Latent class model based diagnostic system utilizing traditional Chinese medicine for patients with systemic lupus erythematosus

Wen-Hsiang Wu,1 Jia-You Liu,1,2 Hen-Hong Chang1,2,*

1Department of Healthcare Management, Yuanpei University, Hsinchu, Taiwan
2Graduate Institute of Traditional Chinese Medicine, Chang Gung University, Taoyuan, Taiwan
3Center for Traditional Chinese Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan

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ABSTRACT

Systemic lupus erythematosus (SLE) can affect nearly any organ system, and is frequently an evolving disease with varied manifestations. Traditional Chinese medicine (TCM) physicians have identified different SLE patterns that they have difficulty summarizing, but the latent class model helps solve this problem. This study applies the latent class model and disease pattern coding system (B-code) to design a TCM diagnostic expert system. This study gathered 2047 valid records and classified three clusters of main disease patterns. Compared with the experience of the TCM expert, the accuracy rate of the expert system reached 77.47%. The results show that this diagnostic system performed well in identifying the disease patterns of SLE and may be clinically useful for TCM physicians.

1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder with variable manifestations, the etiology of which has not yet been fully described but is believed to be multifactorial (Danchenko, Satia, & Anthony, 2006). Pathogenic autoantibodies are the primary cause of tissue damage in patients suffering SLE. These antibodies are produced via complex mechanisms involving every major facet of the immune system (Rahman & Isenberg, 2008). SLE can affect almost any organ system and is frequently an evolving disease, the manifestations of which develop over months or years. The disease course is variable and unpredictable (Maddison, 2002). Although glucocorticoid therapy is the cornerstone of treatment and intravenous methylprednisolone continues to be widely used in clinical practice (Parker & Bruce, 2007), over 90% of patients have reported at least one adverse event associated with glucocorticoid use (Curtis et al., 2006). Infection, which is frequently attributed to glucocorticoid and other immunosuppressant medications, is a major cause of death in SLE (Bernatsky et al., 2006). Despite the improved survival in patients with SLE, there is currently neither curative nor satisfactory treatment available (Mcelhone, Abbott, & Teh, 2006). Consequently, some patients with SLE seek help via traditional Chinese medicine (TCM).

Because the presentations of SLE vary, ranging from rash and arthritis through anemia and thrombocytopenia to serositis, nephritis, seizures, and psychosis, SLE is considered as one of the differential diagnosis in virtually any patient presenting with one of these clinical problems, particularly in female patients between 15 and 50 years of age (Rahman & Isenberg, 2008). Conventional modern medicine has difficulty in accurately diagnosing SLE, and so does TCM, which uses data collected by the naked senses of physicians, including "inspection", "listening/smelling", "inquiry" and "palpation" for diagnosis. Based on observed disease entities and the reports of patients, TCM physicians perform diagnosis and draw conclusions about patient pathological conditions in terms of "patterns" (called "Zheng" in Chinese). The diagnosis is expertise-dependent and most of the symptoms and patterns described by TCM physicians are qualitative (Wang, Qu, Liu, & Cheng, 2004). Owing to the variable manifestations of SLE, nearly 35 disease patterns exist in SLE, depending on the experience of different TCM physicians (Zhu, 2001). Thus a significant issue arises in terms of how to determine disease patterns to help TCM physicians diagnose and treat patients.

Developing an intelligent system to mine the experience of TCM experts might help solve this problem. Gathering the thoughts and experience of TCM experts regarding the diagnosis of the same disease can further summarize the consensus regarding how best to determine disease patterns. Such efforts can also spread diagnostic expertise related to TCM. The clinical experiences of TCM experts can effectively be passed down by expert systems. This passing down of experience can assist the learning of junior TCM physicians. Furthermore, such expert systems can also boost clinical service by increasing the diagnostic precision of TCM physicians. Expert systems for TCM diagnosis have been developed over the
past two decades. Most such systems are rule-based and are not feasible for implementing all possible inferences via training rules. The fully expertise-dependent characteristics of TCM diagnosis and the vagueness regarding medical terms pose significant challenges to knowledge acquisition, which has been a bottleneck for expert systems in TCM (Wang et al., 2004).

