correlation between pathological evidence and tongue manifestation and between tongue manifestation and objective manifestation indicators. Xu et al. [41] applied the TP-1 TCM tongue and pulse condition digital analyzer to study the tongue manifestation of patients with deficiency symptoms of chronic renal failure and found that the tongue color index and the moist and dryness index were of great reference significance for the differentiation, especially the tongue color index was more meaningful. Zhang et al. [42] used a DS01-B tongue information acquisition device to collect tongue color information of 273 nontraumatic femoral head necrosis patients, used frequency analysis and cluster analysis to analyze the distribution characteristics, and concluded that the tongue color indices of different ARCO (Association Research Circulation Osseous) stages have different characteristics. It provides an objective basis for TCM diagnosis of nontraumatic femoral head necrosis.

3.2. Listening and Smelling Examination. Listening and smelling examination is a diagnostic way for physicians to understand the various abnormal sounds and smells emitted by patients through hearing and smelling [43]. Listening to sounds includes voice, breathing, coughing, yawning, sighing, snoring, sneezing, borborigmus, and splashing sound [44]. By smelling and listening, the doctor can determine the nature and location of the disease and predict the progression and prognosis of the disease [45].

3.2.1. Listening Examination. In the listening examination, AI is mainly used in physique identification, disease diagnosis, syndrome type research, and evaluation of clinical efficacy through voice information. Wang [46] collected voices of normal adults aged 20 to 79 years old, used a computer voice analyzer to obtain voice data, and concluded that the voice changes with age; also, there is a positive correlation between the voice changes and exuberance and debilitation of Qi. It provides an objective basis for TCM to understand the deficiency and excess syndromes of voice diseases of different ages. Qian et al. [47] used BD-SZ auxiliary diagnostic instrument to identify the five-phase constitution by audio characteristics of 36 Parkinson's sufferers. The results showed that there were more wood, earth, and water constitution, and less metal constitution, among which wood constitution was the most, suggesting that Parkinson's disease and wood constitution may have a certain correlation. Dong et al. [48] used the "Collection System of TCM Auscultation" to capture the speech signals of chronic pharyngitis patients and obtained the energy feature data of different frequency bands by wavelet packet decomposition method and found that there were different energy characteristics in more frequency bands between patients with chronic pharyngitis and normal people, the chronic pharyngitis lung qi deficiency group, the phlegm-heat accumulation group, and the yin deficiency and lung dryness group. Li et al. [49] collected TCM acoustic parameters of patients with bronchial asthma in remission before and after treatment by using "acoustic information acquisition system" and found that the resonance peak indexes F1 and F2 of patients with asthma in remission were significantly reduced after treatment, which provided an effective basis for the clinical efficacy evaluation of bronchial asthma.

AI has also been applied to the study of the phoneme theory of the five viscera in the listening examination. Based on the theory of "five visceral phonemes," Chen et al. [50] used the "TCM acoustic diagnosis acquisition system" to collect sound signals from patients with lung, liver, spleen, kidney, and heart diseases as well as normal people and analyzed the sound signals using the sample entropy method. The differences in the sample entropy values of the six time-domain frequency bands were statistically significant ($P < 0.05$), which provided an objective basis for the localization of diseases in viscera and bowels based on listening examination information in TCM. Zheng [51] used a 25-tone analyzer to detect and analyze the average frequencies of the voices of women with hot and cold constitutions and found that the difference in the average number of times in the pinnacle and angular regions between cold and hot constitutions was statistically significant.

In addition, AI has also made progress in the recognition of other pathological sounds. Allwood et al. [52] described the progress of AI in signal recognition and processing of hyperactive bowel sounds, and Abeyratne et al. [53] designed an automated algorithm to diagnose pneumonia by extracting parameters from patients' cough and breath sounds.

3.2.2. Smelling Examination. The application of AI in the smelling examination is mainly in the recognition and analysis of odor signals. The e-nose based on advanced array gas sensor technology can grasp the odor information from a holistic perspective [54], which provides good technical support for the objective research of TCM smelling examination. Lin et al. [55] used e-nose to accurately identify the odor map characteristics of type 2 diabetes patients and healthy individuals. Based on the principle of e-nose, Liu [56] combined the sensor technology, signal processing technology, and pattern recognition technology and optimized the artificial neural network recognition algorithm to construct an oral odor detection system for TCM diagnosis.

3.3. Inquiry. Inquiry is a diagnostic method for doctors to obtain complete and true information about a patient's condition through purposeful questioning of the patient and his or her family to understand the occurrence and development of the disease. The content of TCM inquiry is mainly based on the "Ten Question Song" created by Zhang Jingyue, but nowadays, it also incorporates past history, allergy history, and family history in modern medical records [57]. In the early stages of certain diseases, the lack of objective signs of abnormalities makes it important to obtain information about the patient's condition through inquiry [58].

AI facilitates the development of TCM inquiry systems. He et al. [59] combined computer technology, intelligent information processing technology, and TCM theory to try to develop a computerized TCM inquiry system. The system collects the basic information of users and the information of inquiry symptoms through the front desk module and the inquiry processing module, stores them in the inquiry database of user symptoms, and finally makes the preliminary judgment of the inquiry results through the diagnosis module based on the criteria set in the inquiry criteria database. Afterwards, they tested the system on 1767 clinical patients in internal medicine, surgery, gynecology, and pediatrics, compared the test results with the experts' interpretation, and found that the clinical interpretation rate of the system was 90%. Similarly, Zheng et al. [60], based on the TCM splenic inquiry scale, combined with TCM clinical practice, designed a standardized inquiry information collection system for TCM splenic diseases. The system has been tested by experts and clinicians and can collect systematic and standardized clinical information from patients, and the data analysis function is convenient and fast. However, there is a lack of research and evaluation on the accuracy of the diagnosis. Liu et al. [61] have developed a TCM heart disease inquiry system, which provides a complete and standardized record of inquiry information, but the results of the diagnosis are determined by clinical experts on their own.

3.4. Palpation. The method of palpation is for doctors to understand the health status and diagnose the patients' condition by touching and pressing on certain parts of the patient [62]. Among them, the wrist pulse-taking method is the most common and important method of palpation. The movement of qi and blood can affect the changes of the pulse condition, and the pulse condition can be used to understand the location and nature of the disease.

The application of AI in pulse diagnosis is mainly reflected in the acquisition and analysis of pulse condition information, which to some extent solves the problem that the results of pulse diagnosis are susceptible due to the lack of objectivity influenced by the sensitivity of the doctors' fingertips and clinical experience.

Among the methods of pulse condition-information analysis, time-domain analysis, frequency domain analysis, time-frequency analysis, and wavelet analysis are mainly used [63]. Yang et al. [64] applied the ZBOX-I pulse digital analyzer to study the parameters of the pulse map of the three parts of the right wrist pulse condition in patients with IgA nephropathy with spleen-kidney qi deficiency pattern by frequency domain analysis and concluded that the 24 h urine protein quantification was negatively correlated with the pulse map parameters w/t and h3/h1 and positively correlated with h1 and h5, which could provide a relevant basis for the clinical diagnosis and treatment of patients with IgA nephropathy with spleen-kidney qi deficiency pattern. Using a TP-I digital pulse analyzer, Yan et al. [65] compared the distribution of pulse shape and parameters of pulse maps of the right and left hand of 119 pregnant women with those of normal subjects by time-frequency analysis. The results showed that in the normal group, normal pulse and slippery pulse were most common; in the pregnant group, slippery pulse and string-like pulse were most common. The PSR_1 and BF of the left and right pulses of the pregnant group were significantly higher than those of the normal group, and the LMS_2 was significantly lower than those of the normal group. Mo and Wang [66] designed a pulse condition detection system based on wavelet analysis to judge the subhealthy population, which is of high accuracy in identifying subhealth states.

In terms of pulse condition-information acquisition, Sun [67] designed a pulse condition acquisition system based on a mobile terminal. Through comparison experiments with the standard pulse diagnosis system and validation analysis of the pulse characteristics of arteriosclerosis patients, the results showed that the system could accurately acquire pulse information of normal humans and arteriosclerosis patients. Zhang [68] designed a wearable pulse condition detection and analysis system. Jin [69] designed a portable three-position pulse condition acquisition system that can meet the needs of home healthcare and experimental research. In recent years, the development of TCM remote pulse diagnosis systems has also begun to emerge. Wang and Bai [70] designed an adjustable closed-loop remote pulse diagnosis system based on virtual reality technology. She [71] designed the TCM remote pulse diagnosis system to initially complete the acquisition and reproduction of the TCM finger technique and patients' pulse. Wu et al. [72] applied the Junlan pulse diagnosis bracelet to explore the characteristics and regularity of the pulses of healthy female college students during their menstrual cycle and found that the slippery pulse was the most common during the menstrual cycle, and the rough pulse was more common during ovulation.

4. Discussion

AI has great potential in the development of healthcare and presents an opportunity to modernize the development of TCM diagnostics. Over the past decades, many scientists and medical scientists have contributed to the combination of them. The research and development of intelligent TCM diagnostic instruments, the advent of TCM expert diagnostic systems, and the realization of TCM diagnosis based on cell phone platforms are all exciting research results that have greatly promoted the development of TCM diagnosis and healthcare. Combining AI with TCM diagnosis cleverly avoids the malpractice of uncertainty in doctors' subjective judgment, makes the diagnosis information more real, and improves the accuracy of clinical diagnosis. The application of AI in the early screening and diagnosis of certain diseases will facilitate early understanding of the disease and halt its progression.

Although AI has made some achievements in the application of TCM diagnosis, there is still a lot of room for development. For AI diagnostic accuracy in auxiliary TCM diagnosis, there seems to be a lack of relevant reports. For inspection, the application of AI is limited only to facial and tongue diagnosis, and inspection has not been given to other parts of human body. Although objective studies of tongue color, tongue body, and tongue fur have been made in tongue diagnosis, there remain certain difficulties in the study of the motility of the tongue. The tongue color is easily influenced by food and medication, and it is worthwhile to explore how to intelligently identify whether it is influenced by such factors. In the facial diagnosis, it is mainly limited to the analysis of facial color. Although there are studies on the analysis of facial expressions in some countries, it is incapable of establishing a connection between facial changes and TCM symptoms. As to facial color analysis, how to intelligently determine the true nature of the disease, for instance, whether the redness of the face is caused by heat pattern or a pattern of exuberant yin repelling yang, is also a question that will need to be addressed later. The role of AI in the listening examination is mainly to study the speech sounds of different diseases, but the study is limited to lung, vocal cord, and throat diseases, while the study of speech sounds of other clinical diseases and the study of other pathological sounds such as vomiting sounds are less reported. The application of AI in the smelling examination is based on the study of gas composition and the oral odor by electronic nose technology, but it has not been possible to determine the corresponding TCM syndrome and disease by smelling the odor. In the inquiry, human-computer dialogues can be used to obtain information about diseases, which can avoid the problem of emotional stress that affects the presentation of medical information in some patients when facing doctors. However, there are still problems such as the language of inquiry is not standardized and the inquiry of complex diseases is not yet realized. Based on TCM thinking, the development and research of inquiry system programs should also integrate the consultation contents of modern medicine, including past history and family history, to realize the combination of Chinese and Western medicine diagnosis. With the help of AI, experts and scholars need to develop an inquiry system that reflects humanistic care and adopts easy-to-understand language for the elderly and children, which is the direction that experts and scholars need to work on in the future. In recent years, the emergence of remote pulse diagnosis systems, pulse diagnosis bracelets, and wearable pulse diagnosis systems has provided patients with the convenience of remote pulse diagnosis, but more technical support is needed to develop a simulator that can reproduce a completely real pulse condition. Also, there is a saying in TCM theory that "correspondence between nature and human" and the change of pulse condition is related to the seasons and natural climate; for example, spring is dominated by string-like pulse and winter is dominated by sunken pulse.

Over the past decades, a large number of TCM expert diagnostic systems have been developed, but due to the complexity of TCM information, the lack of unified diagnostic criteria, and the inflexibility of the systems, there are still some shortcomings in applying them to clinical diagnosis. Therefore, building a complete and true four-diagnosis information database, establishing international standardized diagnostic standards, and using the application advantages of deep learning algorithms such as CNN, recurrent neural network (RNN), and deep neural network (DNN) in the field of medicine, developing a smarter TCM diagnosis system is a key direction that experts in AI and TCM will need to work on in the future.

