Classifying rheumatoid arthritis by Traditional Chinese Medicine Zheng: a multi-center cross-sectional study

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Abstract

OBJECTIVE: To assess the relationship between disease symptoms and traditional Chinese medicine (TCM) syndrome (Zheng) in rheumatoid arthritis (RA) patients.

METHODS: RA Patients were recruited in Guang’anmen Hospital, China Academy of Chinese Medical Sciences and in the Second Affiliated Hospital of Zhejiang Chinese Medical University, and diagnosed with a particular RA Zheng from their symptoms. Demographic characteristics, self-reported symptoms, and blood samples were collected from patients. All data were input into EpiData and analyzed using SPSS software.

RESULTS: The study included 302 RA patients (age range: 18-86 years). All patients were Chinese, and 85.1% were women. Cold and fatigue triggers were reported by 8.6% of patients, followed by triggers such as childbirth (4.3%), cold (3.0%), dampness (2.0%), menopause (1.3%), and psychentonia (0.7%). The most prevalent Zheng was dampness and heat blockage (Shire Yuzu in Chinese, SRYZ), diagnosed in 39.4% of patients (119), followed by phlegm and stagnation blockage (Tanyu Bizu, TYBZ) in 21.5%, liver and kidney deficiency (Ganshen Buzu, GSBZ) in 18.5%, dual deficiency of Qi and blood (Qixue Liangxu, QXLX) in 9.6%, cold and dampness blockage (Hanshi Bizu, HSBZ) in 6%, and wind and dampness blockage (Fengshi Bizu, FSBZ) in 5%. Increased length of time since RA diagnosis was associated with the GSBZ group. Patients diagnosed with the SRYZ Zheng had the highest disease activity score. Patients diagnosed with the QXLX Zheng had the lowest blood platelet counts; patients diagnosed with the QXLX and HSBZ Zhengs had lower C-reactive protein levels and lower health assessment questionnaire scores. Patients diagnosed with the GSBZ and QXLX Zhengs had the highest health assessment questionnaire scores.

CONCLUSION: The specific Zheng was related to RA characteristics. The findings suggest that eliminating dampness, cooling the patient, and promoting blood circulation may assist in treating severe RA.

Keywords: Arthritis, rheumatoid; Symptoms and signs; Syndrome complex; Cross-sectional studies
INTRODUCTION

Rheumatoid arthritis (RA) is a chronic multi-system autoimmune disease resulting from persistent inflammatory synovitis and subsequent erosion of the joint architecture, and is considered a complex disease with a multi-factorial etiology that is influenced by both genetic and environmental risk factors. Worldwide, approximately 1% of the population is affected, with a higher prevalence in persons of European or Asian ancestry. Arthritis in general and RA in particular are common causes of disability, and more than a third of patients eventually experience work disability because of the disease. RA can develop in persons of any age, with a typical age of onset of approximately 55 years. In China, the lifetime risk of developing rheumatoid arthritis is 0.3%-0.4%. The goal of present-day therapy for RA is to control the underlying inflammatory disease, thereby alleviating pain, restoring patients’ quality of life, and ultimately preserving their independence and ability to perform activities of daily living and vocational pursuits. Common treatments for RA include non-steroidal anti-inflammatory drugs, disease-modifying anti-rheumatic drugs, glucocorticoids, and biologic agents. These drugs, however, exert long-term side effects such as increased risk of infection and potentially fatal liver damage.

Traditional Chinese medicine (TCM) is widely used in China and has been found to be effective in treating RA. In TCM, RA patients are further stratified according to their Zheng (similar to “syndrome” in English) diagnosis. Specific therapy is prescribed according to the Zheng’s pattern. In TCM theory, RA is considered an “impediment disease” (also known as Bi syndrome), a group of disorders caused by the invasion of wind, cold, dampness, or heat pathogens into the meridian channels. The efficacy of TCM treatment for RA is based on successful Zheng differentiation, which guides herbal medicine prescription.

Currently, RA Zheng patterns are mainly established from textbooks, expert experience, and other literature analysis; there is limited evidence concerning clinical validation and scientific assessment. Employing more comprehensive approaches would potentially facilitate the establishment of RA Zheng for research and clinical applications. In this study, we analyzed the relationship between clinically common TCM Zhengs of RA and disease status.

METHODS AND DESIGN

Study design

The study was a multi-center, cross-sectional study. Three-hundred and two RA patients were recruited from Hangzhou (southern China) and Beijing (northern China) between September 2013 and December 2014. The participants were patients at the Department of Rheumatology of Guang’anmen Hospital (GAM), China Academy of Chinese Medical Science and the Second Affiliated Hospital of Zhejiang Chinese Medical University (SAH). Zhengs were diagnosed by associate physicians or above at GAM and SAH. All patients provided informed consent, and the trial was approved by the Ethics Committees of GAM and SAH.

