# Postprint: Clinical Features and Influencing Factors of Rheumatoid Arthritis Pain with Central Sensitization

**Authors:** Liu Longxiao, Xu Yuan, Chen Yanyu, Xue Qi, Fang Yunlong, Luo Ruili, Li Yanqi, Wang Jinping, Tao Qingwen, Wang Jinping, Tao Qingwen

**Date:** 2025-05-07T00:00:00+00:00

## Abstract

Background Central sensitization (CS) constitutes a significant influencing factor of pain in rheumatoid arthritis (RA) patients; however, its clinical characteristics and distribution features of Traditional Chinese Medicine (TCM) syndromes remain unclear and are readily neglected in RA pain management.

Objective To investigate the correlation between RA pain and CS, and to analyze the clinical characteristics and associated risk factors in RA patients with comorbid CS.

Methods A cross-sectional study design was employed. Two hundred RA patients with pain who presented to the Department of Traditional Chinese Medicine Rheumatology at China-Japan Friendship Hospital from January 2024 to September 2024 were enrolled as study subjects. General information and laboratory examination indices were collected. Pain was assessed using the Visual Analogue Scale (VAS), and patients were stratified into mild, moderate, and severe groups based on VAS scores. Disease activity was evaluated using the 28-joint Disease Activity Score (DAS28). CS was scored using the Central Sensitization Inventory (CSI), and patients were categorized into RA-CS and RA-non-CS (RA-nCS) groups based on CS scores. Health status was assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI). TCM syndrome evaluation was conducted according to the "Guidelines for the Diagnosis and Treatment of Rheumatoid Arthritis with Integrated Disease and Syndrome Patterns" . Fatigue was evaluated using the Visual Analogue Scale for Fatigue (VAS-F). Multivariate Logistic regression analysis was utilized to explore influencing factors for RA pain severity and RA-CS. Bootstrap resampling was performed for internal validation, and the Hosmer-Lemeshow test was applied to assess regression model fit.

Results Among the 200 enrolled RA patients, 88 cases (44%) were in the mild group, 80 cases (40%) in the moderate group, and 32 cases (16%) in the severe group. Significant differences were observed among the three groups in age, tender joint count (TJC28), swollen joint count (SJC28), DAS28-ESR, DAS28-CRP, fatigue VAS score, central sensitization score, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) (P<0.05). Multivariate Logistic regression analysis revealed that DAS28-ESR (OR=3.948, 95%CI=1.069~14.579, P=0.039) and central sensitization score (OR=1.066, 95%CI=1.035~099, P<0.001) were independent risk factors for RA pain. Among the 200 RA patients, 57 cases (28.5%) were in the RA-CS group and 143 cases (71.5%) in the RA-nCS group. The RA-CS group exhibited higher disease duration, morning stiffness duration, patient global assessment (PGA), fatigue VAS score, and HAQ-DI, but lower ESR and tumor necrosis factor-$\alpha$ (TNF-$\alpha$) levels compared to the RA-nCS group (P<0.05). The RA-CS group had higher numbers of patients with limited flexion and extension, sweating, lumbar and knee weakness, Liver-Kidney deficiency pattern, and Cold-Dampness Bi obstruction pattern, but fewer patients with joint fever compared to the RA-nCS group (P<0.05). Multivariate Logistic analysis results indicated that fatigue VAS score (OR=1.735, 95%CI=1.261~2.388, P<0.001) and sweating (OR=6.593, 95%CI=1.656~26.242, P=0.007) were risk factors for RA-CS, while joint fever (OR=0.242, 95%CI=0.067~0.872, P=0.030) was a protective factor for RA-CS. Bootstrap validation demonstrated good model consistency. Hosmer-Lemeshow test results showed good model fit ( 2=9.532, P=0.299).

Conclusion RA pain is closely associated with CS. When RA patients present with significant fatigue and sweating without accompanying joint fever, assessment of CS and implementation of multidimensional pain management are essential.

## Full Text

# Analysis of Clinical Characteristics and Influencing Factors of Rheumatoid Arthritis Pain Complicated by Central Sensitization

**LIU Longxiao[1], XU Yuan[2], CHEN Yanyu[1], XUE Qi[1], FANG Yunlong[1], LUO Ruili[1], LI Yanqi[1], WANG Jinping[2], *TAO Qingwen*[2]**

[1]Graduate School, Beijing University of Traditional Chinese Medicine, Beijing 100029, China
[2]Department of TCM Rheumatology, National Center for Integrative Medicine/China-Japan Friendship Hospital, Beijing 100029, China

*Corresponding authors: WANG Jinping, Attending physician; E-mail: wjpbucm@163.com*
*TAO Qingwen, Professor/Doctoral supervisor; E-mail: taoqg1@sina.com*

## Abstract

**Background:** Central sensitization (CS) is a significant factor influencing pain in patients with rheumatoid arthritis (RA). However, the clinical characteristics and distribution patterns of traditional Chinese medicine (TCM) syndromes associated with CS remain unclear, and CS is frequently overlooked in RA pain management.

**Objective:** To investigate the correlation between RA pain and CS, and to analyze the clinical characteristics and associated risk factors of RA patients with pain complicated by CS.