The intelligence of TCM diagnosis will be the path to the early modernization of TCM. For AI to be universally applied in clinical diagnosis, not only do we need to train multidisciplinary crossover talents and complete the development of relevant intelligent devices with certain financial support. Secondly, the state needs to improve relevant policies and regulations to protect patients' personal data and disease-related information from being leaked and applied for other purposes. In addition, a reasonable cost standard for the use of smart diagnostic devices should be set. With the innovation of AI programming and data, there will be more breakthroughs in AI in the field of TCM diagnosis, and the day of realizing diagnosis at home is just around the corner. With the help of AI, TCM diagnosis will certainly be more accurate and convenient in the future and will play an important role in promoting the development of medical practice worldwide.

Data Availability

This study has no laboratory data, but the review study process and reference records are corrected and put in the data center of Heilongjiang University of Chinese Medicine, and these data will be kept for 8 years.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of the paper.

Authors' Contributions

Chuwen Feng, Yuming Shao, and Bing Wang contributed equally to this work. Yang Li and Tiansong Yang made critical revision of the manuscript. All authors read and approved the final manuscript.

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Research Article

Multiview Self-Supervised Segmentation for OARs Delineation in Radiotherapy

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Radiotherapy has become a common treatment option for head and neck (H&N) cancer, and organs at risk (OARs) need to be delineated to implement a high conformal dose distribution. Manual drawing of OARs is time consuming and inaccurate, so automatic drawing based on deep learning models has been proposed to accurately delineate the OARs. However, state-of-the-art performance usually requires a decent amount of delineation, but collecting pixel-level manual delineations is labor intensive and may not be necessary for representation learning. Encouraged by the recent progress in self-supervised learning, this study proposes and evaluates a novel multiview contrastive representation learning to boost the models from unlabelled data. The proposed learning architecture leverages three views of CTs (coronal, sagittal, and transverse plane) to collect positive and negative training samples. Specifically, a CT in 3D is first projected into three 2D views (coronal, sagittal, and transverse planes), then a convolutional neural network takes 3 views as inputs and outputs three individual representations in latent space, and finally, a contrastive loss is used to pull representation of different views of the same image closer ("positive pairs") and push representations of views from different images ("negative pairs") apart. To evaluate performance, we collected 220 CT images in H&N cancer patients. The experiment demonstrates that our method significantly improves quantitative performance over the state-of-the-art (from 83% to 86% in absolute Dice scores). Thus, our method provides a powerful and principled means to deal with the label-scarce problem.

1. Introduction

Radiotherapy is an important treatment option for many cancers, and the complex anatomy and distribution of normal organs in head and neck cancer may lead to damage of organs at risk (OARs), resulting in complications such as the oral mucosa damage, larynx edema, and dysphagia. To mitigate the toxic side effects of radiotherapy, modern radiotherapy techniques, such as intensity-modulated radiotherapy and volumetric-arc-modulated therapy, are capable of implementing highly conformal dose distribution for the target areas of tumors, reducing the radiation dose that endangers OARs, therefore reducing radiation-induced toxicity [1]. A key step in reducing the toxic effects of radiation exposure is the accurate delineation of OARs, which is usually performed manually by clinicians based on computed tomography (CT) scans and requires a great deal of time and effort. In the head and neck case, for example, many tumors are treated over a large area, covering a large number of OARs that have complex anatomical structures. Therefore, OARs delineations in head and neck cancer are time consuming and laborious to outline manually.

Traditional automatic delineation methods are mostly based on Atlas [2], with the drawbacks of the large computational burden and the reliance on Atlas templates. Recently, deep learning methods show their capability of learning anatomical features for delineation directly from the images without templates [3, 4]. Given enough delineation labels, a supervised deep learning model can produce clinically acceptable results. Usually, decent performance requires hundreds of labels. However, collecting manual delineations is expensive and hard to be scaled up. Considering the amount of unlabelled data is substantially more than a limited number of clinician curated labelled data, it is kind of wasteful not to use them. However, the unsupervised learning is very hard and usually works much less efficiently than supervised learning. Recently, self-supervised learning and contrastive learning have shown great promise, achieving state-of-the-art results [5, 6].

To address the label-scarce issue, a novel contrastive learning framework was developed and evaluated on a large-scale head and neck cancer dataset. Clinical validation of the accuracy and efficiency of the new method lays the foundation for its clinical application.

2. Methods

2.1. Multiview Contrastive Learning. Inspired by recent contrastive learning algorithms [5, 6], this study proposes a novel method that learns representations by maximizing agreement between different views of the same patient via a contrastive loss in the latent space. As illustrated in Figure 1, this method comprised the 3D CT image is first projected into three 2D views (coronal, sagittal, and transverse planes), then an existing deep convolutional neural network is used to obtain the representations of the three views, and finally, a contrastive loss is used to pull representation of different views of the same image closer ("positive pairs") and push representations of views from different images ("negative pairs") apart.

As shown in Figure 1, a 3D CT scan is first projected to three correlated views of the same patient, denoted x_1, x_2, and x_3, which are considered as the positive pair. A convolutional neural network- (CNN-) based feature encoder $f(x)$ extracts representation vectors h from previous 2D images. For the easily adaption to the segmentation task, we choose the commonly used UNet [7]. Only the encoder part of UNet is used during this self-learning stage. The whole UNet is joint trained later during the full-supervised stage. A multiple-layer perceptron (MLP) $g(h)$ projects representations to the space where contrastive loss is applied. An MLP with one hidden layer and batch normalization is used to obtain the projected z. Finally, a contrastive loss function is defined to distinguish between similar and dissimilar representations:

$$L_{i,j} = \frac{-\log \exp\left(z_i^T z_j/\tau\right)}{\sum_k 1_{[k\neq i]\exp}\left(z_i^T z_j/\tau\right)}, \quad (1)$$

where the contrastive loss is defined for a positive pair (i, j), $1_{[k\neq i]}$ is the indicator function whose value equates to 1 if and only if $k \neq i$, and τ is the temperature. The loss is computed across all positive pairs in a minibatch. Typical contrastive training relyies on large minibatch sizes such as 4098, but we avoid such hardware demanding setting by adopting the memory banks technology, which uses a slow-moving average network (momentum encoder) to maintain consistent representations of negative pairs drawn from a memory bank. Formally, denoting the parameters of query encoders f and g as θ_q and those of key encoders as θ_k, we update θ_k as

$$\theta_k = m\theta_k + (1 - m)\theta_q, \quad (2)$$

where m is a momentum parameter that exponentially moving averages parameters. The network parameter θ_q is optimized as usual. The advantage of this design is that it provides a principle way to discriminate information from 3 views for the same patient to obtain the improved representations for a downstream segmentation task.

2.2. Data. We used two datasets in this study. Dataset 1 contains an in-house collection of 188 CT scans from Shanghai Huashan Hospital. We manually annotate 24 OARs for this dataset, which include the brain, brain stem, spinal cord, spinal cord cavity, left eyeball, right eyeball, left crystal, right crystal, left optic nerve, right optic nerve, optic nerve cross, pituitary gland, left parotid gland, right parotid gland, oral cavity, mandible, left mandibular joint, right mandibular joint, left temporal lobe, right temporal lobe, larynx, pharynx, trachea, and thyroid. The organs were divided into 4 categories based on their importance. Among them, organ class A distributes among many CT slices, and the automatic delineation can reduce the repetitive manual drawing; organ class B has few slices but is delineated more frequently; organ class C is used less for planning; and class D involves critical physiology functions but is smaller and has less time-consuming drawing. Dataset 2 consists of a CT scans Head-Neck Cetuximab (HNC) dataset, which is collected from The Cancer Imaging Archive (TCIA) which is publicly available [8]. HNC consists of 32 patients' data from a clinical trial for stage III and IV head and neck carcinomas. We followed the same procedure as described in generating dataset 1 to annotate OARs in each of the CT scans.

2.3. Experiment Organization. We first train the network with all available samples from two datasets in the proposed self-supervised way and then fine tune the network on the 150 labelled patients in dataset 1. The remaining 38 patients in dataset 1 and 32 patients in dataset 2 are used to evaluate the performance. Four NVIDIA TITAN 3090 GPUs and PyTorch [9] deep learning framework are used to develop codes. We implement the details suggested in literature [6] to boost the performance, i.e., LARS, cosine learning rate, and the MLP projection head. The initial learning rate is set to 0.001 for 60,0000 iterations during the unsupervised training stage, and the initial learning rate is set to 0.0001 for 5,000 iterations during the fine tuning stage.

2.4. Quality Evaluation Metrics. Dice coefficients and Hausdorff distances are used to quantify and analyze the accuracy of the automatic delineation. The Dice is used to evaluate the accuracy of the inner region of OARs, and Hausdorff is used to evaluate the accuracy of the OARs boundaries.

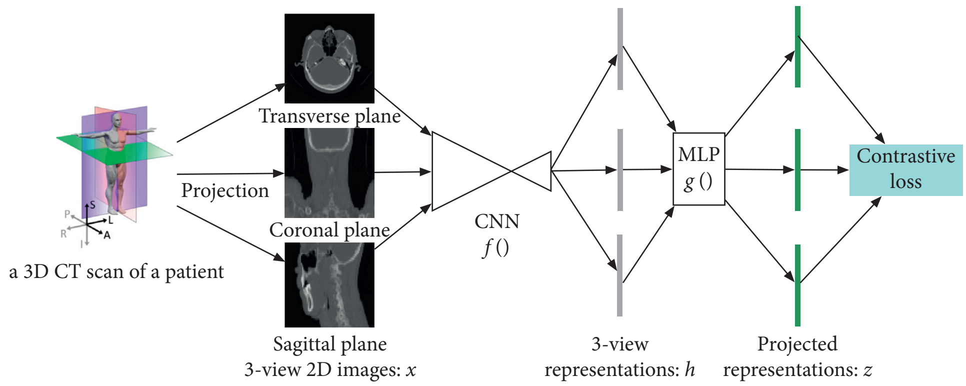

Figure 1: A overall illustration of the multiview self-supervised learning.

Table 1: Comparison of the proposed method with the state-of-the-art supervised methods (the higher the Dice, the better).

OARs	Our's	Ua-Net [3]	Anatomy-Net [4]
Brain	0.970	N/A	N/A
Brain stem	0.860	0.881	0.826
Spinal cord	0.862	0.856	0.803
Spinal cord cavity	0.891	N/A	N/A
Eye L	0.927	0.897	0.884
Eye R	0.927	0.919	0.892
Len L	0.801	0.793	0.772
Len R	0.821	0.746	0.78
Optical nerve L	0.798	0.693	0.725
Optical nerve R	0.750	0.718	0.729
Chiasm	0.770	0.618	0.605
Pituitary	0.724	N/A	N/A
Parotid L	0.837	0.839	0.822
Parotid R	0.872	0.847	0.822
Oral cavity	0.901	0.948	0.876
Mandible	0.921	0.925	0.919
Mandible joint L	0.873	0.824	0.816
Mandible joint R	0.865	0.837	0.817
Temporal lobe L	0.896	0.8478	0.866
Temporal lobe R	0.901	0.8413	0.857
Larynx	0.899	0.933	0.83
Pharynx	0.794	N/A	N/A
Trachea	0.866	0.812	0.793
Thyroid	0.857	0.827	0.718
Mean	*0.86*	*0.83*	*0.80*

3. Results and Discussion

3.1. Contour Accuracy. In order to verify the quality of the new method's delineations, it is compared with the Ua-Net [3] and Anatomy-Net [4] methods. Ua-Net was published in Nature 2019 and is the current best deep learning-based method. Anatomy-Net is another deep learning method dedicated to OARs of head and neck cancer, published in Medical Physics in 2018. The Dice score of the three methods are reported in Table 1. As shown in the table, the accuracy of our method was better than the other methods for most OARs. The average Dice score of the three methods was 0.86, 0.83, and 0.80, respectively. Our method improved the accuracy by 3.5% over Ua-Net and by 6.5% over Anatomy-Net. Ua-Net outperformed our method on the brain stem, oral cavity, and trachea, which may be attributed to its 3D nature, which is advantageous for organs with a large transverse span.