Sample size

Based on our earlier retrospective study of TCM Zheng at GAM, we speculated that the prevalence of TCM Zheng of RA was 0.2 - 0.8. We therefore set our parameters as $P = 0.5$, $d = 0.1$, $P = 0.1 \times 0.5 = 0.05$, and $\alpha = 0.05$. According to the formula below, we calculated that N was approximately 300 cases, and we selected these 300 cases randomly.

$$n = \left( \frac{1}{\alpha} \right)^2 \times \frac{P(1-P)}{d^2}$$

Inclusion criteria

Patients were included if they (a) were aged more than 18 years; (b) met the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria for RA; (c) resided in Beijing or Hangzhou for more than 2 years; (d) signed a written informed consent form.

For TCM Zheng diagnosis criteria, we referred to the standard clinical path of RA in TCM by the State Administration of Traditional Chinese Medicine in 2010 (Table 1).

Exclusion criteria

Patients were excluded if pregnant. Subjects with psychological issues that could not express his condition clearly were also excluded.

Recruitment strategies

Patients were recruited through multiple advertising strategies, including posters at GAM and SAH and advertisements on online official medical media channels, such as websites, Micro Blog, and We Chat of the Rheumatology Department of GAM and SAH. Referrals from outpatient services were also used to recruit patients into the study.

Study protocol

Patients reported to a thermo-regulated (22.0 ± 0.9) °C vascular laboratory after fasting for 12 h overnight. For ethical reasons, drug therapies were not interrupted. All participants underwent a detailed clinical examination, and demographic information was collected by questionnaire. The disease activity score using 28 joint counts (DAS28) and the Stanford Health Assessment Questionnaire (HAQ) were completed. A blood sample was also obtained. Patients in the study were assessed at one time-point only.
Table 1 Traditional Chinese Medicine (TCM) Zheng diagnosis criteria for rheumatoid arthritis (2010)

<table>
<thead>
<tr>
<th>TCM Zheng</th>
<th>Primary symptom</th>
<th>Secondary symptom</th>
<th>Tongue</th>
<th>Pulse</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSBZ</td>
<td>Migratory joint pain, heavy joint</td>
<td>Aversion to wind</td>
<td>Red tongue, greasy coating</td>
<td>Moisten or slippery</td>
</tr>
<tr>
<td>HSBZ</td>
<td>Cold joint pain, local swelling</td>
<td>Aversion to cold</td>
<td>Fat tongue, greasy or white coating</td>
<td>Slow or tight</td>
</tr>
<tr>
<td>SRYZ</td>
<td>Joint local redness, burning, pain, heavy feeling</td>
<td>Irritability, thirst not wanting to drink</td>
<td>Red tongue, yellow greasy coating</td>
<td>Slippy</td>
</tr>
<tr>
<td>TYBZ</td>
<td>Joint stinging, fixed pain</td>
<td>Induration, ecchymosis, swarthy</td>
<td>Dark purple tongue, greasy coating</td>
<td>String astringent</td>
</tr>
<tr>
<td>QXLX</td>
<td>Joint soreness, limb numbness, muscle atrophy</td>
<td>Fatigue, spontaneous perspiration, palpitations</td>
<td>Pale tongue, thin white coating</td>
<td>Weak</td>
</tr>
<tr>
<td>GSBZ</td>
<td>Joint deformation, stiff joint</td>
<td>Lassitude of waist and knee</td>
<td>Red tongue, thin white coating</td>
<td>Fine</td>
</tr>
</tbody>
</table>

Notes: a syndrome (Zheng) can be diagnosed by two primary symptoms + tongue/pulse or one primary symptom + one secondary symptom + tongue/pulse. FSBZ: wind and dampness blockage (Fengshi Bizu in Chinese); HSBZ: cold and dampness blockage (Hanshi Bizu); SRYZ: dampness and heat blockage (Shire Yuzu); TYBZ: phlegm and stagnation blockage (Tanyu Bizu); QXLX: dual deficiency of Qi and blood (Qixue Liangxu); GSBZ: liver and kidney deficiency (Ganshen Buzu).

The score of DAS28 was calculated as $1.08 \times \frac{0.56 \times \text{sqrt}(t_{28}) + 0.28 \times \text{sqrt}(sw_{28}) + 0.70 \times \text{Ln}(ESR)}{0.16}$.