**Methods:** This cross-sectional study enrolled 200 RA patients with pain who visited the Department of TCM Rheumatology at China-Japan Friendship Hospital between January 2024 and September 2024. General information and laboratory indicators were collected. Pain was assessed using the Visual Analogue Scale (VAS), and patients were categorized into mild, moderate, and severe pain groups based on VAS scores. Disease activity was evaluated using the 28-joint Disease Activity Score (DAS28). CS was assessed using the Central Sensitization Inventory (CSI), and patients were divided into RA-CS and RA-non-CS (RA-nCS) groups. Health status was evaluated using the Health Assessment Questionnaire-Disability Index (HAQ-DI). TCM syndrome differentiation was performed according to the *Guidelines for the Diagnosis and Treatment of Rheumatoid Arthritis with Integrated Disease and Syndrome Concepts*. Fatigue was assessed using the Visual Analogue Scale for Fatigue (VAS-F). Multivariate logistic regression analysis was used to explore factors influencing RA pain severity and RA-CS. Bootstrap resampling was used for internal validation, and the Hosmer-Lemeshow test was used to evaluate model fit.

**Results:** Among the 200 RA patients, 88 (44%) were in the mild pain group, 80 (40%) in the moderate pain group, and 32 (16%) in the severe pain group. Significant differences were observed among the three groups in age, tender joint count (TJC28), swollen joint count (SJC28), DAS28-ESR, DAS28-CRP, fatigue VAS score, CS score, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) ($P<0.05$). Multivariate logistic regression analysis revealed that DAS28-ESR (OR=3.948, 95%CI=1.069–14.579, P=0.039) and CS score (OR=1.066, 95%CI=1.035–1.099, $P<0.001$) were independent risk factors for RA pain severity. Among the 200 RA patients, 57 (28.5%) were in the RA-CS group and 143 (71.5%) in the RA-nCS group. The RA-CS group had significantly longer disease duration, morning stiffness duration, patient global assessment (PGA), fatigue VAS score, and HAQ-DI, but lower ESR and tumor necrosis factor-$\alpha$ (TNF-$\alpha$) levels compared to the RA-nCS group ($P<0.05$). The RA-CS group also had higher frequencies of limited joint mobility, sweating, lumbar and knee weakness, liver-kidney deficiency syndrome, and cold-dampness obstruction syndrome, but lower frequency of joint fever compared to the RA-nCS group ($P<0.05$). Multivariate logistic analysis showed that fatigue VAS score (OR=1.735, 95%CI=1.261–2.388, $P<0.001$) and sweating (OR=6.593,

95%CI=1.656-26.242, P=0.007) were positively associated with RA-CS, while joint fever (OR=0.242, 95%CI=0.067-0.872, P=0.030) was negatively associated with RA-CS. Bootstrap validation demonstrated good model consistency, and the Hosmer-Lemeshow goodness-of-fit test confirmed adequate model fit ( $^2$=9.532, P=0.299).

**Conclusion:** RA pain is closely associated with CS. When RA patients present with prominent fatigue and sweating without joint fever, evaluation for CS and implementation of multidimensional pain management are essential.

**Keywords:** rheumatoid arthritis; pain; central sensitization; analysis of influencing factors; logistic regression

## 1. Subjects and Methods

### 1.1 Study Subjects

This cross-sectional study enrolled 200 RA patients with pain who visited the Department of TCM Rheumatology at China-Japan Friendship Hospital between January 2024 and September 2024. Professional researchers strictly screened patients according to inclusion and exclusion criteria. **Inclusion criteria:** (1) Age 18-70 years, regardless of gender; (2) Met RA diagnostic criteria; (3) Voluntary participation with signed informed consent. **Exclusion criteria:** (1) Comorbid other rheumatic immune diseases or severe pain caused by other conditions (such as diabetic neuropathy or postherpetic neuralgia); (2) History of mental illness or cognitive dysfunction; (3) Pregnant or lactating women; (4) Comorbid malignancy. This study was approved by the Ethics Committee of China-Japan Friendship Hospital (NO.2024-KY-058-2), and all participants provided written informed consent.

### 1.2 Diagnostic and Assessment Criteria

#### 1.2.1 Diagnostic Criteria:

(1) **Western medicine diagnosis:** RA diagnosis followed the 1987 American College of Rheumatology (ACR) or 2010 ACR/EULAR classification criteria.
(2) **TCM syndrome differentiation:** Based on the *Guidelines for the Diagnosis and Treatment of Rheumatoid Arthritis with Integrated Disease and Syndrome Concepts*, RA was classified into wind-dampness obstruction syndrome, cold-dampness obstruction syndrome, damp-heat obstruction syndrome, phlegm-stasis obstruction syndrome, blood-stasis obstructing collaterals syndrome, liver-kidney deficiency syndrome, qi-yin deficiency syndrome, and qi-blood deficiency syndrome.

**1.2.2 General Data Collection:** Patient demographics, age, disease duration, morning stiffness duration, tender joint count (TJC), swollen joint count (SJC), and patient global assessment (PGA) were recorded in case report forms.

**1.2.3 Laboratory Indicators:** Erythrocyte sedimentation rate (ESR) was measured by the Westergren method; rheumatoid factor (RF) and C-reactive protein (CRP) by immunoturbidimetry; immunoglobulins (IgG, IgA, IgM), complement (C3, C4), anti-cyclic citrullinated peptide (CCP) antibodies, and cytokines (IL-1$\beta$, IL-2, IL-6, IL-8, TNF-$\alpha$, INF-$\alpha$, INF-$\gamma$) by enzyme-linked immunosorbent assay (ELISA); and T lymphocytes, CD4+ T cells, CD8+ T cells, NK cells, and B lymphocytes (B1, B2 cells) by Beckman-Coulter FC500 flow cytometry. All tests were performed at China-Japan Friendship Hospital.