Since medical terms in TCM are vague and cannot accommodate statistical analysis, Chang, Wu, Chen, Lo, and Ma (2000) designed a TCM disease pattern coding system, known as “B-code”, to accommodate disease patterns for statistical analysis. The first portion of the B-code is a variable representing the disease causes (病因 bingyin); the second code represents the diseased organ in various viscera and bowels (藏府 zangfu); the third code represents the diseased aspect (病机 bingji, namely qi, xue, yin, yang) and body parts (部位 buwei); and the fourth code represents the pathomechanisms (病机 bingji) and various patterns (病候 zhenghou). The most obvious choice is to use Arabic numerals for the encoding, where “0” represents “nothing. A less common choice is to use English letters for the encoding (for example, “Z” represents “complex”). The encoding began at [0, 0, 0, 0] and ended at [Z, Z, Z, Z].

The TCM disease patterns described by physicians are mostly qualitative, and the attributes in patient records are discrete variables which usually contain just two values—present and absent. Because disease patterns coded with B-code are categorical variables, latent class models are employed to identify homogeneous groups from these categorical multivariate data. Latent class models are frequently used to investigate physicians’ medical diagnoses and the agreement among them (Hesketh & Skrondal, 2008). Another major application of latent class models is to identify the subgroup with the same phenotypes from different populations in certain diseases (Henderson et al., 2008; Shevlin, Murphy, Dorahy, & Adamson, 2007). This study uses this statistical method to establish a TCM diagnostic expert system for recognizing disease patterns in patients with SLE.

The process of the proposed diagnostic system divides seven steps into two phases, as shown in Fig. 1: using B-code to rearrange data obtained from patients with SLE and then applying the latent class model to cluster the various disease patterns.

2. Process of diagnostic system

2.1. Generating the patient record database

The SLE patients were diagnosed according to the 1997 American College of Rheumatology Revised Criteria for the classification of
systemic lupus erythematosus (Hochberg, 1997). Patients with four or more of the following 11 criteria were diagnosed with SLE: malar rash, discoid rash, photosensitivity, oral ulcers, non-erosive arthritis, serositis, renal disorder, neurological disorder, hematological disorder, immunological disorder, and anti-nuclear antibodies.

The diagnostic system accumulated and organized medical record data according to TCM physicians’ diagnosis on SLE patients. After deleting empty and anomalous data, a total of 2,155 valid data were inputted.

2.2. TCM pattern identification and coding

Manifestations of SLE are complex and continuously changing, and for purposes of data management and statistical analysis, the disease patterns of SLE patients were coded using a B-code system. (Chang, Wu, Chen, & Lin, 2008). The disease pattern of SLE patients is presented below as an example: (1) cause of disease: heat (热 re); (2) viscera or bowels: liver (肝 gan) and kidney (肾 shen); (3) level or body parts: qi (気), blood (血 xu), and yin (陰); (4) pathomechanism (病機 bingji) or patterns (形態 zhenghou): vacuity (虚虚 yin xu), stasis (癥 stasis), blood vacuity (血虚 xu), qi vacuity (氣虛 qi xu), stasis (瘀 yu), liver (肝), kidney (腎), reversal (反 jue), and water-rheum (水飲 shuiyin) (see Table 1).

2.3. Transforming the data

Statistical analysis transforms the B-codes into categorical data. With regard to symptoms in SLE patients, “1” indicates their existence, while “0” indicates their absence. Table 2 shows the replacement of the “pathomechanism or patterns” section of Table 1, and the other sections are reorganized in the same way.

2.4. Selecting suitable variables

After calculating the frequency for each code, the less frequently occurring variables were eliminated to prevent statistical bias and ensure overall accuracy. The codes were then arranged in order from highest to lowest, as shown in Table 3 and Fig. 2.

In the 2,155 valid records, “heat” (热 re) and Yin vacuity (虚虚 yin xu) are the first and second most common codes, being reported 2,102 times and 2,092 times, respectively. However, as shown in Fig. 2, a turning point exists around the variables of water-rheum (水飲 shuiyin) and wind (風 feng). Since some SLE patients may be suffering a common cold that is misinterpreted as wind, this variable was eliminated from the present analysis. Therefore, variables with frequencies exceeding 295 times were considered more important, and were analyzed using the latent class model. Fig. 2 lists these variables in descending order of frequency.