To validate the organ boundary accuracy of our method over the supervised deep learning method, Figure 2 reports the Dice difference and Hausdorff difference of the two methods. (a) Dice difference of >0 indicates that our method is superior, and a Hausdorff difference of <0 indicates that our method is superior. As shown in the figure, the Dice difference between the two methods is very small (Dice difference on the left vertical axis) with a mean value of 0.0001. However, the Hausdorff difference between the two methods is very large (Hausdorff difference on the right vertical axis) with a mean value of −5.96, indicating that our method has better organ boundary accuracy.

Figure 3 compares the delineation results of our method and the supervised deep learning method [7] on two sets of

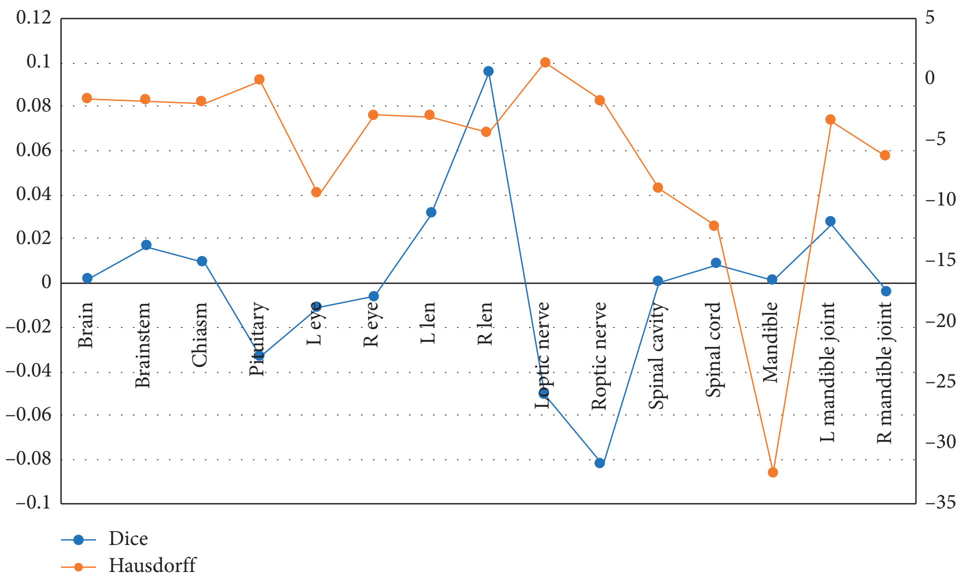

Figure 2: Quantitative comparison of our method with the supervised deep learning methods.

Figure 3: Qualitative comparison of our method with supervised deep learning methods. (a) Supervised deep learning methods. (b) Our method.

data. As seen in the figure, the delineation from the supervised method misses the optic nerves while our method delineates the optic nerves correctly. Similarly, the supervised method incorrectly predicts the chiasm, while our method correctly delineated this organ.

4. Conclusions

This study proposes and evaluates a novel deep-learning-based delineation method. Clinical evaluations show that our method has a delineation accuracy of 3.5% (Dice) and a boundary accuracy of 5.96 (Hausdorff) higher than the current best method. The advantage of our method is the integration of information from all three views of the CT to achieve better delineations than a single view.

This study has the following limitations. First, only CT images were used to delineate OARs. Some anatomical structures, such as crystals, have a low contrast on CT and are difficult to delineate with CT alone. Therefore, it is very important to integrate information from other modal images (e.g., MRI). Secondly, although delineation labels are defined by a senior physician, there will always be errors in manual delineation. Therefore, a standard delineation dataset is required in the future. One advantage of deep learning in this regard is that it ensures that the delineations are consistent across hospitals and individuals. Third, the number of delineation labels is still small, which limits the capacity of the deep network. There is a need to collect more standard delineation from more sources to improve the cross-domain adaptability and generalization of the deep network in the future.

In summary, a novel deep learning method is proposed in this study, which can delineate OARs in head and neck cancer, with better accuracy than the current state-of-the-art methods. The new method can save the clinician's manual delineation time and, thus, is clinically applicable and has the potential of clinical promotion.

Data Availability

The CT data used to support the findings of this study have not been made available because of patient privacy.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Research Article

Study of the Relationship between ICU Patient Recovery and TCM Treatment in Acute Phase: A Retrospective Study Based on Python Data Mining Technology

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Background. Data was mined with the help of an artificial intelligence system based on Python, data was collected, and a database was established using a Python crawler, and the relationship between the outcome of neurosurgery ICU patients and treatment using traditional Chinese medicine was ascertained through data management and statistical processing. *Method*. The source data cases ($n = 2237$) were selected. By following the experimental design, data ($n = 739$) were obtained through artificial intelligence processing, including $n = 480$ in the group with traditional Chinese medicine treatment and $n = 259$ in the group without traditional Chinese medicine treatment. An evaluation was carried out using characteristics of patents' ICU stays and summated rating scales. *Results*. There were statistical differences in 5 evaluation items ($P < 0.05$), and other comparison items also showed data with results favoring the outcomes in the intervention group using traditional Chinese medicine. *Discussion*. Traditional Chinese medicine as an alternative medical protocol effectively alleviates the stress and treatment fatigue brought about by modern medicine. Artificial intelligence data mining is a favorable medium to quantify this. Python will play a greater role in future clinical research because of its own characteristics.

1. Background

In the treatment of neurosurgery ICU patients, in addition to conventional ICU medication, nursing, and monitoring, traditional Chinese medicine has gradually become an alternative medical protocol that cannot be ignored [1]. However, the clinical evidence for the application of Chinese medicine in the treatment of seriously ill patients, especially in neurosurgery ICU patients, is insufficient. However, methods using Chinese medicine are still welcomed by patients and their families, as well as by ICU medical staff [2]. Is TCM really effective or are we just seeing the "survivorship bias"? In this paper, the author attempts to explore the role of traditional Chinese medicine in the treatment of neurosurgical ICU patients by looking at clinical research evidence [3, 4].

Data mining technology is a kind of data processing technology. It is a process of extracting potentially useful information and knowledge of which we are not aware beforehand from a large amount of incomplete, noisy, fuzzy, and random data. For data mining, the appropriate analysis tools need to be selected based on the data information in the data warehouse [5], and the information needs to be processed using statistical methods, case-based reasoning, decision trees, rule-based reasoning, fuzzy sets, even neural networks, and genetic algorithms to obtain useful information for analysis. The process of data mining is a "recycling" process. If at any step the expected goal is not achieved, we need to go back to the previous steps, readjust them, and execute them. Data mining technology has been applied relatively early to clinical research, with a relatively wide range of applications [6]. However, in this research, the current relatively advanced high-level computer language "Python" was adopted to design the data mining program code. Python is a high-level scripting language that combines interpretation, compilation, interactivity, and object orientation. Python was designed to have a strong readability. Compared with other languages, it often uses English keywords and some punctuation marks from other languages. In addition, it has more distinctive grammatical structures than other languages. Python has many advantages, such as its ease of learning, readability, ease of maintenance, extensive standard library, interactive mode, portability, extensibility, database [7], GUI programming, and embeddability. The prime advantage is that it is powerful, friendly to beginners, and naturally attractive to clinical workers [8].

Data was collected and a database was established using a Python crawler. Afterwards, code was written with Python [9]. A large number of clinical data were mined [10]. The relationship between neurosurgery ICU patients and traditional Chinese medicine treatment was ascertained through statistical processing [11].

2. Methods

2.1. Data Selection. From June 2015 to October 2020, all electronically stored cases ($n = 2237$) of patients who had been admitted to the ICU at the Neurosurgery Department of Blue Cross Brain Hospital affiliated with Shanghai Tongji University were selected. The research database was established by using Python data mining technology [12]. The STROBE checklist was used as the experiment design guidance method, and the data were cleaned according to the inclusion and exclusion criteria [13]. The preprocessed data ($n = 739$) were obtained. The preprocessed data were divided into two parts according to the actual clinical treatment methods used in the cases: a group with traditional Chinese medicine treatment ($n = 480$) and a group without traditional Chinese medicine treatment ($n = 259$). For the data mining schematic, please see Figure 1.

2.1.1. Inclusion Criteria. Inclusion criteria are as follows [14]: (a) cases with a clear ICD-10 diagnosis code; (b) hospital admission cases during the target time period; (c) cases that have complete medical records and can match the evaluation requirements; (d) cases with a history of transfer to a neurosurgery department ICU; (e) cases whose data can be crawled by a Python crawler.

It is particularly necessary to explain that in this research, when beginning to use Python to write the code, the private information in the patients' medical records, such as name, date of birth, residential address, and other information that cannot be crawled by a Python crawler, was prevented from being captured at the data mining tool level. Therefore, ethical issues in this scientific research were effectively avoided. The ethical committee demonstrated that informed consent cannot be signed because there is no clear subject in this research.

2.1.2. Exclusion Criteria. Exclusion criteria are as follows: (a) patients with an unclear diagnosis, or with secondary or primary serious cardiovascular or cerebrovascular diseases, or with liver, kidney, hematopoietic system, or other diseases; (b) patients with mental illness and in a stage of acute onset; (c) patients with incomplete medical records or a lack of important information regarding diagnosis and treatment; and (d) patients whose case records are not compatible with the STROBE checklist.

2.2. Interventions

2.2.1. The Group with Traditional Chinese Medicine Treatment. The subjects included in this group received a clear traditional Chinese medicine treatment intervention in the treatment process. After being processed by Python artificial intelligence, the data showed that these interventions were mainly acupuncture, cupping, massage, and moxibustion. Please see Figure 2.

2.2.2. The Group without Traditional Chinese Medicine Treatment. The subjects included in this group did not receive treatment from traditional Chinese medicine during treatment. Only conventional ICU treatment protocols were used.

2.2.3. Python Code and Workflow. (a) For data acquisition, organize the database, write the crawler code, and use the Python crawler to obtain the basic database material [15]. (b) For data management, through the data mining process, starting from data integration, through data cleaning, data selection, data collation, and other processes, obtain the preprocessed data. (c) Divide the preprocessed data into groups according to the experimental design for statistical comparison. Please see Figure 3.

3. Evaluation

In addition to the regular evaluation methods, that is, ICU days, urinary catheter removal time, nasal feeding tube removal time, ventilator weaning time, and the time to first flatus after surgery, evaluation methods such as the APACHE II Score (Acute Physiology and Chronic Health Score II) [16], GCS Score (Glasgow Coma Score), Delirium Assessment Scale (CAM-ICU), and Murray Lung Injury Score were selected and adopted.

3.1. The Apache II Score (Acute Physiology and Chronic Health Score II) System. The APACHE II score is composed of acute physiology scores, the age score, and chronic health scores. The higher the score, the more severe the disease, the worse the prognosis, and the higher the mortality rate. The Acute Physiology Score (APS) includes 12 physiological indices. The worst values (the highest or the lowest values) in the first 24 hours of ICU admission are selected and scored according to the attached table, and the higher scores are selected. The age score is divided into 5 stages from below 44 years old to above 75 years old, respectively, rated as A6 points. For the chronic health score, patients are required to meet the diagnosis of chronic organ dysfunction or immunosuppression before admission. For patients with chronic organ dysfunction or in a state of immunosuppression, if they are

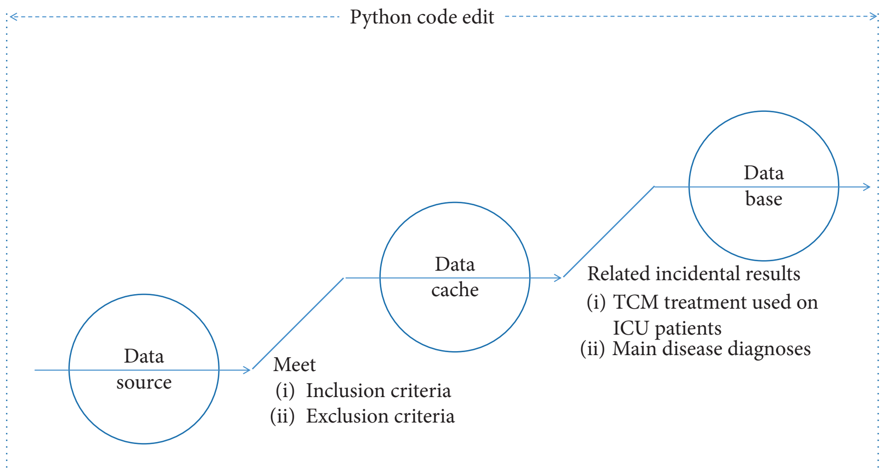

Figure 1: Data mining schematic.