**1.2.4 Pain Assessment and Grouping:** Pain was assessed using the Visual Analogue Scale (VAS). Patients marked their current pain level on a 10 cm line, with scores ranging from 0–10: 0–3 indicated mild pain, 4–6 moderate pain, and 7–10 severe pain. Patients were divided into mild, moderate, and severe pain groups accordingly.

**1.2.5 Disease Activity Assessment:** Disease activity was evaluated using the 28-joint Disease Activity Score (DAS28), including DAS28-CRP and DAS28-ESR. The formulas were:

$$\text{DAS28-CRP} = 0.56\times\sqrt{\text{TJC28}}+0.28\times\sqrt{\text{SJC28}}+0.36\times\ln(\text{CRP}+1)+0.14\times\text{PGA}+0.96$$

$$\text{DAS28-ESR} = 0.56\times\times\sqrt{\text{TJC28}}+0.28\times\sqrt{\text{SJC28}}+0.7\times\ln(\text{ESR})+0.014\times\text{PGA}$$

where SQRT is the square root function and ln is the natural logarithm. Scoring criteria: DAS28 <2.6 indicated remission, 2.6–3.2 low disease activity, 3.2–5.1 moderate activity, and >5.1 high activity.

**1.2.6 Central Sensitization Assessment and Grouping:** The Central Sensitization Inventory (CSI) was used, which has demonstrated high reliability and validity in Chinese populations. The CSI assesses somatic symptoms, emotional status, and pain sensitivity-related questions, with total scores ranging from 0–100. Higher scores indicate more severe CS, and scores $ $40 were considered indicative of CS. Patients were divided into RA-CS and RA-non-CS (RA-nCS) groups based on CSI scores.

**1.2.7 Health Status Assessment:** The Health Assessment Questionnaire-Disability Index (HAQ-DI) was used, with scores calculated based on difficulty levels across various items to represent functional disability.

**1.2.8 TCM Syndrome Assessment:** Based on the *Guidelines for the Diagnosis and Treatment of Rheumatoid Arthritis with Integrated Disease and Syndrome Concepts*, RA was classified into the same eight syndrome types mentioned above. TCM syndrome differentiation was performed by two senior TCM rheumatology clinicians, with disagreements resolved by consultation with a third senior clinician.

**1.2.9 Fatigue Assessment:** Fatigue was evaluated using the Visual Analogue Scale for Fatigue (VAS-F). Patients rated their fatigue over the past 24 hours on a 10 cm scale divided into 10 equal parts, with total scores ranging from 0-10. Higher scores indicated more severe fatigue.

### 1.3 Statistical Methods

SPSS 22.0 software was used for statistical analysis. Normally distributed continuous data were expressed as mean ± standard deviation ($\bar{x}\pm s$) and compared between two groups using independent samples t-test and among multiple groups using one-way ANOVA. Non-normally distributed data were expressed as median (P25, P75) and compared between two groups using Mann-Whitney U test and among multiple groups using Kruskal-Wallis test. Categorical data were expressed as frequencies and percentages and compared using $^2$ test. Multivariate logistic regression analysis was used to explore independent influencing factors. Bootstrap resampling with 1,000 iterations was used for internal validation, and Hosmer-Lemeshow test was used to evaluate model fit. $P<0.05$ was considered statistically significant. For multiple comparisons, Bonferroni/Tamhane correction was applied, with the significance level adjusted to $\alpha' = 0.05/3 = 0.017$ for three-group comparisons, where $P<0.017$ indicated statistical significance.

---

## 2. Results

### 2.1 Comparison of General Data and Clinical Characteristics Among RA Patients with Different Pain Levels

A total of 200 RA patients were included: 88 (44%) in the mild pain group, 80 (40%) in the moderate pain group, and 32 (16%) in the severe pain group. Significant differences were observed among the three groups in age, TJC28, SJC28, DAS28-ESR, DAS28-CRP, fatigue VAS score, CS score, CRP, and ESR ($P<0.05$). Specifically, the mild group and moderate group had lower TJC28, DAS28-ESR, DAS28-CRP, and fatigue VAS scores compared to the severe group ($P<0.017$). The mild group also had lower TJC28, SJC28, DAS28-ESR, DAS28-CRP, fatigue VAS score, and CS score compared to the moderate group ($P<0.017$). See Table 1 .

### 2.2 Multivariate Logistic Regression Analysis of Factors Influencing RA Pain Severity

Using RA pain severity as the dependent variable (mild=1, moderate=2, severe=3) and variables with statistical significance in univariate analysis as independent variables (all assigned as measured values), multivariate logistic regression analysis showed that DAS28-ESR (OR=3.948, 95%CI=1.069-14.579, P=0.039) and CS score (OR=1.066, 95%CI=1.035-1.099, $P<0.001$) were independent risk factors for RA pain severity. See Table 2 .

### 2.3 Comparison of General Data and Clinical Characteristics Between RA-CS and RA-nCS Groups

Among the 200 RA patients, 57 (28.5%) were in the RA-CS group and 143 (71.5%) in the RA-nCS group. The RA-CS group had significantly longer disease duration, morning stiffness duration, PGA, fatigue VAS score, and HAQ-DI compared to the RA-nCS group (P<0.05). See Table 3 .