Since heat (热 re) and Yin vacuity (虚虚 yin xu) appear in almost all the valid records, this study deletes records not reporting these two symptoms, leaving a total of 2,047 valid records. The variables analyzed by this system include: dampness (濕湿 shi), impediment (滯滞 bi), blood vacuity (血虚 xu), qi vacuity (氣虛 qi xu), stasis (瘀 yu), liver (肝), kidney (腎), reversal (反 jue), and water-rheum (水飲 shuiyin).

2.5. Analyzing the clusters using the latent class model

The latent groups of disease patterns belong to multivariate multinomial mixtures, and thus cluster analysis is a suitable statistical tool which takes similar variables from a data pool and groups them into clusters. This system is designed to help TCM physicians diagnose disease patterns, and performs this role adequately. Two clustering algorithms are applied to the latent class model, namely the expectation maximization (EM) algorithm and the fuzzy clustering algorithm (FCA). This system applies both clustering algorithms to estimate the variables and classify the latent disease patterns (Lin, Chen, & Wu, 2004).

2.6. Clustering algorithm for latent class models

Disease patterns of the patient population can be considered a model comprising finite distribution, with a population including C subpopulations (or clusters) where C > 1. The probability density function of an observation (or a patient) can thus be represented using the finite mixture multinomial form. This diagnostic system is based on the maximum likelihood principle estimating the latent disease pattern clusters. Both the EM algorithm and the fuzzy clustering algorithm are iterative optimization procedures that use the maximum likelihood principle to estimate the parameters of mixed and multinomial distributions. The fuzzy clustering algorithm assumes that fuzzy membership function of μC(xk) falls within the interval [0,1], such that ∑Ck=1 μC(xk) = 1 for all xk ∈ X. Therefore, μC(xk) denotes the grade of membership (belonging) of xk in the kth fuzzy subset of X (Lin et al., 2004). The other parameters of the fuzzy clustering algorithm are listed below:

\[ z_k = \frac{\sum_{l=1}^{C} h_{kl}(x_k)}{\sum_{k=1}^{C} h_{kl}(x_k)} \quad k = 1, 2, ..., C, \]

\[ z_k \text{ denotes the proportion of class } k \text{ in the population, where } z_k \in (0, 1) \text{ and } \sum_{k=1}^{C} z_k = 1; \]

\[ \theta_{ijl} = \frac{\sum_{k=1}^{C} x_{kj} h_{kl}(x_k)}{\sum_{k=1}^{C} h_{kl}(x_k)} \quad k = 1, 2, ..., C; \]

\[ j = 1, 2, ..., J; \quad i = 1, 2, ..., L_j, \]

\[ \theta_{ijl} \text{ represents the probability of response level } l, \text{ for the } jth \text{ manifest variables, } j = 1, ..., J, \text{ in the } kth \text{ class, and } \sum_{k=1}^{C} \theta_{ijl} = 1 \text{ and,} \]

\[ \hat{\mu}_c(x_k) = \left\{ \left\{ \sum_{l=1}^{L_j} \left[ \ln \theta_{ijl} + \theta_{ijl} \ln z_k \right] \right\} / \left\{ \sum_{k=1}^{C} \left[ \sum_{l=1}^{L_j} \ln \theta_{ijl} + \theta_{ijl} \ln z_k \right] \right\} \right\}^{1/\theta_{ijl}}, \]

\[ k = 1, 2, ..., C; \quad i = 1, ..., n. \]
<table>
<thead>
<tr>
<th>Symptoms/phenomena</th>
<th>Heat</th>
<th>Yin vacuity</th>
<th>Impediment</th>
<th>Liver</th>
<th>Kidney</th>
<th>Large Intestine</th>
<th>Wind</th>
<th>Reversal</th>
<th>Blood vacuity</th>
<th>Stomach</th>
<th>Skin</th>
<th>Heart</th>
<th>Large Intestine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>2102</td>
<td>2092</td>
<td>1899</td>
<td>1002</td>
<td>899</td>
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**Table 3**

Frequency table for SLE disease pattern variables.

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### Fig. 2. Bar chart representing SLE disease pattern variables.