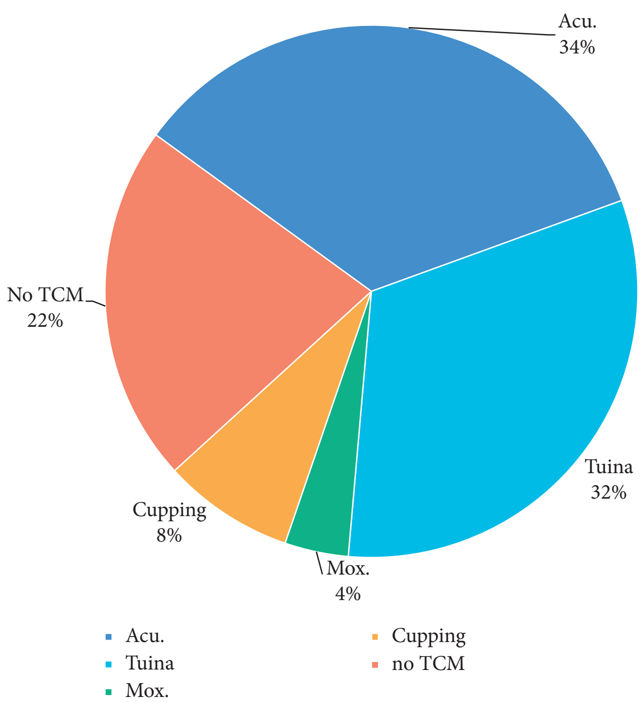

Figure 2: Several forms of TCM that were used in treatment. A histogram or pie chart of the four methods: acupuncture, cupping, Tuina, and moxibustion.

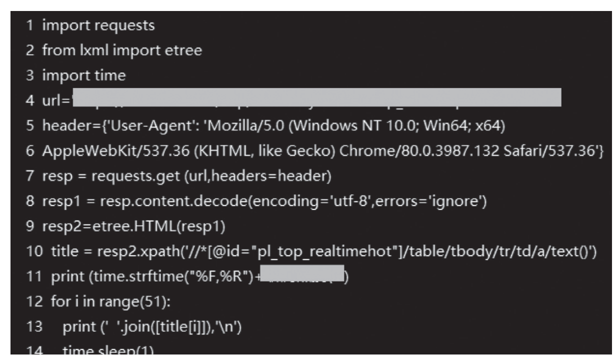

Figure 3: Some Python code screenshots.

admitted to ICU after elective surgery, the score is 2 points, and for those who are admitted to ICU after emergency surgery or nonsurgery, the score is 5 points. The final APACHE II score is the sum of the three scores. The APACHE II score was originally designed with the worst score within 24 hours of entering the ICU, so it is generally not used for the continuous dynamic evaluation of the severity of patients' condition.

3.2. The GCS Score (Glasgow Coma Score). Evaluation using the Glasgow Coma Index includes three aspects: eye opening response, language response, and body movement. The sum of these three points is the coma index. The coma index is a medical index to evaluate the degree of coma degree in patients. Nowadays, the Glasgow Coma Index is the most widely used index.

3.3. Delirium Assessment Scale (CAM-ICU). The diagnosis of delirium is mainly based on clinical examination and history. The confusion assessment method for the diagnosis of delirium in the ICU mainly includes the following aspects: the patient shows sudden changes or fluctuations in their state of consciousness, a lack of concentration, or confusion of thought and decreased clarity of consciousness.

3.4. Murray Lung Injury Score. Murray proposed a scoring method for the degree of lung injury in 1988. This scoring method makes a quantitative analysis of the degree of lung injury in acute respiratory distress syndrome (ARDS). Murray evaluated the degree of lung injury according to the partial pressure of oxygen in arterial blood/fractional inspired oxygen (PaO2/FiO2), the level of positive end-expiratory pressure (PEEP), the scores of the number of affected quadrants in chest X-rays, and the changes in lung compliance. The patient is evaluated as having acute lung injury, that is, ARDS, if the score is greater than 2.5. Patients with scores of 0.1–2.5 are evaluated a having mild-to-moderate lung injury. This standard emphasizes the continuous developmental process of lung injury from mild to severe and provides quantitative evaluation for lung injury. Studies by Owens et al. showed that the lung injury score had a significantly positive correlation with the extent of affected lung tissue ($r = 0.75$, $P < 0.01$) and was also closely associated with pulmonary vascular permeability ($r = 0.73$, $P < 0.01$). It can be seen that the Murray Lung Injury Score can accurately evaluate the degree of lung injury and is currently the most widely used score in clinical studies.

4. Statistical Analyse

SPSS 19.0 statistical software was adopted to conduct a statistical analysis of the data. Measurement data were expressed by mean and standard deviation. A paired t-test was adopted for comparison within groups, and an independent sample t-test was adopted for comparison among groups. Count data were expressed by rate or constituent ratio, and a chi-square test was adopted for comparison among groups. A Ridit analysis was adopted for comparison among groups of ranked data. $P < 0.05$ indicates that the difference is statistically significant.

5. Flow Chart

Flow chart of the study is shown in Figure 4.

6. Results

Through mining and processing by the artificial intelligence program, 739 cases conforming to data requirements were found and included, including 480 cases from the group with traditional Chinese medicine treatment and 259 cases from the group without Chinese medicine treatment. The main diseases covered included neurosurgical diagnoses such as cerebral hemorrhage (ICD-10 I61.902), craniocerebral trauma (ICD-10 S06.9059), subarachnoid hemorrhage (ICD-10 I60.901), and aneurysm rupture (ICD-10 I60.801).

6.1. Baseline. The baseline data is listed in Table 1.

6.2. Data Comparison between ICU Patients with and without TCM Treatment. The comparison data between ICU patients with and without TCM treatment are shown in Table 2.

The data mined through Python artificial intelligence are used for conducting statistical processing with the data obtained after processing. As mentioned in Tables 1 and 2 above, among brain surgery ICU patients treated with TCM, in each comparison item such as ICU hospital stay, urinary catheter removal time, nasal feeding tube removal time, ventilator weaning time, and time to first flatus after surgery, the durations were shorter than those in the group without TCM. Among these, the P value of the ICU hospital stay, the urinary catheter removal time, time to first flatus after surgery, and the time to first improved muscle strength was less than 0.05, which shows a statistically significant difference. For the evaluation of muscle strength at discharge, according to the GCS score at discharge, APACHE II (Acute Physiology and Chronic Health Score II) scoring system at discharge, VAS score at discharge, and Delirium Evaluation Scale at discharge (CAM-ICU), the group with TCM treatment performed better than the group without TCM treatment. However, only the GCS scoring items, $P < 0.05$, showed a statistically significant difference. In the evaluations according to the number of cases of ICU-acquired delirium and the number of cases of ICU-acquired weakness, the values in the group with TCM treatment were less than the values in the group without TCM treatment; however, there was no statistically significant difference.

7. Discussion and Outlook

TCM and Western medicine study the same issue, that is, the health and illness of people. The main issue lies in the fact that their perspectives are different. Therefore, the two have their own characteristics and advantages and also have their limitations. If they can bring their respective advantages together, then the best diagnosis and treatment protocols can be provided to patients [17]. In a difficult surgery, the success on the operating table is only half a success. The ICU is the guarantee of a successful surgery, having a high requirement for equipment, environment, and talent [18]. However, the ICU is limited by a higher level of work intensity needed and greater pressure on the patient, and it often leads to excessive fatigue. This is also reflected in the results of patient treatment. The alternative medical protocol of introducing TCM has effectively alleviated the pressure caused by modern healthcare, intensive healthcare, intensive equipment use, and intensive treatment [18]. The above results show the impressive effect that TCM has on the treatment of patients in the neurosurgery ICU and provide an ideal improved treatment solution in the neurosurgery ICU. Due to the benefits of data mining technology, this fact can be presented to us by using the data.

With data mining technology, we can find potential and meaningful patterns and associations from the massive amount of information in the real world, especially in the context of the current fierce collision between modern medicine and traditional medicine. With deeper research, more and more investigators are using data (such as frequency statistics, association rules, and cluster analyses) to explore potential relationships between modern medicine and traditional medicine. Various data mining technologies are being applied to the model of each department of traditional medicine and clinical medicine and are showing a relatively high accuracy. However, there is currently a lack of verification of the effectiveness of such models and of comparative analysis with traditional disease evaluation tools. In the future, it will be necessary to carry out multicenter and prospective studies to verify the effectiveness of these models. There is a certain conflict between the professionalism of clinical doctors and the development of data mining technology in medical data. In comparison with numerous data mining tools, Python distinguishes itself due to its ease of learning and use. Additionally, Python meets

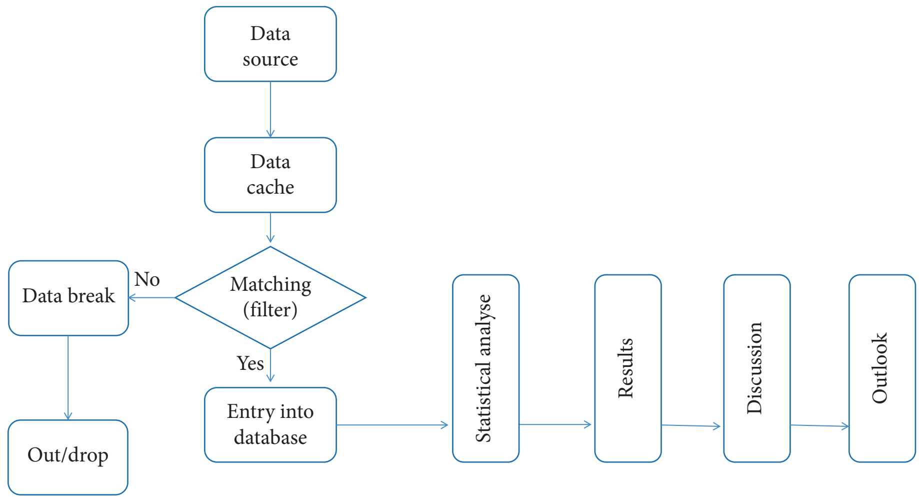

Figure 4: Flow chart for the study from data source mining to the end. The date was collected from the source into data cache, with the filter working following the inclusion/exclusion criteria; date was divided into two parts, only when the data matched; it can be put into database. Otherwise, the other part of data will be broken down and taken out of the study.

Table 1: Baseline data.

Baseline data	With TCM	Without TCM
The final number of cases included in the research	$N = 480$	$N = 259$
Age (mean ± SD)	67.38 ± 25.62	69.21 ± 28.10
Gender (male/female) (*n* case)	209/271	102/157
Maximum weight (kg)	126	110
Minimum weight (kg)	38	42
BMI (mean ± SD)	22.17 ± 10.66	23.41 ± 11.09
Cerebral hemorrhage (n cases)	162	97
Cerebral hemorrhage death (*n* cases)	29	8
Craniocerebral trauma (*n* cases)	140	82
Craniocerebral trauma death (*n* cases)	11	6
Subarachnoid hemorrhage (*n* cases)	62	35
Subarachnoid hemorrhage 3 death (*n* cases)	8	3

Table 2: Comparison data.