### 2.4 Comparison of Laboratory Indicators Between RA-CS and RA-nCS Groups

The RA-CS group had significantly lower ESR and TNF-$\alpha$ levels compared to the RA-nCS group (P<0.05). No significant differences were observed between the two groups in serum CRP, RF, anti-CCP, immunoglobulins (IgG, IgA, IgM), complement (C3, C4), lymphocyte counts (T lymphocytes, CD4+ T cells, CD8+ T cells, CD4+/CD8+ ratio, NK cells, B1 cells, B2 cells), or cytokine levels (IL-1$\beta$, IL-2, IL-6, IL-8, INF-$\alpha$, INF-$\gamma$) (P>0.05). See Table 4 .

### 2.5 Distribution of TCM Symptoms and Syndromes Between RA-CS and RA-nCS Groups

In terms of TCM symptoms, the RA-CS group had significantly higher frequencies of limited joint mobility, sweating, lumbar and knee weakness, but lower frequency of joint fever compared to the RA-nCS group (P<0.05). See Table 5 . Significant differences were also observed between the two groups in the distribution of liver-kidney deficiency syndrome and cold-dampness obstruction syndrome (P<0.05). See Table 6 .

### 2.6 Multivariate Logistic Regression Analysis of Factors Influencing RA-CS

Using RA-CS status as the dependent variable (RA-nCS=0, RA-CS=1) and variables with statistical significance in univariate analysis as independent variables, multivariate logistic regression analysis (with categorical variable assignments shown in Table 7 and continuous variables assigned as measured values) revealed that fatigue VAS score (OR=1.735, 95%CI=1.261-2.388, P<0.001) and sweating (OR=6.593, 95%CI=1.656-26.242, P=0.007) were independent risk factors for RA-CS, while joint fever (OR=0.242, 95%CI=0.067-0.872, P=0.030) was an independent protective factor. See Table 8 .

### 2.7 Internal Validation

Bootstrap resampling with 1,000 iterations was used for internal validation of the regression model, yielding a C-index of 0.723, indicating good model consistency. The Hosmer-Lemeshow test showed good model fit ( $^2$=9.532, P=0.299).

## 3. Discussion

Pain is the primary complaint of RA patients and directly impacts their quality of life and prognosis. Persistent chronic pain is a risk factor for disability and multiple systemic complications. Studies have shown that CS is a key factor in RA chronic pain, causing some patients to experience ongoing pain even after achieving inflammatory remission, leading to widespread analgesic use despite limited efficacy evidence and side effect risks. Currently, RA-CS is often overlooked in clinical practice due to unclear clinical characteristics. Therefore, exploring the clinical features and influencing factors of RA-CS is crucial for early identification and targeted treatment.

Pain is a hallmark feature of RA inflammation. DAS28-ESR, DAS28-CRP, TJC28, SJC28, and acute-phase reactants including ESR and CRP are essential components for evaluating disease activity. Our findings support a strong correlation between pain and inflammatory indicators as well as clinical assessment methods. Additionally, multivariate analysis demonstrated a positive correlation between CS score and RA pain severity, consistent with previous research. In RA joints, synovial inflammation caused by cytokines can activate or sensitize nociceptive fibers, which transmit pain signals to the spinal dorsal horn. Ascending signals are then propagated through several pathways, including the spinothalamic tract to the thalamus and higher processing centers. Pro-inflammatory cytokines can also directly act on mechanosensitive nociceptors, postsynaptic pathways in spinal and supraspinal circuits, and glial cells and immune cells in the nervous system to induce pain.

The prevalence of RA-CS in this study was 28.5%. Current literature reports RA-CS prevalence ranging from 17.0% to 62.5%, with variations likely due to different CS definition criteria and study populations. Our univariate analysis suggested longer disease duration in the RA-CS group, consistent with POLLARD et al., who reported that RA patients with longer disease duration have lower pain thresholds, indicating that CS mechanisms progress with disease course. Furthermore, our study identified fatigue VAS score as an independent risk factor for RA-CS. Multiple studies have reported that increased pain over time is associated with greater fatigue, which may impair sleep quality and subsequently alter central pain processing by attenuating descending analgesic mechanisms, leading to pain exacerbation. CS interacts with multiple factors including fatigue, mood disorders, and sleep disturbances.

Research indicates that after peripheral nervous system damage in RA, microglia and astrocytes in the spinal cord are activated, producing cytokines such as TNF-$\alpha$, IL-1, and IL-6, which subsequently cause rapid increases in excitatory synaptic transmission in spinal neurons, directly inducing CS. IL-6 and IL-4 can directly act on dorsal root ganglia and are considered potential key cytokines involved in RA-CS pain. Animal studies have also found that TNF-$\alpha$ binding to receptors TNFR1 and TNFR2 in dorsal root ganglia causes hyperalgesia. Our univariate analysis showed that compared to the RA-nCS group, RA-CS patients

had lower serum ESR and TNF-$\alpha$ levels but higher DAS28-ESR, suggesting that pain perception and subjective disease assessment in RA-CS patients are more severe and not proportional to peripheral inflammation levels, highlighting the significant role of CS in RA pain. Peripheral nociceptive input can impair endogenous analgesic mechanisms, resulting in persistent pain despite controlled inflammation. RAOOF et al. found that persistent pain after anti-TNF-$\alpha$ therapy may be due to antibodies not crossing the blood-brain barrier to effectively block spinal TNF-$\alpha$, and animal studies have shown that established spinal excitability can be maintained through downstream mechanisms independent of spinal TNF-$\alpha$.