**Blood sampling**
Serum was analyzed for routine blood parameters (including hemoglobin, platelet count, and white blood cell counts), C-reactive protein, erythrocyte sedimentation rate, and rheumatoid factor.

**General demographic information**
General information (sex, age, time since RA diagnosis, education level, occupation, season of onset, height, and weight) was collected from the participants, as well as information on past interventions and treatments and current RA occurrence.

**Signs and symptoms associated with RA**
(a) Joint condition (migratory joint pain, heavy joints, cold joint pain, local swelling, local joint redness, burning, pain, heavy feeling, stinging, fixed pain, joint soreness, limb numbness, muscle atrophy, joint deformation, and stiff joints); (b) chills and fever, sweating, color of face and skin, diet, urination and defecation characteristics, and mental consciousness.

**Tongue and pulse conditions**
Tongue coating, tongue body, tongue texture, and pulse conditions.

**Zheng classifications**
The excess syndromes: wind and dampness blockage, cold and dampness blockage, dampness and heat blockage, phlegm and stagnation blockage. The deficiency syndromes: dual deficiency of Qi and blood, liver and kidney deficiency.

**TCM terminology**

**Quality control**
To guarantee the successful implementation of the study, the investigator was an eligible-entitled associate chief physician or chief physician. The standard operating procedures for research execution were implemented to ensure the accuracy and integrity of the data at each step, such as identification, registration, and recruitment (Figure 1). Moreover, centralized training was conducted to ensure standardized terminology and consistency among investigators. Two TCM experts were present in each center to evaluate the symptoms, signs, and patterns. Generally, the two experts can arrive at the same diagnosis pattern in most situations; disagreement regarding Zheng was resolved by the responsible physician at the center and the project leader to yield the final diagnosis.

![Figure 1 Flow chart of Traditional Chinese Medicine (TCM) Zheng diagnosis of rheumatoid arthritis (RA)](image)
**Statistical analysis**

Statistical analysis was performed with SPSS 20.0 (IBM SPSS, Armonk, NY, USA). Variables were tested for normality by the Kolmogorov-Smirnov test. Mean and standard deviation (±) were calculated for normally distributed continuous variables, and proportions for categorical variables. Non-normally distributed data are given as the median (25th to 75th percentile values). Log transformation was performed for positively skewed variables, as appropriate. Variations in degrees of freedom reflect occasionally missing data. All comparisons were two-tailed, and \( P < 0.05 \) was considered significant.

**RESULTS**

**Characteristics of study subjects**

A total of 302 RA patients were enrolled: 45 male (14.9%) and 257 female (85.1%). Average age was 53 ± 12 years (range: 18-86 years). Two hundred and ten patients were from Beijing (GAM hospital), and 92 patients were from Hangzhou (SAH hospital). Most did not have a university education; 31.1% of patients had completed junior high school (Figure 2).

Among the patients surveyed, approximately 216 cases (71.5%) had no obvious RA triggers. Cold and fatigue triggers were reported by 8.6% of patients, followed by triggers such as childbirth (4.3%), infection (3.0%), dampness (2.0%), menopause (1.3%), and psychentonia (0.7%) (Figure 3).

**TCM Zheng distribution**

One hundred and nineteen patients (39.4%) were diagnosed with the dampness and heat blockage Zheng (Shire Yuzu in Chinese, SRYZ). Sixty-five patients (21.5%) were diagnosed with the phlegm and stagnation blockage Zheng (Tanyu Bizu, TYBZ), 56 patients (18.5%) with the liver and kidney deficiency Zheng (Ganshen Buzu, GSBZ), and 29 patients (9.6%) with the dual deficiency of Qi and blood (Qixue Liangxu, QXLX). Only a few patients were diagnosed with wind and dampness blockage (Fengshi Bizu, FSBZ) and cold and dampness blockage (Hanshi Bizu, HSBZ) (Figure 4).

**Relationship between sex and Zheng**

More female RA patients were diagnosed with the liver and kidney deficiency Zheng, GSBZ (Table 2).

**Relationship between age and Zheng**

Analysis of variance showed that there were significant differences in age between two Zheng groups (\( F = 3.172, \ P = 0.008 \)). Further comparison showed that the age of FSBZ was lower, and there was no significant difference in the age of other groups (Table 3).

**Relationship between TCM Zheng and duration of RA**

The length of time since RA diagnosis in each Zheng group differed significantly from that of the liver and kidney deficiency Zheng (GSBZ), which was the longest. This can imply that RA inflammation leads over time to liver and kidney impairment (Figure 5).