Data comparison between ICU patients with and without TCM treatment Comparison items (mean ± SD)	With TCM	Without TCM
The final number of cases included in the research	$N = 480$	$N = 259$
ICU hospital stay (days)	17.29 ± 11.03	22.91 ± 16.30
Urinary catheter removal time (days)	5.02 ± 4.73	7.74 ± 5.00
Nasal feeding tube removal time (days)	9.38 ± 6.27	11.60 ± 7.39
Ventilator weaning time (days)	12.49 ± 7.90	12.41 ± 8.51
Time to first flatus after surgery (days)	1.02 ± 1.33	1.97 ± 1.58
Time to first improved muscle strength (days)	2.37 ± 0.48	2.29 ± 0.99
Evaluation of muscle strength at discharge (grade)	3.80 ± 1.95	3.05 ± 2.06
VAS score at discharge (score)	2.75 ± 2.08	3.09 ± 1.55
Number of cases of ICU-acquired delirium (n)	42	32
Number of cases of ICU-acquired weakness (n)	30	15

the requirements of artificial intelligence because of its powerful functionality. At this stage, after decades of development, Python has entered the stage of Python 3.1 and above, and an increasing amount of medical workers is beginning to use it to conduct scientific study designs and research applications relating to advanced artificial intelligence.

However, there are still areas that need to be further perfected in the future. For example, in this research, we only discussed the difference between the outcomes of patients treated with TCM and without TCM; however, we did not conduct a data-based exploration on whether there is a difference in the curative effect according to specific methods of TCM. There were 4 main diseases involved in this research, but there was, for example, no discussion carried out on the basis of each disease as a subgroup. The reason for this is that there are still relatively few reports from retrospective studies of clinical data using Python, a complete exploration system has not yet been formed, and there is still space for development regarding the benefits of using Python for writing data mining artificial intelligence systems. It is believed that more clinical scientific study protocols based on this computer language will emerge in the future and will become an important part of clinical scientific study and data management with respect to artificial intelligence deep learning and neural networks.

Data Availability

This research was registered (internally) at the Clinical Trial Registration Center at Shanghai Tongji University; all experimental data and related codes shall be saved here for 10 years. The original data, database and python code used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Research Article

Oral Microbial Diversity Formed and Maintained through Decomposition Product Feedback Regulation and Delayed Responses

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Oral microbial diversity plays an important role on oral health maintenance. However, there are only few kinds of substrates available for the microbial flora in oral cavity, and it still remains unclear why oral microbial diversity can be formed and sustained without obvious competitive exclusion. Based on experimental phenomena and data, a new hypothesis was proposed, namely, the decomposition product negative feedback regulation on microbial population size and microbial delay responses including reproductive, reaction, interspecific competition, and substrate decomposition delay responses induced by oral immunity. According to hypothesis and its cellular automata (CA) model, the CA simulation results sufficiently proved that the decomposition product negative feedback regulation and four microbial delay responses could significantly alleviate the interspecific competitions and inhibit the emergence of dominant species, causing the formation and sustenance of oral microbial diversity. This study could also offer effective guidance of prevention and treatment of oral cavity diseases.

1. Introduction

As is known, oral microorganisms are one of the five major microbial florae of the human body, oral microbial diversity is an important indicator to evaluate the oral health status of people, and simultaneously, it also closely related to systemic diseases occurrence, such as digestive system [1], movement system [2], nervous system [3, 4], and circulatory system [5], playing a significant role in our health care [6].

Oral microorganisms come mainly from outside environment through the air, water, and food and colonize different places of oral cavity, such as saliva, gingiva, and oral walls. Compared with substrates in natural environments, however, the types and amounts of substrates in oral cavity can provide for microbial growth is extremely limited. According to the competitive exclusion principle in ecology, microbial species would have to compete fiercely over few varieties of substrates under this circumstance, and only a few microbial species can coexist via substrate niche differentiation, which is unfavorable for microbial diversity [7, 8]. Why oral microbial diversity can be formed and maintained in a way apparently violating competitive exclusion principle remains mysterious so far [9].

In the research, 50 mixed-gender athletes with healthy oral cavity were randomly selected as testers, and the abundance, intracellular triglycerides, and specific growth rates of the five common genera, *Streptococcus*, *Prevotella*, *Haemophilus*, *Rothia*, and *Veillonella* were analyzed and obtained through periodical sampling from their oral floras. The results show that intracellular triglycerides of all genera were significantly higher than their homogenous genera in natural environment, and it has been reported that the microbial species could only utilize the intracellular energy substances to grow independent of ambient substrates

(Wilkinson, 1963). Nevertheless, there were quite different specific growth rates between genera, and the abundances consistently stayed in unstable states with a tendency of asynchronously convergent fluctuations and low Simpson α diversity index. Through these experimental phenomena and data, two fundamental oral microbial delay responses including reproductive delay and reaction delay were identified based on delay logistic equation and digital simulation, which are inevitably accompanied by other two delay responses, i.e., interspecific competition delay and LMOM decomposition delay according microbial ecology.

As we know that microbes need to break down large molecular organic matters (LMOMs) into small molecular organic matters (SMOMs) that can be directly absorbed and assimilated by cells, such as starches and celluloses were broken down into monosaccharides and oligosaccharides, proteins into oligopeptides and amino acids, fat into glycerol and fatty acids. The processes of decomposing LMOMs into SMOMs need to greatly consume metabolic energy and often take place in the extracellular environments, whereas SMOMs are absorbed and assimilated inside the cells. Hence, SMOMs could be considered as the public goods that could directly be utilized by all microbial species [10, 11].

Therefore, in the article, a new dynamic mechanism of oral microbial diversity formation and maintenance was put forward as follows:

According to adaptabilities to the oral environment, the oral microbial species could be divided to two types, *collaborators* and *scammers*. As colonized in oral cavity, *collaborators* could well adapt to oral environment and get an enhanced LMOM decomposition ability, resulting in accelerated growth of *collaborator* populations, and simultaneously more SMOMs can also be produced. In contrast, *scammers* cannot acclimate to the oral environment without enhancement of LMOM decomposition capacities. As the *collaborators* and *scammers* are combined into an oral microbial flora, the *scammers* might be more prone to utilizing these ready-made SMOMs produced by *collaborators*. Since the *collaborators* would have to entail the high cost of LMOM decomposition, the *scammers* would pay nothing to obtain SMOMs; hence, *scammers* could easily win in the interspecific competition and competitively exclude *collaborators* gradually [12]. Once the population of *collaborators* drops drastically, however, SMOM decrease would ensue to undoubtedly hinder the further growth of the *scammer* population due to starvation. Hence, an SMOM-based negative feedback regulation on microbial population size might exist in oral microbial community. If the *collaborators* went extinct and *scammers* would be eradicated inexorably, the oral microbial diversity could not be formed and sustained in oral cavity at all. Owing to existence of abovementioned four delay responses, however, both *collaborators* and *scammers* would not go extinct at all. The SMOM-based negative feedback regulation and delay responses would drive the oral microbial flora succession with asynchronously convergent fluctuations of populations. Referring to the classic *Lotka–Volterra* equations, the interspecific competition intensity mainly depends on the product of population size, and the asynchronously convergent fluctuations of microbial populations could significantly alleviate the interspecific competitions and inhibit the emergence of dominant species, forming and maintaining the oral microbial diversity by a strategy of species-for-quantity exchange.

Based on the assumptions and experimental data, a highly valid cellular automata (CA) model was established to describe oral microbial community succession, and its local rules could sufficiently represent the SMOM-based negative feedback regulation on microbial population size and the four delay responses. The digital simulation results confirmed the hypothesis proposed undoubtedly from the view of time and space dimensions simultaneously, and this study can lay the theoretical foundation to understand the mechanism of the forming and maintenance of microbial diversity in oral cavity, offering effective guidance of prevention and treatment of oral cavity diseases.

2. Materials and Methods

2.1. Source of the Samples. The 50 students with mixed-gender and aged 18 to 25 were randomly selected from undergraduates and postgraduates in Shandong Sport University.

All participants should meet the following inclusion criteria during the experiment:

- Without periodontitis, oral mucosal diseases, dental caries, and other oral diseases
- Without systemic diseases and behavioral disorders
- Physical and psychological indicators were basically normal
- Nonsmoking and alcohol-free
- No drug dependence or history of drug addiction
- Not using antibiotics in the past 3 months
- No more than 2 missing teeth with the exception of extracted third molars
- Mean clinical attachment level (CAL) $\leq$0.5 mm, no interproximal sites with CAL $\geq$ 3 mm [13]

Besides, all participants were asked to rinse their mouths with sterile saline (0.9%) for 1 to 2 min to remove the debris. No eating, drinking, smoking, or chewing gum during this period. Each participant kept saliva in the mouth for at least 1 min, chewed the swab from a saliva sampling tube (Salivette®, SARSTEDT) and placed the swab back into the tube. The entire tubes were then centrifuged at 10,000 rpm for 5 min. After discarding the supernatant, the collected cells were used as samples for measurement and analysis of the relative abundances, intracellular triglycerides, and specific growth rates of the five most common genera, *Streptococcus*, *Prevotella*, *Haemophilus*, *Rothia*, and *Veillonella*.

2.2. Determination of Intracellular Lipids of Oral Microorganisms. To compare of the intracellular storage substance content of oral microorganisms in the external and oral environment, the cells in above samples were resuspended in 1 ml of 0.1 mol L^{-1} phosphate buffer. The test solution was again centrifuged with the above parameters after ultrasonic fragmentation. The intracellular lipid content was determined using a triglyceride assay kit and analyzed by a UV spectrophotometer at 420 nm.

2.3. Determination of Specific Microbial Growth Rate. The cells in above samples were also resuspended in 2 mL of sterile saline (0.9%), for high-throughput sequencing to obtain relative changes in the numbers of different populations. The main steps are as follows: (1) DNA extraction, the genome DNA was extracted by column genomic DNA extraction kit, and the integrity of the extracted genomic DNA was tested using 1% agarose gel electrophoresis. (2) 16S rDNA amplification, then, the primers were obtained according to the conserved region design, and sequencing barcodes were added at the end of the primers for PCR amplification. The PCR amplification primers used were 515F: GTGCCAGCMGCCGCGG and 907R: CCGTCAATTCMTTTRAGTT. PCR reaction conditions were *a*: 2 min, 95°C; 1 time cycle; *b*: 30 s, 95°C; 30 s, 55°C; 45 s, 72°C; 28 cycles; and *c*: 10 min, 72°C, 4°C until termination. (3) After recovery and purification of amplified products, DNA libraries were constructed and their quality was evaluated, and sequencing of the qualified libraries was performed on the platform Illumina HiSeq 2500. The original image data files were converted into sequenced reads by base calling analysis, and the results were stored in FASTQ file format, which contained the sequence information of reads and the corresponding sequencing quality information [14].

Based on the experimental data of exponential growth stage, the growth rate of microbial population could be defined as follows:

$$\frac{dx}{dt} = \mu x, \tag{1}$$

where x is the microbial population at t, μ is the specific growth rate, and the μ could be calculated by $\mu = \Delta x / x\Delta t$ from the corresponding discrete form of equation (1).

2.4. Delay Response Identification. The delay logistic equation equation (2) was used to identify the fundamental delay responses (Ellermeyer et al, 2003):

$$\frac{dx}{dt} = \mu x\left(t - \tau_1\right)\left[1 - \frac{x\left(t - \tau_2\right)}{K}\right], \tag{2}$$

where x and μ have the same meaning as they are in equation (1) and τ_1 and τ_2 are microbial reproductive delay and reaction delay, respectively. In the research, dynamic response optimization was used to identify these two fundamental delay responses, based on experimental data and digital simulation on the platform of Matlab/Simulink.

2.5. CA Modeling and Simulation. Because oral cavity is peculiar ecosystem, the relationships and interactions between microbial species and their biotic/abiotic environment are extremely complicated with strong nonlinearity and uncertainty, and it is difficult to carry out prototype experiments or analytical and numerical methods for investigation and elucidation of the dynamic mechanisms to drive oral microbial flora succession. The CA modeling and simulation has been extensively applied for theoretical investigation of complex systems, such as medicine, biology, and sociology. Based on local rules, CA can simulate extremely complicated structure and dynamic behaviors to predict the unexpected holistic emerging characteristics which cannot be realized by traditional ordinary and partial differential equation modeling at all [15]. Therefore, a highly valid CA models were developed and digital simulations were conducted to obtain the general pattern of spatiotemporal succession in combination with system cluster analysis, since its local update rules could fully embody preceding two decisive succession mechanisms, i.e., the decomposition product negative feedback regulation on microbial population size and four microbial delay responses induced by oral immunity.