Minimize $C_m,w(\mu, x, \Theta)$

$$= - \sum_{k=1}^{C} \sum_{i=1}^{n} \mu_k(x_i) \left\{ \ln f_i(x_i; \theta_k) + w \ln z_k \right\}$$

$$= - \sum_{k=1}^{C} \sum_{i=1}^{n} \mu_k(x_i) \sum_{j=1}^{l_k} \ln \phi_{kjl} - w \sum_{k=1}^{C} \sum_{i=1}^{n} \mu_k(x_i) \ln z_k$$

Subject to $\sum_{k=1}^{C} \mu_k(x_i) = 1$, $\sum_{k=1}^{C} z_k = 1$ and $\sum_{i=1}^{l_k} \theta_{kjl} = 1$.

where $m > 1$ and $w > 0$ are fixed constants.

The difference between the EM and fuzzy clustering algorithms is that the fuzzy clustering algorithm permits the power (weighting exponential) of $\mu_k(x_i)$ to be increased to $\mu_k(x_i)$ and adds a weight, $w$, for $\ln z_k$ to $\ln z_k$, where $w > 0$ is a fixed constant.

Given the necessary conditions of Eqs. (1)–(3), the fuzzy clustering algorithm can be summarized as follows:

Step 1: Fix $2 < C \leq n$ and fix any $\epsilon_g > 0, g = 1, 2, 3$, given an initial value of $\hat{\mu}_k^{(0)}(x_i)$.

Step 2: Calculate $\hat{z}_k^{(t)}$ with $\hat{\mu}_k^{(t-1)}(x_i)$ using Eq. (1).

Step 3: Calculate $\hat{\theta}_{kjl}^{(t)}$ with $\hat{z}_k^{(t)}$ and $\hat{\mu}_k^{(t-1)}(x_i)$ using Eq. (2).

Step 4: Calculate $\hat{\mu}_k^{(t)}(x_i)$ with $\hat{z}_k^{(t)}$ and $\hat{\theta}_{kjl}^{(t)}$ using Eq. (3).

Step 5: Compare $\hat{z}_k^{(t)}$ with $\hat{z}_k^{(t-1)}$ with $\hat{\theta}_{kjl}^{(t-1)}$ and $\hat{\mu}_k^{(t-1)}(x_i)$ with $\hat{\mu}_k^{(t-1)}(x_i)$.

Repeat Steps 2–5 until some convergence criterion is satisfied. If for all $||\hat{z}_k^{(t)} - \hat{z}_k^{(t-1)}|| < \epsilon_1, ||\hat{\theta}_{kjl}^{(t)} - \hat{\theta}_{kjl}^{(t-1)}|| < \epsilon_2$ and $||\hat{\mu}_k^{(t)}(x_i) - \hat{\mu}_k^{(t-1)}(x_i)|| < \epsilon_3$, then stop, otherwise $t = t + 1$ and return to Step 2.

Step 6: Finally, $x_i$ must be classified using the decision rule: if $\hat{\mu}_k(x_i) = \max_{s=1, \ldots, C} \hat{\mu}_k(x_i)$; $k = 1, \ldots, s, \ldots, C$, then $x_i$ is a member of Class $s$.

The Akaike information criterion (AIC) is a model that selects the number of components in a mixture, and this system uses this criterion to select the most suitable cluster. Fig. 3 shows that three to five are the most suitable clusters because of having the lowest value with the same solution in different initial iteration values.

According to Lin, when $m \to 1$ and $w = 1$, then all parameters of the fuzzy clustering algorithm will approach the results of the EM algorithm Lin et al. (2004). Therefore, a stable cluster would be similar using both algorithms. This system applies $m = 1.2$ and $w = 1$ in the fuzzy clustering algorithm to identify the most stable of the various different clusters.

Next, the system compares the classification results between different clusters and calculates the discordant case numbers between the EM algorithm and FCA. The most suitable cluster is obtained by identifying the clustering result with the least discordant case numbers and ratio. From Table 4, the least discordant case
numbers appear in three clusters. Consequently, this system selects the three clusters for classifying the disease patterns.