**Relationship between TCM Zheng and DAS28 scores**

Analysis of variance showed that there were significant differences in DAS28 scores between two Zheng groups (\( F = 2.872, \ P = 0.015 \)): there were significant differences between the dampness and heat blockage (SRYZ) Zheng and the phlegm and stagnation blockage (TYBZ) Zheng (Figure 6).
Table 2: Relationship between sex and Traditional Chinese Medicine (TCM) Zheng in rheumatoid arthritis patients [n (%)]

<table>
<thead>
<tr>
<th>TCM Zheng</th>
<th>n</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSBZ</td>
<td>15</td>
<td>2 (0.7)</td>
<td>13 (4.3)</td>
</tr>
<tr>
<td>HSBZ</td>
<td>18</td>
<td>1 (0.3)</td>
<td>17 (5.6)</td>
</tr>
<tr>
<td>SRYZ</td>
<td>119</td>
<td>26 (8.6)</td>
<td>93 (30.8)</td>
</tr>
<tr>
<td>TYBZ</td>
<td>65</td>
<td>10 (3.3)</td>
<td>55 (18.2)</td>
</tr>
<tr>
<td>QXLX</td>
<td>29</td>
<td>4 (1.3)</td>
<td>25 (8.3)</td>
</tr>
<tr>
<td>GSBZ</td>
<td>56</td>
<td>2 (0.7)</td>
<td>54 (17.9)</td>
</tr>
</tbody>
</table>

Notes: FSBZ: wind and dampness blockage (Fengshi Bizu in Chinese); HSBZ: cold and dampness blockage (Hanshi Bizu); SRYZ: dampness and heat blockage (Shire Yuzu); TYBZ: phlegm and stagnation blockage (Tanyu Bizu); QXLX: dual deficiency of Qi and blood (Qixue Liangxu); GSBZ: liver and kidney deficiency (Ganshen Buzu). *P < 0.05, compared with the number of male patients.

Table 3: Relationship between duration of rheumatoid arthritis (RA) and Traditional Chinese Medicine (TCM) Zheng

<table>
<thead>
<tr>
<th>TCM Zheng</th>
<th>n</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSBZ</td>
<td>15</td>
<td>41±22</td>
</tr>
<tr>
<td>HSBZ</td>
<td>18</td>
<td>49±12</td>
</tr>
<tr>
<td>SRYZ</td>
<td>119</td>
<td>52±14’</td>
</tr>
<tr>
<td>TYBZ</td>
<td>65</td>
<td>51±15’</td>
</tr>
<tr>
<td>QXLX</td>
<td>29</td>
<td>50±17’</td>
</tr>
<tr>
<td>GSBZ</td>
<td>56</td>
<td>57±12’</td>
</tr>
</tbody>
</table>

Notes: FSBZ: wind and dampness blockage (Fengshi Bizu in Chinese); HSBZ: cold and dampness blockage (Hanshi Bizu); SRYZ: dampness and heat blockage (Shire Yuzu); TYBZ: phlegm and stagnation blockage (Tanyu Bizu); QXLX: dual deficiency of Qi and blood (Qixue Liangxu); GSBZ: liver and kidney deficiency (Ganshen Buzu). *P < 0.05, compared with the FSBZ group.

Relationship between TCM Zheng and blood parameters

There was no correlation between rheumatoid factor or erythrocyte sedimentation rate and Zheng (*P > 0.05, analysis of variance and rank-sum test). Blood platelet and C-reactive protein levels differed between Zhengs (*P < 0.05): the Q test revealed that platelet counts were lower among patients diagnosed with the dual deficiency of Qi and blood (QXLX), wind and dampness blockage (FSBZ), and cold and dampness blockage (HSBZ) Zhengs (Table 4 and Figure 7).
DISCUSSION

The prevalence of RA has been reported to be three times higher in women than in men;\(^1\) in our cohort, 85% of the patients were female. The medical classic *Huang Di Nei Jing* states: "when women are seven years old the kidney Qi begins to vibrate... at forty-nine (seven times seven), the Ren meridian becomes deficient and Tiangui exhausted (menopause)." RA has been associated with estrogen and progesterone levels,\(^1\) explaining the high proportion of women in our cohort; its prevalence has also been associated with lower levels of literacy in the United States,\(^2\) corresponding with the educational characteristics of the RA patients in the present study. The *Huang Di Nei Jing* also states: "the three pathogenic wind, cold, and dampness compose the Bi syndrome", implying that physical labor or childbirth can lead to Qi and blood deficiency, increasing susceptibility to the causes of RA.