3. Results and Discussion

3.1. Microbial Response Characteristics to Oral Environment

3.1.1. Relative Abundances and Diversity Dynamic Characteristics. The relative abundances of *Streptococcus*, *Prevotella*, *Haemophilus*, *Rothia*, and *Veillonella* in oral cavity and corresponding Simpson α diversity were obtained via periodical samplings and analyses (Figure 1).

As illustrated in Figure 1, these time-series data showed apparently the oral microbial flora consistently stayed in unstable states with asynchronous convergent fluctuations of microbial populations and high evenness [16].

3.1.2. Intracellular Triglycerides and Specific Growth Rate. As illustrated in Figure 2, the intracellular triglycerides of all oral microbial genera were significantly higher than their homogenous strains existing in natural environment. In terms of specific growth rate, however, compared with their counterparts in natural environment, *Haemophilus* and *Veillonella* are significantly higher, *Prevotella* is significantly lower, and *Streptococcus* and *Rothia* have no significant difference.

3.1.3. Identification of Microbial Delay Responses. Generally, along with the reproductive delay (τ_1) and the reaction delay (τ_2) increase in delay logistic equation (Equation (1)), the population dynamic characteristics vary from asymptotical stabilization to convergent fluctuation (Figure 3).

Based on experimental data (Figure 1), delay logistic equation (Equation (1)), and digital simulations (Figure 3), the τ_1 and τ_2 of *Streptococcus*, *Prevotella*, *Haemophilus*, *Rothia*, and *Veillonella* were precisely identified through dynamic response optimization (Table 1).

3.1.4. Hypothesis of Formation and Maintenance of Microbial Diversity in Oral Cavity. Based on oral microbiology,

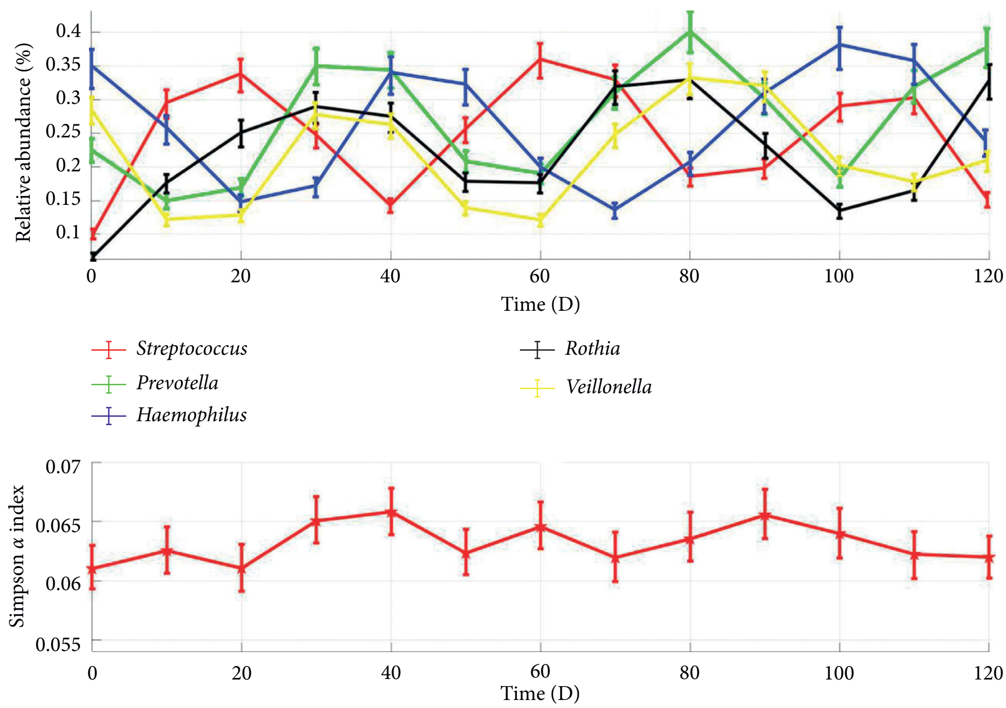

Figure 1: Dynamic characteristics of microbial populations and Simpson α diversity in oral cavity.

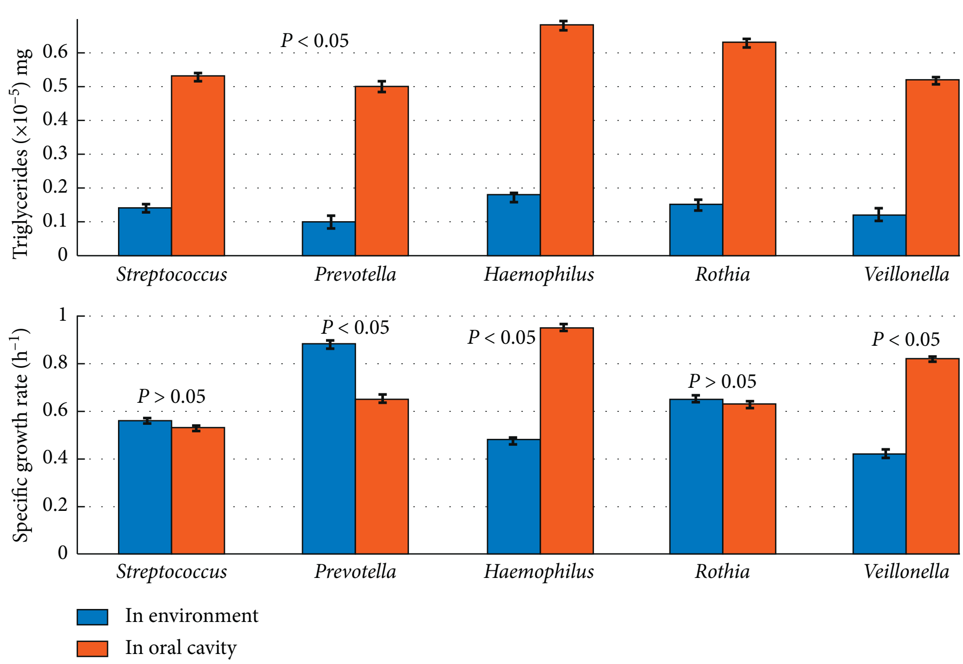

Figure 2: Variation of intracellular triglyceride content and specific growth rate of microbial populations in natural environment and oral cavity.

microbial ecology, phenomena observed, and experimental data (Figures 1–3), a new assumption of oral microbial diversity formation and maintenance was proposed as follows.

Although microbial species have capabilities to decompose LMOMs into SMOMs for survival in natural environment, as colonized in oral cavity, some microbial species (called *collaborators*), such as *Haemophilus* and *Veillonella*, could well adapt to oral environment and get an enhanced LMOM decomposition ability resulting in accelerated growth and simultaneously more SMOMs could be produced. In contrast, other species (called *scammers*), such as *Streptococcus*, *Rothia*, and *Prevotella*, do not have such adaptively physiological and behavioral response characteristics to oral environment, which reflected in the specific growth rate of *Streptococcus* and *Rothia* had no

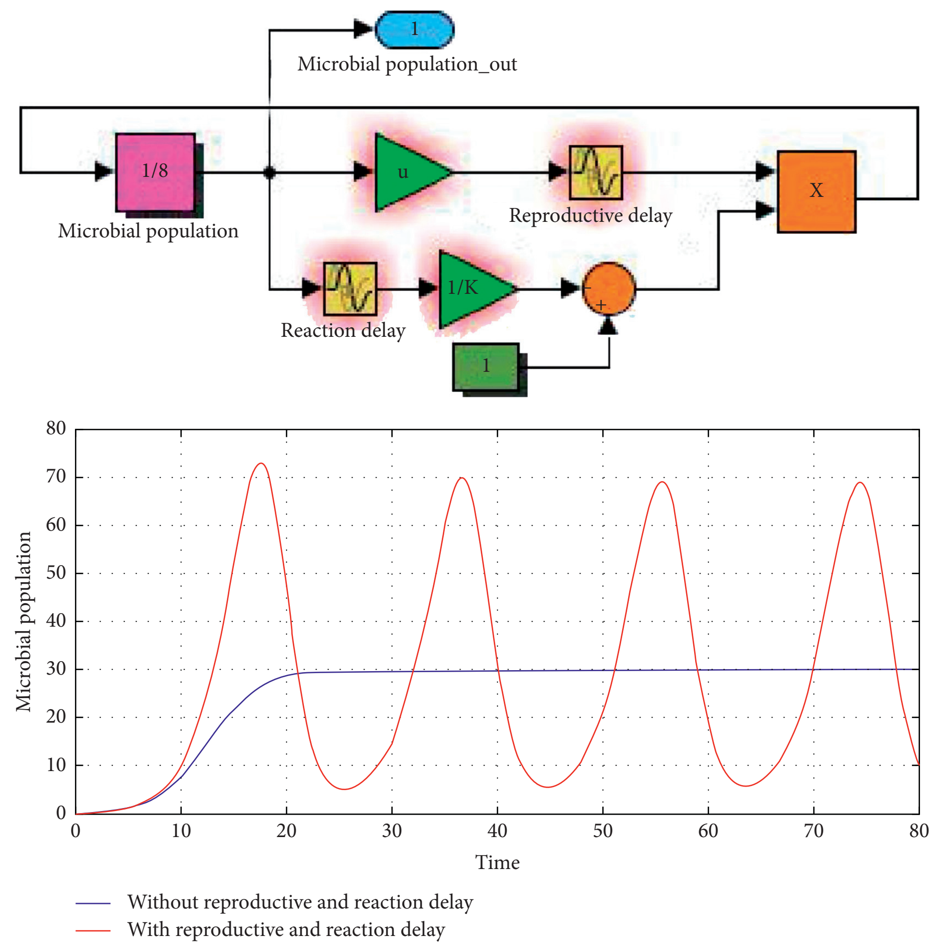

Figure 3: Microbial population dynamic response characteristics without and with delay effects.

Table 1: Point estimation and 95% interval estimation of reproductive delay and reaction delay of the microbial population in oral cavity (unit: h).

Strains	Reproductive delay	Reaction delay
Streptococcus	2.85 ∈ [1.72, 3.92]	2.95 ∈ [1.88, 3.57]
Prevotella	2.45 ∈ [1.29, 3.98]	5.29 ∈ [4.50, 8.05]
Haemophilus	4.02 ∈ [2.18, 5.56]	8.53 ∈ [6.38, 10.07]
Rothia	2.85 ∈ [2.12, 3.92]	2.17 ∈ [1.88, 3.57]
Veillonella	3.28 ∈ [2.20, 4.18]	7.04 ∈ [4.50, 8.15]

change, and *Prevotella* growth was significantly inhibited, and it also indicated that their LMOM decomposing capacity could not be strengthen in oral environment.

Since the *collaborators* would have to entail the high cost of LMOM decomposition, they would benefit more from cooperation than competition, and interspecific cooperation begins to dominate. However, the *scammers* would pay nothing to obtain SMOMs, so *scammers* could easily win in the interspecific competition to competitively exclude *collaborators* [12]. Once the *collaborator* population drops drastically, the accompanying decrease of SMOMs appears inexorably and would undoubtedly hamper the further growth of the *scammer* population due to starvation. If the *collaborators* went extinct, *scammers* would be extirpated, and oral microbial diversity could not be formed and sustained at all.

From Figure 2, we might speculate that, as SMOM is plentiful, both *collaborators* and *scammers* could assimilate SMOMs which could convert into intracellular energy substances such as triglycerides, in order to overcome adversity in the future. At this time, microbial species might stay in time-lag state of reproduction and reaction [17, 18], and microbial cells did not divide until environmental factors such as SMOM amount and interspecific competition strengths were suitable for them in the oral environment.