3. Result

Because “heat” and “yin vacuity” occurred in almost all the valid records, they are reinserted among the main disease patterns in an additional table (Table 5). The proposed system selects the disease patterns with probability exceeding 0.5 as the major disease patterns, and then selects those with probability below 0.5 and 300 times higher than other clusters as the minor disease patterns. The latent class model analysis yields the three groups and their respective frequencies, as listed in Table 6:

1. Cluster 1: contains 887 observations and includes the major disease patterns “Heat, Yin Vacuity, Qi vacuity, Dampness, and Blood vacuity” (肝腎陰血虛夾濕熱) as well as the minor disease pattern “Kidney and Water-rheum” (腎,水飲).
2. Cluster 2: contains 483 observations and includes the major disease patterns “Heat, Yin Vacuity, Kidney, Liver, Dampness, Impediment, and Blood vacuity” (肝腎陰血虛夾溼熱) as well as the minor disease pattern “Water-rheum” (水飲).
3. Cluster 3: contains 677 observations and includes the major disease patterns “Heat, Yin Vacuity, Dampness, and Impediment” (肝腎陰血虛夾溼熱).

This study assesses the accuracy of this system by comparing the results of clustering with the experience of TCM experts. The expert was asked to complete a questionnaire dealing with the clustering results calculated using the expert system (see Appendix A). The accuracy is estimated based on the ratio of scores assessed using a TCM expert versus the expected full scores. The accuracy of each main cluster is listed in Table 6 and the overall accuracy is 77.47%.

This system can calculate the probability of each SLE patient classified in different clusters and select the highest probability for determining the main cluster to which each patient belongs, and then suggests appropriate herbal treatments for the patient. For example, if a patient displays the disease patterns “Heat, Yin Vacuity, Qi vacuity, Dampness and Water-rheum”, the most likely cluster calculated by this system is cluster 1 and the treatment for cluster 1 is presented, as illustrated in Fig. 4. Based on this system, TCM physicians can modify the prescription dosage and herbs.

4. Discussion

In the proposed diagnostic system, the changing manifestations of SLE are summarized into three main disease patterns, helping to simplify disease pattern complexity and help TCM physicians in indicating concordant treatments. Good accuracy is achieved in diagnosing SLE compared to the experience of TCM physicians. More important is the fact that the proposed system can “mine” the implications of the clinical database achieving something that even TCM experts have not proposed. In SLE, “Qi vacuity” (氣虛) and “Water-rheum” (水飲) are two key clues for differentiating disease pattern clusters. Both of these clues are infrequent disease patterns but, once they appear, indicate a critical point of the disease progression. From the results, main cluster 1 comprises patients affected by more serious conditions and who require immediate consultation and intervention.

Based on the experience of TCM experts, this study collected and recommended commonly used herbal formulas and herbs into different main clusters, as listed in Table 7. This latent class model
based system performs well in diagnosing patients with SLE, and may also provide treatment suggestions for the various clusters.

Few consensuses exist among practitioners regarding TCM diagnosis and treatment for certain diseases, particularly those with variable manifestations, such as rheumatoid arthritis (Zhang, Bausell, Lao, & Lee, 2004). Using B-code can help integrate different clinical databases involving different experts.

As an interface, the B-code combines all the TCM diagnostic attributes and transforms the subjective clinical descriptions into quantifiable data. Although this study adopts a data set as an examples of single expert, this study applies the methodology to integrate clinical databases from different TCM experts. After merging these clinical databases, it is possible to establish a more comprehensive diagnostic expert system.

Regarding other expert systems, Bayesian network is another data-driven method for extracting expert knowledge, but cannot disclose the thinking process and diagnosis logic as the system presented here can. Furthermore, the system presented here can deal with infrequent attributes which are hard to manage in Bayesian network (Wang et al., 2004). Sometimes, those infrequent attributes are important clues in differentiating disease patterns and determining therapeutic strategies. Consequently, the proposed system selects attributes with probabilities exceeding certain thresholds as minor disease patterns (five times probability more than other clusters in this study). However, problems of high dimensionality occur because of excessive numbers of disease patterns. In the proposed system, variables with frequencies of less than 295 times were eliminated to simplify the dimensionality.