Notes: FSBZ: wind and dampness blockage (Fengshi Bizu in Chinese); HSBZ: cold and dampness blockage (Hanshi Bizu); SRYZ: dampness and heat blockage (Shire Yuzu); TYBZ: phlegm and stagnation blockage (Tanyu Bizu); QXLX: dual deficiency of Qi and blood (Qixue Liangxu); GSBZ: liver and kidney deficiency (Ganshen Buzu).  \(^{*} P < 0.05\), compared with the QXLX group; \(^{a} P < 0.05\), compared with the GSBZ group; \(^{b} P < 0.05\), compared with the SRBZ group; \(^{c} P < 0.05\), compared with the HSBZ group. Results are expressed as mean ± standard deviation.
GSBZ Zheng were over 50 years old. The reason could be that the young patients are full of vital-Qi, and when the evil-Qi was violated, the confliction between vital-Qi and evil-Qi were obvious. Almost 40% of our RA patients were diagnosed with the SRYZ Zheng. The primary symptoms were multi-joint swelling, joint pain, and limited mobility. Zhu Danxi, a noted physician who lived during the Yuan Dynasty, said: "Among six climatic factors, dampness and heat are about eight or nine of ten." In the Ru Men Shi Qin, Zhang Zihe, a physician from the Jin Dynasty, said: "As for Bi syndrome, heat and dampness are the source, and cold and wind are the secondary pathogens, and the combination of the three climatic factors composes the Bi syndrome."

In our study, the liver and kidney deficiency Zheng was more common in female patients. Throughout their life, women experience menstruation, leucorrhea, pregnancy, and delivery, which can lead to Qi and blood deficiency.

During the early stage of RA, vital Qi is still sufficient; the clinical manifestations of RA patients are mostly migrant joint pain (FSBZ Zheng). Over time, owing to blood-parameter imbalances and vital Qi deficiency, RA patients commonly experience joint deformity, fatigue, and lassitude of the waist and knee (GSBZ Zheng).

The currently available disease composite activity indices for RA that provide a single number on a continuous scale are DAS, DAS28, the Simplified Disease Activity Index, and the Clinical Disease Activity Index. DAS28 is considered the only gold standard in measuring disease activity in RA patients. In our study, the DAS28 activity scores were highest for patients diagnosed with the SRYZ Zheng, whose clinical manifestations were mostly feelings of heat in joints, redness, and a high erythrocyte sedimentation rate. The full HAQ is designed to measure five generic dimensions: physical function, pain, drug side effects, healthcare utilization, and mortality. The shortened (two-page) HAQ, however, scores patients by disability index, pain level, and global health status. We found that the HAQ scores of patients diagnosed with the FSBZ and HSBZ Zhengs were the lowest, while the HAQ scores of patients diagnosed with the GSBZ and QXLX Zhengs were the highest. Patients with higher HAQ values are often in the active or late-period stage of RA, probably related to dampness, heat, phlegm, and blood-parameter imbalances. In contrast, deficiencies in Qi, blood, or Yin and Yang can lead to a serious decline in joint function and quality of life. Although the HAQ is highly subjective, it does mirror disease activity to some extent; in TCM treatment planning, the HAQ can be used to assess the efficacy of the indicators.

As mentioned above, the majority (39.4%) of our RA patients were diagnosed with the SRYZ Zheng. Over time, physicians gradually realized that in addition to cold, wind, and dampness, Bi syndrome was also caused or exacerbated by heat and blood stasis. In recent years, with environmental and climatic changes, heat and dampness have become substantial contributing factors in RA, along with changes in lifestyle and diet and lack of physical exercise. Moreover, RA recurrence often requires long-term or repeated use of corticosteroids and immunosuppressive agents, and these drugs can damage the spleen and stomach, leading to functional impairment. This can result in blockage of the Qi of food, water, and dampness, which remains in the body and increases the heat and dampness.

Most patients with moderate to severe active RA were diagnosed with the dampness-heat blockage Zheng; cooling and promoting blood circulation may assist these patients. There are study limitations to note. First, RA is a chronic persistent disease, and patients may exhibit two or more syndromes (Zhengs) simultaneously; we only considered the primary syndrome in our analysis. Second, the hospitals participating in this study are national clinical rheumatism centers, and most RA patients were in the active or late period of the disease, explaining why the majority were diagnosed with the SRYZ and GSBZ Zhengs. Some patients, however, were in the early stage.

In conclusion, the most common triggers of RA reported by patients were cold and fatigue, followed by childbirth. We suggest avoiding strenuous labor and cold weather, and attempting to prevent the features of childbirth that are conducive to the induction of RA. As most patients diagnosed with the SRYZ Zheng had high DAS28 scores, drying, cooling, and promoting blood circulation are suggested in managing severe RA.

REFERENCES