Based on the above analysis, two crucial fundamental succession mechanisms might exist in oral microbial flora as follows:

(1) The SMOM-based negative feedback regulation on microbial population size: as the population of the *collaborators* increases, which is followed by accumulation of SMOMs, the *scammer* population will also grow and inevitably exert competitive exclusion against *collaborators*, causing the *collaborator* population drop drastically and the accompanying decrease of SMOMs appears, which undoubtedly hinders the further growth of the *scammer* population and reduce the intraspecific competition between *scammers* and the strength of competitive exclusion to *collaborators.* Since the *scammer* population declines, the *collaborator* population rebounds. At this time, the microbial community succession seems to return to the original point and completes a cycle. Hence, SMOMs might play a role on a negative feedback regulation of microbial population to cause *collaborator* and *scammer* population fluctuation.

(2) The delay responses of microbial species: the reproductive and reaction delay responses were produced to acclimate for oral environment mainly by intracellular energy substance storage. Theoretically, these two fundamental delays must be accompanied by interspecific competition delay and LMOM decomposition delay. These four delay effects would further exacerbate population fluctuations [18, 19].

Referring to the classic *Lotka–Volterra* equations, the interspecific competition intensity only depends on the product of their population size in the case of the competition coefficient unchanged; hence, these two decisive dynamic mechanisms could give rise to asynchronously convergent fluctuations of microbial populations, which can significantly alleviate the interspecific competitions and inhibit the emergence of dominant species, causing formation and maintenance of the microbial diversity with higher richness and evenness by a strategy of species-for-quantity exchange.

Based on preceding hypotheses, a valid CA model describing oral microbial flora spatiotemporal succession was developed and a great number of digital simulations were conducted to confirm proposed hypotheses.

3.2. CA Modeling and Simulation of Oral Microbial Flora Spatiotemporal Succession

3.2.1. Cells. A cell represents a microbial individual of a certain species with 4 states as follows:

$$S = (\text{Pos, Spe, isLag, Lat, Clr}), \tag{3}$$

where

(1) Pos (i, j) denotes whether or not a position (i, j) was occupied by a microbial individual, and **1** and **0** represent “occupied” and “unoccupied”, respectively.

(2) Spe (i, j) denotes the type of a microbial individual at position (i, j), and 1 and 0 represent “*collaborators*” and “*scammers*”, respectively.

(3) isLag (i, j) denotes whether or not a microbial individual at position (i, j) stays in time-lag state, and 1 and 0 represents “yes” and “no”, respectively.

(4) Lat (i, j) records the lag time of a microbial individual at position (i, j).

(5) Clr (i, j) denotes the color of a microbial individual at the position (i, j), specified by an RGB value.

3.2.2. Cellular Space and Boundary Conditions

(1) Lattice: 2D domain with $10^3 \times 10^3$ uniform square meshes.

(2) Neighbor type: Moore-type was applied for CA modeling and simulation (Figure 4), each cell has 8 neighboring cells.

(3) Boundary conditions: periodic boundary.

In order to obtain a general pattern of microbial community spatiotemporal succession in oral cavity, periodic boundary was used for CA simulation, indicating cellular space was connected up and down and left and right to form a torus structure, which could be considered as an infinite cellular space extensively applied for theoretical investigation.

3.2.3. Update Rules. The key part of the CA modeling is update rules sufficiently embodying the two fundamental dynamic mechanisms driving oral microbial community succession as follows:

(1) *Delay Response Rules*. For a microbial individual at position (I, j) and time t, its delay response is dependent on the total sum, MLL (I, j), of *collaborator* and *scammer* individuals in the nearest neighborhood:

$$\begin{aligned}\text{MLL}(i, j) = {} & \text{Spe}(i-1, j-1) + \text{Spe}(i, j-1) \\ & + \text{Spe}(i+1, j-1) + \text{Spe}(i-1, j) \\ & + \text{Spe}(i+1, j) + \text{Spe}(i-1, j+1) \\ & + \text{Spe}(i, j+1) + \text{Spe}(i+1, j+1).\end{aligned} \tag{4}$$

For a *collaborator* individual at position (i, j), if its neighboring *scammer* individuals meet $6 \le \text{MLL}(i, j) \le 8$, $3 \le \text{MLL}(i, j) \le 5$, $0 \le \text{MLL}(i, j) \le 2$, then it would enter lag phase with probability α_1, α_2, α_3, respectively, satisfying $\alpha_1 > \alpha_2 > \alpha_3$.

For a *scammer* individual at position (i, j), if its neighboring *collaborator* individuals meet $6 \le \text{MLL}(i, j) \le 8$, $3 \le \text{MLL}(i, j) \le 5$, $0 \le \text{MLL}(i, j) \le 2$, then it would enter lag phase with probability β_1, β_2, β_3, respectively, satisfying $\beta_1 < \beta_2 < \beta_3$.

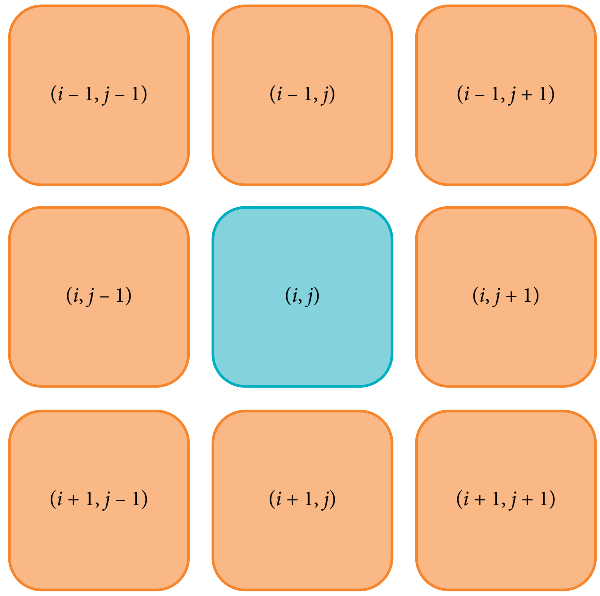

Figure 4: CA neighbor type.

It is also worth pointing out that a microbial individual staying in lag phase is similar as the dead one, except for the former needs to occupy a position (Pos $(i, j) = 1$), and the latter will release space (Pos $(i, j) = 0$). Once *collaborator* and *scammer* individuals stay in lag phase, they would not decompose LMOMs, absorb and assimilate SMOMs, compete or cooperate with other neighboring individuals, and divide to create offspring to occupy other positions. The microbial individual would recover from the lag phase; however, the microbial individual would come to death with a probability p as long as the lag time exceeds maximum time-lag phase, Lat $(i, j) \times n$, where n is an integer, for depletion of intracellular energy substance storage.

(2) *Rule of Birth and Death.* Although the life and death of microbial individuals is mainly dependent on the interspecific competition intensity of the nearest neighboring individuals, the *collaborator* and *scammer* individuals would die off naturally with probability d $(d < p)$ at each time step.

(3) *Rule of Move.* This rule expresses microbial cell proliferation with the moving radius of 3. If a position, Pos (i, j), is vacant, its neighboring 48 individuals of three layers centered on Pos (i, j) could move to this position with the same probability m.

3.3. CA Simulation of Oral Microbial Flora Spatiotemporal Succession

3.3.1. Spatial Pattern of Oral Microbial Flora Succession. The N kinds of microbial species including n_1 kinds of the *collaborators* and N-n_1 kinds of the *scammers* are computer-generated to completely random seeding on the grids of cellular space. Since a microbial species could be considered as a characteristic parameter vector with set intervals (Table 2), hence N kinds of microbial species could be obtained by uniformly and independently random selection from these parameter intervals through Monte Carlo experiments and set to the CA model for simulation. For example, a *collaborator* species could be defined as a parameter vector $[\alpha_1, \alpha_2, \alpha_3, \beta_1, \beta_2, \beta_3, m, p, d, Lat, n]$ whose magnitude was mapped into interval of [0,1] and then assigned to Clr (i, j), causing color change of a grid in lattice occurred.

Driven by SMOM feedback regulation of microbial population and microbial delay responses, the spatial pattern of oral microbial flora succession is illustrated in Figure 5. Because the relatedness of the microbial individuals is embodied in color similarity between them, they showed apparently a specific spatial pattern of aggregated distributions.

Therefore, system cluster analysis was conducted to investigate the similarity of microbial individuals in these patches, and the *Minkowski* method and *Centroid* method were used to measure the distance of two microbial characteristic vectors and generate a hierarchical cluster tree (Figure 6), respectively, since these two methods corresponded to maximum *cophenetic* correlation coefficient (0.97). Hence, it was concluded that the microbial individuals were randomly scattered on the grids in the beginning stage of succession, while microbial individuals with closer affinities began to gradually aggregate to form patches, along with succession process.

The CA simulation results were highly similar to the phenomena observed in the experiments [20], i.e., microbial species with a close relationship locally tended to aggregate in patches, which could effectively ease the interspecific competitions to be propitious to form and maintain the microbial diversity.

Table 2: Parameters in the CA model of microbial community succession in oral cavity.

Name	Parameter	Range
Probability of entering lag phase	α_1	[0.7, 1]
Probability of entering lag phase	α_2	[0.3, 0.7]
Probability of entering lag phase	α_3	[0, 0.3]
Probability of entering lag phase	β_1	[0, 0.3]
Probability of entering lag phase	β_2	[0.3, 0.7]
Probability of entering lag phase	β_3	[0.7, 1]
Probability of move	m	[0, 0.2]
Probability of death exceeding lag phase	p	[0.8, 1]
Probability of natural death	d	[0.1, 0.3]
Lag phase time	Lat	[6, 10]
Maximum factor	n	[1, 3]
Initial kinds of microbial species	N	$[5\cdot10^2, 10^3]$
Ration of *collaborator* richness to richness of initial microbial community	N_p	[0.4, 0.6]
Initial population of each microbial species	M	$[10^4, 10^5]$
Ration of *collaborator* cells to the total number of microbial cells	M_p	[0.3, 0.7]

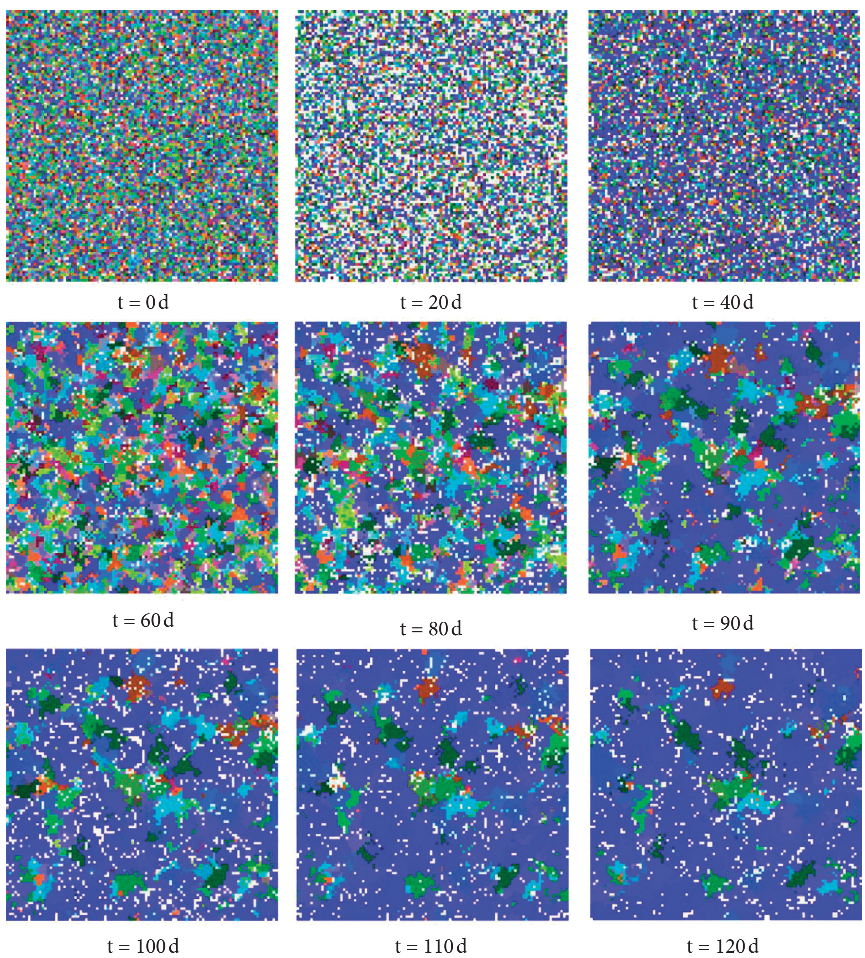

Figure 5: Pattern of microbial community spatiotemporal succession process in oral cavity.