ESR, as an inflammatory marker, is susceptible to multiple factors, and previous studies have not demonstrated a specific relationship between ESR and CS. Our multivariate analysis did not find significant correlations between RA-CS and peripheral serological indicators, possibly due to selection bias. CS affects RA disease activity scores and reduces treatment satisfaction, representing an important factor driving medical visits and increasing healthcare burden even without inflammatory manifestations such as elevated ESR. Therefore, when deciding whether to escalate anti-inflammatory therapy in RA, it is crucial to consider the dissociation between CS-related pain and peripheral inflammatory activity and the potentially misleading influence of patient-reported components on DAS28. Future studies with larger sample sizes are needed to further investigate serological characteristics of RA-CS.

Syndrome differentiation and treatment based on symptom patterns are characteristic features of TCM clinical practice. Our univariate analysis found that RA-CS patients more frequently presented with limited joint mobility, sweating, lumbar and knee weakness, cold-dampness obstruction syndrome, and liver-kidney deficiency syndrome, while joint fever was less common. Further multivariate analysis revealed that RA-CS was positively correlated with sweating and negatively correlated with joint fever. Our research team believes that RA-CS is closely related to cold syndromes. Previous studies have suggested that RA cold-dampness obstruction syndrome is significantly associated with CS, clinically manifesting as aversion to cold, pain aggravated by cold, and infrequent joint fever. According to the *Suwen · Bilun*, "When wind, cold, and dampness combine, they cause bi syndrome; when cold qi predominates, it causes painful bi," and "Pain results from excess cold." On one hand, cold-dampness obstruction pain is caused by cold pathogen contraction and dampness stagnation leading to impeded qi and blood flow, resulting in pain without joint fever. On the other hand, the *Suwen · Yinyang Yingxiang Dalun* states that "excessive cold causes floating," and the *Suwen · Shengqi Tongtian Lun* explains that "due to cold, the movement is like a pivot, daily life becomes startling, and the spirit qi floats," elucidating the pathogenesis of CS-related pain from the perspective of cold causing spirit floating—specifically, cold-dampness injuring yang, yang deficiency failing to consolidate, leading to internal stirring of heart spirit and external floating of spirit qi, subsequently causing sensitization and decreased pain threshold. Additionally, body fluids lose yang qi consolidation, resulting in abnormal sweat-

ing. Modern medicine suggests that central nervous system damage may cause autonomic dysfunction leading to hyperhidrosis. Autonomic imbalance may participate in RA pathogenesis, with close functional interactions between pain neural circuits and autonomic regulatory mechanisms. Reduced vagal tone may enhance nociceptive signal transmission in the spinothalamic tract. Studies in patients with palpitations have found correlations between cold/heat syndromes and sympathetic/vagal tone balance through heart rate variability analysis, with deficiency/excess syndromes related to overall autonomic tone. Sympathetic-adrenal system inhibition and hyperfunction are important mechanisms in cold and heat syndrome formation, and animal experiments have shown that warming Chinese herbs can effectively improve cold stomach syndrome by regulating sympathetic-adrenal system function. Furthermore, modern TCM practitioners widely believe that kidney deficiency is an important factor in bi syndrome pathogenesis. The kidney belongs to cold water, and cold-dampness pathogen injures the kidney and penetrates to the bone due to same-qi induction. Since liver and kidney share the same origin, kidney deficiency fails to nourish liver wood; the kidney governs bones and the liver governs tendons, so liver-kidney deficiency leads to malnourishment of tendons and bones, causing pain due to lack of nourishment. The liver stores blood and houses the ethereal soul, so liver blood deficiency causes loss of soul lodging. Additionally, "defensive qi originates from the kidney," and kidney deficiency leads to dysfunction of defensive qi opening and closing, causing abnormal sweating. Therefore, RA patients with fatigue, sweating, and cold syndrome patterns should be evaluated for CS, with treatment focusing on supplementing liver-kidney, dispelling cold and eliminating dampness. The *Lingshu* states that "when there is pain, the spirit returns; when the spirit returns, there is heat; when there is heat, the pain resolves," suggesting that warming yang and regulating spirit provide new approaches for pain management. Studies have shown that aconite can regulate gene expression in spinal cord and dorsal root ganglia to improve hyperalgesia, while alkaloid components from Chinese herbs such as *Sinomenium acutum*, *Corydalis yanhusuo*, and *Ligusticum chuanxiong* can effectively relieve central neuropathic pain through multi-target effects. Acupuncture can increase pain thresholds by regulating glial cell activation-mediated central sensitization, demonstrating the great potential of fully exploring and utilizing TCM advantages to reduce pain burden in RA patients.

This study has several limitations. It is a single-center observational clinical study, and regional population characteristics may affect the results. The study did not include CS-related factors such as mood and sleep, which should be addressed in future prospective, multicenter, large-sample clinical studies to further explore and clarify risk factors for RA pain to optimize RA pain management.

---

**Author Contributions:** LIU Longxiao and WANG Jinping conceived the research idea and designed the study protocol. XU Yuan and WANG Jinping

revised the manuscript. CHEN Yanyu, XUE Qi, FANG Yunlong, and LUO Ruili were responsible for data collection and organization. LIU Longxiao and LI Yanqi performed statistical analysis and prepared tables and figures. LIU Longxiao drafted the manuscript. WANG Jinping and TAO Qingwen were responsible for quality control and review, supervised the overall work, and provided oversight.

**Funding:** This study was supported by the "Elite Program" Talent Cultivation Project of China-Japan Friendship Hospital (ZRJY2023-QM21), the National Natural Science Foundation of China Youth Fund Project (82204901), and the Special Clinical Research Project for High-Level Hospital Clinical Business Expenses of China-Japan Friendship Hospital (2022-NHLHCRF-LX-02-02).