Fuzzy neural network (FNN) is another way of constructing an expert system, but is also unable to construct expert knowledge. FNN classifier must be based on the rules according to how the ex-

Table 7
The recommended herbal treatments of the expert system.

<table>
<thead>
<tr>
<th>Main cluster</th>
<th>Major disease patterns</th>
<th>Herbal formulas</th>
<th>Herbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1</td>
<td>“Heat, Yin Vacuity, Dampness, Qi vacuity, and Blood vacuity”</td>
<td>Polyporus decoction (猴術湯)</td>
<td>Miltilorhizae Radix (虎杖)</td>
</tr>
<tr>
<td></td>
<td>“Kidney”</td>
<td>Sweet Dew Beverage (甘蔗飲)</td>
<td>Codonopsis Radix (重參)</td>
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<tr>
<td></td>
<td>“Water-rheum”</td>
<td>Anemarrhena, Phellodendron, and Rehmannia Pill (紅棗地黃丸)</td>
<td></td>
</tr>
<tr>
<td>Cluster 2</td>
<td>“Heat, Yin Vacuity, Kidney, Liver, Dampness, Impediment, and Blood vacuity”</td>
<td>Large Gentian and Turtle Shell Powder (牛黃清心湯)</td>
<td>Miltilorhizae Radix (虎杖)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sweet Dew Beverage (甘蔗飲)</td>
<td>Milettae Radix et Cauilis (重血藤)</td>
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<tr>
<td></td>
<td></td>
<td>Lycium Berry, Chrysanthemum, and Rehmannia Pill (紅棗地黃丸)</td>
<td></td>
</tr>
<tr>
<td>Cluster 3</td>
<td>“Heat, Yin Vacuity, Dampness, and Impediment”</td>
<td>Sweet Dew Beverage (甘蔗飲)</td>
<td>Miltilorhizae Radix (虎杖)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anemarrhena, Phellodendron, and Rehmannia Pill (紅棗地黃丸)</td>
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</table>
erts work, and thus the application is limited to the original data set (Xu, Meng, Wang, Lu, & Li, 2009). However, this system can extract more expert knowledge after accumulating more databases. Comparing with FNN, this system didn’t have good enough accu-

racy, and the reason for this may be resulted from the limitation for the completeness of doctor data and loss of the infrequent but important variables.

Although the proposed system can identify the main cluster and propose herbal treatments for SLE patients, it lacks decision rules between disease patterns and symptoms. Because the definitions of symptoms in TCM remain incomplete, it is difficult to create a database of symptoms.

This system may assist TCM physicians in identifying the main clusters of SLE patients. This method can be used to interpret the decision rules used in clustering the TCM disease pattern, as well as for future construction of a clinical decision-support system. The system also has potential to serve as a teaching system for TCM students to help them in learning clinical experience from experts.

To summarize, this expert system gathered 2047 valid records and classified three clusters of key disease patterns. Compared with the experience of the TCM expert, the accuracy rate is 77.47%. This diagnostic system helps determine the disease patterns of SLE and may help TCM physicians in making clinical suggestions.

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Appendix A. The questionnaire of accuracy of the clustering results of latent class model

This questionnaire is aim to know whether the SLE patients could be divided into different classical disease pattern clusters to be a reference of clinical treatment. According to your clinical experience, if the SLE patients having these B-codes in this table were suitable for divided into the disease pattern cluster in this list, please mark a check in the right column. (‘‘1’’ stands for ‘‘Yes’’ and ‘‘0’’ stands for ‘‘No’’).

<table>
<thead>
<tr>
<th>Disease pattern cluster “Heat, Yin Vacuity, Dampness, Blood vacuity, and Qi vacuity”</th>
<th>Very suitable</th>
<th>Suitable</th>
<th>Acceptable</th>
<th>Unsuitable</th>
<th>Very unsuitable</th>
</tr>
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<tbody>
<tr>
<td>Yin Vacuity</td>
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<td>Heat Dampness</td>
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<td>Impediment Blood vacuity</td>
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<td>Qi vacuity</td>
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<td>Stasis</td>
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<td>Liver</td>
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<td>Kidney</td>
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<td>Reversal Water-rheum</td>
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<td>1 1 1 0 1</td>
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Note: this table is a part of the original questionnaire as an example.

References