3.3.2. Time-Domain Response Characteristics of Oral Microbial Flora Succession. In order to confirm the role of microbial delay responses on formation and maintenance of oral microbial diversity, parameters closely relevant to time-lags, such as α_1, α_2, α_3, β_1, β_2, β_3, were set to very small. In this case, the lag effects could not be generated via Monte Carlo simulation at all.

The time-domain response characteristics of oral microbial flora succession without and with lag effects could be obtained through accumulation of all individuals of the same species at different positions at the same time, similar to double integral in 2D cellular space (Figure 7).

From Figure 7 (top), all populations would grow exponentially at the beginning of microbial community

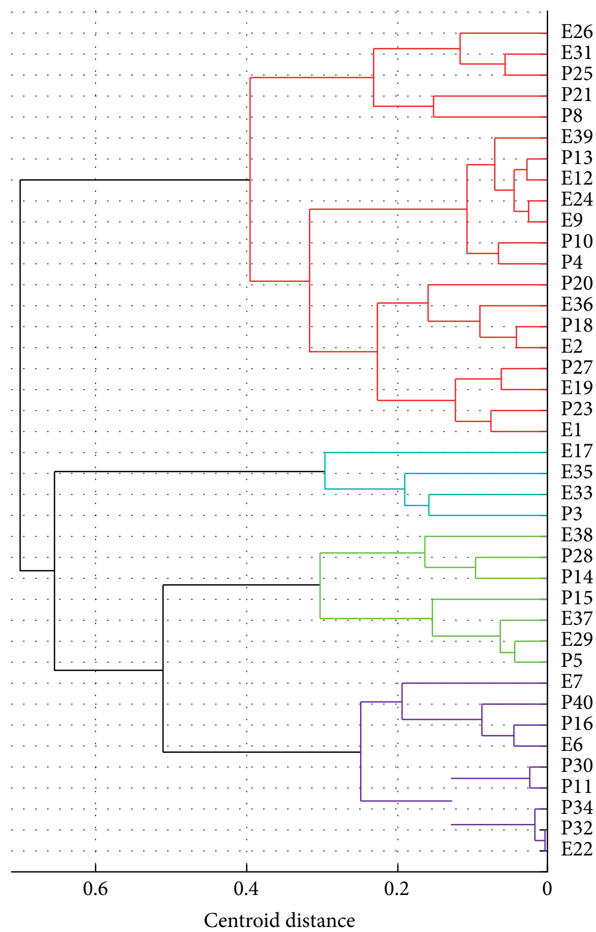

Figure 6: Cluster analysis of climax microbial community resulting from CA simulation in oral cavity.

succession, but their growth rates would have to slow down inevitably as niches are continuously filled up in oral cavity, and a turning point would appear sooner or later due to species differences in intrinsic growth rates, competitive capabilities, and carrying capacities. Some species would stop growing, whereas other species would keep increasing, and the latter would further exclude the former to make them extinct eventually (Hardin, 1960; Ives and Carpenter, 2007); eventually, only a few kinds of dominant species could coexist via transient responses, and their populations would asymptotically stabilize at a fixed level. For most oral microbial species, however, it would go extinct due to competitive exclusion and oral microbial diversity could not be formed and maintained at all.

From Figure 7 (bottom), the digital simulation results illustrated that the most of oral microbial species could coexist, and their populations appeared periodical vibrations with shifted phases via unordered transient responses, forming an oral microbial climax community with higher richness and evenness (Figure 8). Because the microbial populations are asynchronously convergent fluctuations, as one species population is at a relatively high level, the other species populations might at relatively low levels due to phase differences, and these dynamic response characteristics could effectively reduce their interspecific competitions through minimization of interspecific competitive strengths which are mainly dependent on the product of microbial populations size, according to the classic *Lotka–Volterra* equations.

It is worth mentioning that the spatiotemporal succession patterns (Figures 5 and 7) of oral microbial flora were quite general and universal, this is because these emerging spatiotemporal patterns were insensitive to initial values of state variables and parameters in the CA model.

4. Discussion

Generally speaking, oral microbial delay responses are mainly caused by the oral immunity [16]. For example, the lysozyme and salivary cytokines such as IL-6, IL-17, IL-10, and TNF-α adversely influenced microbial cell division [21, 22]. From an ecological point of view, the oral immunity could be considered as an intermediate disturbance factor for the oral microbial community, which could effectively inhibit the overgrowth of dominant species and prevent nondominant species from going extinct. Hence, the intermediate disturbance could greatly increase evenness of oral microbial flora to enhance the microbial diversity. However, oral immunity did not kill oral microbial individuals directly but induced them to produce delay

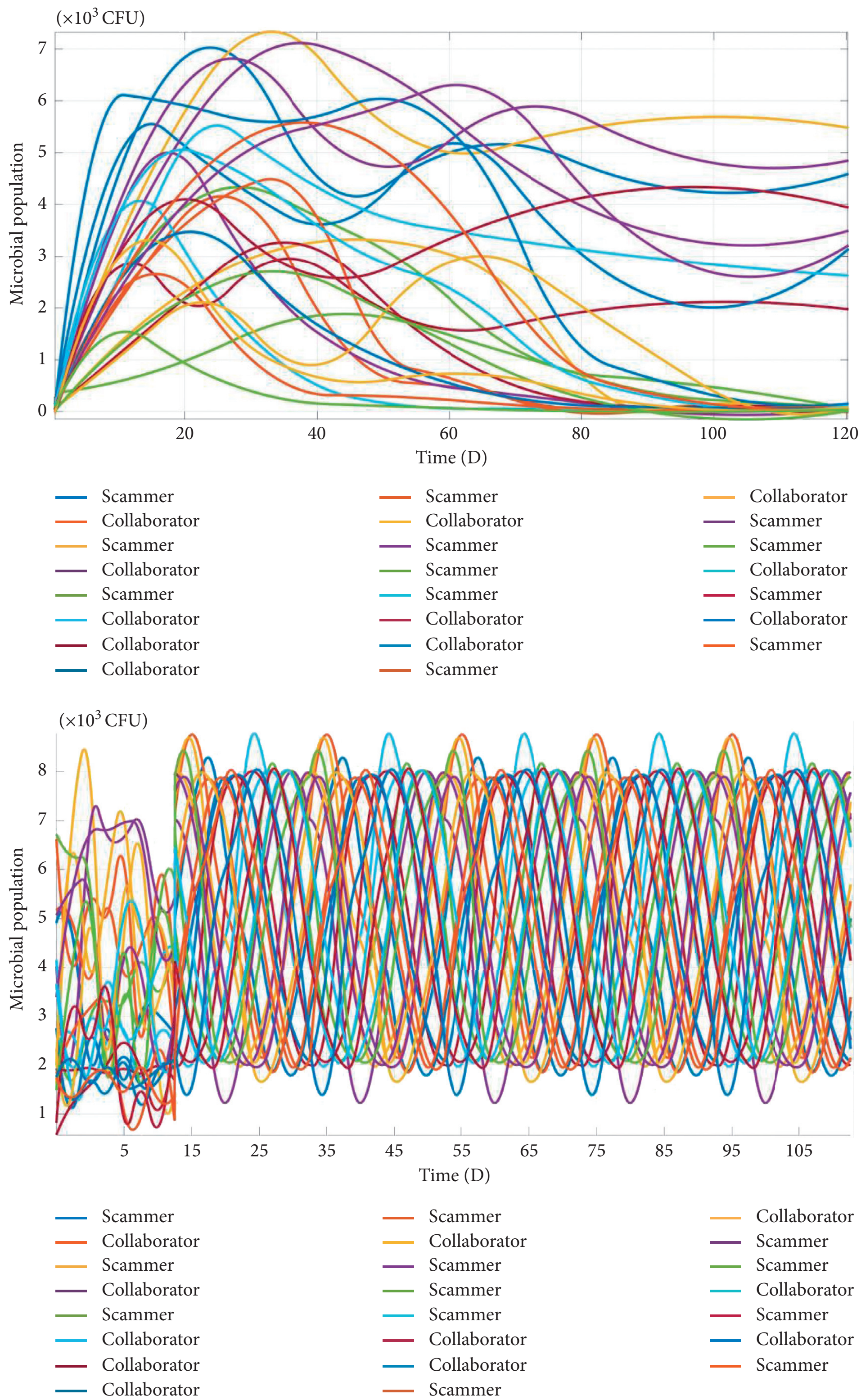

FIGURE 7: Dynamic response characteristics of oral microbial populations without (top) and with (bottom) delay effect community spatiotemporal succession process in oral cavity.

responses. Driven the decomposition product negative feedback regulation and delay responses, the microbial populations could present the asynchronously convergent fluctuations to effectively alleviate interspecific competition. In such circumstance, each microbial population would stay in a nonequilibrium state, and the microbial populations would start a new round of fluctuation to avoid going extinct due to competitive exclusion.

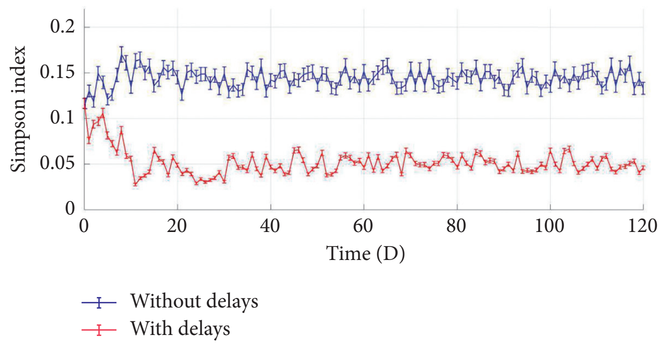

Figure 8: Simpson α index dynamics of oral microbial community without and with delay effects.

In the future research, oral microbial flora will need to be cultivated in the laboratory, and in-depth research studies will be carried out to elucidate the mechanism of microbial delayed responses from physiological, biochemical, and genetic levels in the emulated oral environment. Based on this study, specific medicines might be developed to enhance the oral immunity for promotion of the delayed responses of oral microorganisms [23].

5. Conclusion

Based on oral microbiology, microbial ecology, and experimental phenomena, a new hypothesis on formation and maintenance mechanism of oral microbial diversity was put forward and sufficiently confirmed by CA modeling and simulation in combination with experimental data, which demonstrated some oral microbial species such as *Haemophilus* and *Veillonella,* which could acclimate for oral environment with higher specific growth and substrate decomposition capability, while other species such as *Streptococcus*, *Rothia*, and *Prevotella* have no or weak adaptability with lower higher specific growth and substrate decomposition capability, which could form the decomposition product negative feedback regulation on microbial population size. In addition, the intracellular triglyceride accumulation of microbial species could produce reproductive and reaction delay responses in adversity, accompanying with interspecific competition and substrate decomposition delay responses.

Driven by decomposition product feedback regulation on microbial population sizes and four microbial delay responses, (1) from the view of time, oral microbial populations show asynchronously convergent fluctuations, significantly alleviating the interspecific competitions and inhibiting the emergence of dominant species. The oral microbial diversity could be formed and maintained by a strategy of species-for-quantity exchange; (2) from the view of space, the closely related microbial species would tend to aggregate in patches with different sizes, which also helped to further alleviate the interspecific competition strengths.

Hence, this study could not only lay the theoretical foundation for understanding of oral microbial diversity formation and maintenance but also offer effective guidance of prevention and treatment of oral cavity diseases.

Data Availability

The data used to support the findings of this study are available from the corresponding author on request.

Ethical Approval

This study was carried out in strict accordance and compliance with the Statement on Ethical Conduct in Research Involving Humans Guidelines of the Science and Ethics Committee of the Shandong Sport University (No. SD2020010).

Consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

The authors declare no conflicts of interest in this article.

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