**Conflict of Interest:** The authors declare no conflicts of interest.

**ORCID IDs:**
LIU Longxiao: https://orcid.org/0009-0003-3239-1851
WANG Jinping: https://orcid.org/0000-0002-9751-0327
TAO Qingwen: https://orcid.org/0000-0002-9163-8426

**References**

[1] DI MATTEO A, BATHON J M, EMERY P. Rheumatoid arthritis[J]. Lancet, 2023, 402(10416): 2019-2033. DOI: 10.1016/s0140-6736(23)01525-8.

[2] National Clinical Research Center for Dermatologic and Immunologic Diseases (Peking Union Medical College Hospital), Chinese Association of Rheumatology and Immunology Physicians, Rheumatology and Immunology Rehabilitation Committee of Chinese Association of Rehabilitation Medicine, et al. 2024 Chinese guidelines for the diagnosis and treatment of rheumatoid arthritis[J]. Chinese Journal of Internal Medicine, 2024, (11): 1059-1077. DOI: 10.3760/cma.j.cn112138-20240531-00360.

[3] TAYLOR P C. Pain in the joints and beyond; the challenge of rheumatoid arthritis[J]. Lancet Rheumatol, 2023, 5(6): e351-360. DOI: 10.1016/S2665-9913(23)00094-2.

[4] SARZI-PUTTINI P, ZEN M, ARRU F, et al. Residual pain in rheumatoid arthritis: is it a real problem?[J]. Autoimmun Rev, 2023, 22(11): 103423. DOI: 10.1016/j.autrev.2023.103423.

[5] HIRAGA S I, ITOKAZU T, NISHIBE M, et al. Neuroplasticity related to chronic pain and its modulation by microglia[J]. Inflamm Regen, 2022, 42(1): 15. DOI: 10.1186/s41232-022-00199-8.

[6] SALAFFI F, CAROTTI M, FARAH S, et al. Early response to JAK inhibitors on central sensitization and pain catastrophizing in patients with active rheumatoid arthritis[J]. Inflammopharmacology, 2022, 30(3): 1119-1128. DOI: 10.1007/s10787-022-00995-z.

[7] XU Yuan, LUO Jing, HAN Man, et al. Discussion on clinical advantages of

traditional Chinese medicine in treating rheumatic immune diseases[J]. Chinese Journal of Experimental Traditional Medical Formulae, 2022, 28(09): 198-204. DOI: 10.13422/j.cnki.syfjx.20220995.

[8] ALETAHA D, NEOGI T, SILMAN A J, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative[J]. Arthritis Rheum, 2010, 62(9): 2569-2581. DOI: 10.1002/art.27584.

[9] JIANG Quan, WANG Hailong, GONG Xun, et al. Guidelines for the diagnosis and treatment of rheumatoid arthritis with integrated disease and syndrome concepts[J]. Journal of Traditional Chinese Medicine, 2018, 59(20): 1794-1800. DOI: 10.13288/j.11-2166/r.2018.20.018.

[10] WAN Li, ZHAO Qing, CHEN Jun, et al. Chinese expert consensus on the application of pain assessment scales (2020 edition)[J]. Chinese Journal of Painology, 2020, 16(3): 11. DOI: 10.3760/cma.j.cn101379-20190915-00075.

[11] ANDERSON J K, ZIMMERMAN L, CAPLAN L, et al. Measures of rheumatoid arthritis disease activity: patient (PtGA) and provider (PrGA) global assessment of disease activity, disease activity score (DAS) and disease activity score with 28-joint counts (DAS28), simplified disease activity index (SDAI), clinical disease activity index (CDAI), patient activity score (PAS) and patient activity score-II (PASII), routine assessment of patient index data (RAPID), rheumatoid arthritis disease activity index (RADAI) and rheumatoid arthritis disease activity index-5 (RADAI-5), chronic arthritis systemic index (CASI), patient-based disease activity score with ESR (PDAS1) and patient-based disease activity score without ESR (PDAS2), and mean overall index for rheumatoid arthritis (MOI-RA)[J]. Arthritis Care Res, 2011, 63(Suppl 11): S14-36. DOI: 10.1002/acr.20621.

[12] NEBLETT R, COHEN H, CHOI Y, et al. The central sensitization inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample[J]. J Pain, 2013, 14(5): 438-445. DOI: 10.1016/j.jpain.2012.11.012.

[13] XU C, YAO S X, WEI W, et al. Cross-cultural adaptation and validation for central sensitization inventory: based on Chinese patients undergoing total knee arthroplasty for knee osteoarthritis[J]. J Orthop Surg Res, 2023, 18(1): 960. DOI: 10.1186/s13018-023-04375-3.

[14] ALLANORE Y, BOZZI S, TERLINDEN A, et al. Health Assessment Questionnaire-Disability Index (HAQ-DI) use in modelling disease progression in diffuse cutaneous systemic sclerosis: an analysis from the EUSTAR database[J]. Arthritis Res Ther, 2020, 22(1): 257. DOI: 10.1186/s13075-020-02322-8.

[15] BOEREN A M P, VERSTAPPEN M, LOOIJEN A E M, et al. Patients with rheumatoid arthritis presenting with mono- or oligo-arthritis and high VAS-

ratings remain the most fatigued during 5 years of follow-up[J]. Rheumatology, 2024, 63(6): 1574-1581. DOI: 10.1093/rheumatology/kead429.

[16] CHEN Bingwei. Medical Statistics[M]. 4th ed. Nanjing: Southeast University Press, 2023: 81-82.

[17] ANDERSSON M, SVENSSON B, BERGMAN S. Pain in rheumatoid arthritis: a seven-year follow-up study of pain distribution and factors associated with transition from and to chronic widespread pain[J]. Scand J Rheumatol, 2022, 51(5): 345-354. DOI: 10.1080/03009742.2021.1944304.

[18] SALAFFI F, GIACOBAZZI G, DI CARLO M. Chronic pain in inflammatory arthritis: mechanisms, metrology, and emerging targets-a focus on the JAK-STAT pathway[J]. Pain Res Manag, 2018, 2018: 8564215. DOI: 10.1155/2018/8564215.

[19] SIMON L S, TAYLOR P C, CHOY E H, et al. The jak/STAT pathway: a focus on pain in rheumatoid arthritis[J]. Semin Arthritis Rheum, 2021, 51(1): 278-284. DOI: 10.1016/j.semarthrit.2020.10.008.

[20] YAM M F, LOH Y C, TAN C S, et al. General pathways of pain sensation and the major neurotransmitters involved in pain regulation[J]. Int J Mol Sci, 2018, 19(8): 2164. DOI: 10.3390/ijms19082164.

[21] RAOOF R, WILLEMEEN H L D M, EIJKELKAMP N. Divergent roles of immune cells and their mediators in pain[J]. Rheumatology, 2018, 57(3): 429-440. DOI: 10.1093/rheumatology/kex308.

[22] POPIOLEK-BARCZYK K, MIKA J. Targeting the microglial signaling pathways: new insights in the modulation of neuropathic pain[J]. Curr Med Chem, 2016, 23(26): 2908-2928. DOI: 10.2174/0929867323666160607120124.

[23] BOYDEN S D, HOSSAIN I N, WOHLFAHRT A, et al. Non-inflammatory causes of pain in patients with rheumatoid arthritis[J]. Curr Rheumatol Rep, 2016, 18(6): 30. DOI: 10.1007/s11926-016-0581-0.

[24] GULER M A, CELIK O F, AYHAN F F. The important role of central sensitization in chronic musculoskeletal pain seen in different rheumatic diseases[J]. Clin Rheumatol, 2020, 39(1): 269-274. DOI: 10.1007/s10067-019-04749-1.

[25] POLLARD L C, IBRAHIM F, CHOY E H, et al. Pain thresholds in rheumatoid arthritis: the effect of tender point counts and disease duration[J]. J Rheumatol, 2012, 39(1): 28-31. DOI: 10.3899/jrheum.110668.

[26] BERRICHI I, TAIK F Z, HADDANI F, et al. Prevalence and associated factors of central sensitization in patients with chronic inflammatory rheumatic disease[J]. Curr Rheumatol Rev, 2024. DOI: 10.2174/0115733971309885241011105213.

[27] FILATOVA E, POGOZHEVA E, AMIRDZHANOVA V, et al. ab0165 central sensitization in rheumatoid arthritis[J]. Ann Rheum Dis, 2021, 80: 1109. DOI: 10.1136/annrheumdis-2021-eular.3074.

[28] DRUCE K L, JONES G T, MACFARLANE G J, et al. The longitudinal course of fatigue in rheumatoid arthritis: results from the Norfolk arthritis register[J]. J Rheumatol, 2015, 42(11): 2059-2065. DOI: 10.3899/jrheum.141498.

[29] FELDTHUSEN C, GRIMBY-EKMAN A, FORSBLAD-D' ELIA H, et al. Explanatory factors and predictors of fatigue in persons with rheumatoid arthritis: a longitudinal study[J]. J Rehabil Med, 2016, 48(5): 469-476. DOI: 10.2340/16501977-2090.

[30] NICASSIO P M, ORMSETH S R, KAY M, et al. The contribution of pain and depression to self-reported sleep disturbance in patients with rheumatoid arthritis[J]. Pain, 2012, 153(1): 107-112. DOI: 10.1016/j.pain.2011.09.024.

[31] LEE Y C, LU B, EDWARDS R R, et al. The role of sleep problems in central pain processing in rheumatoid arthritis[J]. Arthritis Rheum, 2013, 65(1): 59-68. DOI: 10.1002/art.37731.

[32] SCHAIBLE H G. Nociceptive neurons detect cytokines in arthritis[J]. Arthritis Res Ther, 2014, 16(5): 470. DOI: 10.1186/s13075-014-0470-8.

[33] KAWASAKI Y, ZHANG L, CHENG J K, et al. Cytokine mechanisms of central sensitization: distinct and overlapping role of interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha in regulating synaptic and neuronal activity in the superficial spinal cord[J]. J Neurosci, 2008, 28(20): 5189-5194. DOI: 10.1523/JNEUROSCI.3338-07.2008.

[34] CHOY E H S, CALABRESE L H. Neuroendocrine and neurophysiological effects of interleukin 6 in rheumatoid arthritis[J]. Rheumatology, 2018, 57(11): 1885-1895. DOI: 10.1093/rheumatology/kex391.

[35] COOK A D, CHRISTENSEN A D, TEWARI D, et al. Immune cytokines and their receptors in inflammatory pain[J]. Trends Immunol, 2018, 39(3): 240-255. DOI: 10.1016/j.it.2017.12.003.

[36] GEORGE A, BUEHL A, SOMMER C. Tumor necrosis factor receptor 1 and 2 proteins are differentially regulated during Wallerian degeneration of mouse sciatic nerve[J]. Exp Neurol, 2005, 192(1): 163-166. DOI: 10.1016/j.expneurol.2004.11.002.

[37] KÖNIG C, ZHARSKY M, MÖLLER C, et al. Involvement of peripheral and spinal tumor necrosis factor $\alpha$ in spinal cord hyperexcitability during knee joint inflammation in rats[J]. Arthritis Rheumatol, 2014, 66(3): 599-609. DOI: 10.1002/art.38271.

[38] MESCI N, MESCI E, KANDEMIR E U, et al. Impact of central sensitization on clinical parameters in patients with rheumatoid arthritis[J]. North Clin Istanb, 2024, 11(2): 140-146. DOI: 10.14744/nci.2023.81231.

[39] SEKI K, IMAGAMA T, SEKI T, et al. Central sensitivity syndrome affects the disease activity index and treatment satisfaction in patients with rheuma-

toid arthritis[J]. Int J Rheum Dis, 2024, 27(4): e15159. DOI: 10.1111/1756-185X.15159.

[40] CHEN Yanyu, LI Yanqi, LIU Longxiao, et al. Analysis of clinical characteristics and related factors in rheumatoid arthritis patients with cold-dampness obstruction syndrome[J]. Chinese Journal of Experimental Traditional Medical Formulae, 2025, 31(3): 140-146. DOI: 10.13422/j.cnki.syfjx.20250498.

[41] LI Xueke, WU Shengxian, DU Yawei. Analysis of pain syndrome based on the theory of "cold predominance causing floating" [J]. China Medical Herald, 2024, 21(22): 126-130. DOI: 10.20047/j.issn1673-7210.2024.22.23.

[42] CHEN Nong. Analysis of difficult sentences in the *Neijing*—discussion on the sentence "due to cold, the movement is like a pivot" [J]. Shanghai Journal of Traditional Chinese Medicine, 1986, 20(5): 36-37. DOI: 10.16305/j.1007-1334.1986.05.023.

[43] WANG Yiwen, ZHANG Suming, WU Chao, et al. Clinical observation of autonomic nervous function in rheumatoid arthritis patients[J]. Chinese Journal of Pain Medicine, 2021, 27(5): 348-353. DOI: 10.3969/j.issn.1006-9852.2021.05.007.

[44] KOENIG J, FALVAY D, CLAMOR A, et al. Pneumogastric (vagus) nerve activity indexed by heart rate variability in chronic pain patients compared to healthy controls: a systematic review and meta-analysis[J]. Pain Physician, 2016, 19(1): E55-78.

[45] CHEN Liaoyi, GUO Xiaoyu, YUAN Xiaochun, et al. Correlation analysis between heart rate variability (HRV) and autonomic nerve tension (sympathetic and vagal) in palpitation patients with cold and heat syndromes[J]. Journal of Practical Traditional Chinese Internal Medicine, 2019, 33(1): 10-13. DOI: 10.13729/j.issn.1671-7813.z20190040.

[46] QIN Huazhen, MA Xiaobin, JIANG Fangjing, et al. Effects of volatile oils from three *Alpinia* species on body temperature and sympathetic-adrenal system in rats with cold stomach syndrome[J/OL]. Chinese Journal of Traditional Chinese Medicine, 1-13. [2025-02-10]. http://kns.cnki.net/kcms/detail/21.1546.R.20250205.1158.012.html.

[47] ZHANG Xiaodong, WANG Jie. Experience of Professor Zhao Shaoqin and Professor Jiao Shude in treating rheumatoid arthritis[J]. Guangming Journal of Chinese Medicine, 2024, 39(8): 1533-1536. DOI: 10.3969/j.issn.1003-8914.2024.08.019.

[48] CAI Xiaolu, XIE Qingyu, MENG Qinggang. Guiding value of "all cold-induced contraction belongs to the kidney" in rheumatoid arthritis treatment[J]. Chinese Archives of Traditional Chinese Medicine, 2015, 33(3): 599-603. DOI: 10.13193/j.issn.1673-7717.2015.03.026.

[49] ZHANG Ningyi, ZHOU Chunxiang. Interpretation of "defensive qi originates from the kidney" [J]. Journal of Yunnan University of Traditional Chinese Medicine, 2008, 31(6): 20-21. DOI: 10.19288/j.cnki.issn.1000-2723.2008.06.008.

[50] SONG Jingyi, ZHANG Shuofeng, MA Dan, et al. Pharmacodynamic and mechanistic study of aconite intervention on pain sensitivity in rats with cold and heat bi syndromes[J]. Global Traditional Chinese Medicine, 2020, 13(7): 1142-1149. DOI: 10.3969/j.issn.1674-1749.2020.07.004.

[51] JIANG W, TANG M Z, YANG L M, et al. Analgesic alkaloids derived from traditional Chinese medicine in pain management[J]. Front Pharmacol, 2022, 13: 851508. DOI: 10.3389/fphar.2022.851508.

[52] WANG J Y, GAO Y H, QIAO L N, et al. Repeated electroacupuncture treatment attenuated hyperalgesia through suppression of spinal glial activation in chronic neuropathic pain rats[J]. BMC Complement Altern Med, 2018, 18(1): 74. DOI: 10.1186/s12906-018-2134-8.

[53] LIANG Y, QIU Y J, DU J Y, et al. Inhibition of spinal microglia and astrocytes contributes to the anti-allodynic effect of electroacupuncture in neuropathic pain induced by spinal nerve ligation[J]. Acupunct Med, 2016, 34(1): 40-47. DOI: 10.1136/acupmed-2015-010773.

(Received: February 12, 2025; Revised: March 28, 2025)

*Note: Figure translations are in progress. See original paper for figures.*