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Research article

Rheumatoid arthritis characteristics and classification of heat and cold patterns–an observational study

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ABSTRACT

Introduction: Traditional Chinese medicine (TCM) has been proven to be an effective complementary therapy in treating rheumatoid arthritis (RA). The cold pattern and the heat pattern were the two main TCM patterns for RA, which is crucial for TCM treatment. The cold pattern is characterized by fear of cold and wind, joint pain with a thin white tongue coating which can be relieved by hot herbs. In contrast, heat pattern patients suffer from severe joint pain with a yellow coating, with red swelling of the skin and high skin temperature which can be relieved by cooling herbs.

Objective: We aimed to classify the heat and cold patterns in RA patients with cluster analysis and factor analysis. Moreover, we aimed to explore the association of RA characteristics between these two patterns.

Methods: and Design: A cross-sectional observational research method was used, and data was collected on 300 RA patients in Hangzhou in China. Signs and symptoms associated with RA were clustered using SPSS 22.0 software. In addition, factor analysis was also used for the classification. After classification of heat and cold patterns, characteristics and treatment of the RA participants between the two patterns were explored.

Results: RA patients in the study were divided into two categories using cluster analysis. Twenty-two symptoms in the first category were included in the heat pattern of RA patients. After factor analysis, nine principal components were extracted to heat pattern. The component with the highest eigenvalue (2.530) were mainly contributed by shortness of breath, palpitation, heavy limbs, chest tightness and yellow greasy tongue with high factor loading values (0.765, 0.703, 0.504, 0.429 and 0.402, respectively). Ten symptoms in the second category were included in the cold pattern of RA patients. Four principal components were extracted to cold pattern. The component with the highest eigenvalue (2.089) were mainly contributed by joint distension and pain, joint stiffness, fatigue and upset with high factor loading values (0.597, 0.590, 0.491 and 0.481, respectively). Although there were no statistical differences between the levels of rheumatoid factor and anti-cyclic peptide containing citrulline (anti-CCP), the levels of C-reactive protein, platelet count and the disease activity score using 28 joint counts were significantly higher in the heat pattern RA patients compared to the ones in cold pattern. Moreover, heat pattern RA patients were more likely to be prescribed two more disease-modifying anti-rheumatic drugs (DMARDS) combined with Methotrexate (MTX) (70.59% versus 49.72%; $P = 0.000$).

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Conclusions: In conclusion, heat and cold patterns in RA patients could be classified well using cluster analysis and factor analysis. Most of RA patients with heat pattern were active and likely to be prescribed two more DMARDs combined with MTX.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent inflammatory synovitis and joint architecture destruction [1]. Currently, RA patients are generally treated by disease-modifying anti-rheumatic drugs (DMARDs),biologics, and non-steroidal anti-inflammatory drugs(NSAIDs) to control the inflammation and alleviate the pain [2]. However, long-term use of these drugs could cause side effects such as increased risk of infection and liver and kidney impairment [3].

Traditional Chinese medicine (TCM) has been proven to be effective in treating RA [4,5]. A crucial part of TCM therapeutic theory is pattern classification, which is based on symptoms, tongue appearance, and pulse-touching [6]. The proper prescriptions used to treat RA are based on successful pattern classification [6,7].

According to the theory of pattern classification in TCM, Yin, Yang, interior, exterior, cold, hot, deficiency and excess were the main eight principles. Among the principles, Yin and Yang were the general principles. Thus, it is very crucial to differentiate Yin and Yang in TCM treatment. Heat pattern, which belongs to Yang, refers to the syndrome when the body feels heat evil or yang qi is hyperactive and yin fluid is deficient. In contrast, cold pattern, which belongs to Yin, refers to the functional decline caused by cold evil or insufficient yang qi or excessive Yin qi.

Clinically, RA patients can be classified into two main TCM patterns: the cold pattern and the heat pattern. The cold pattern is characterized by fear of cold and wind, joint pain with cold, and a thin white tongue coating which can be relieved by hot herbs. In contrast, heat pattern patients suffer from severe joint pain with skin swelling and high skin temperature, which can be relieved by cooling herbs. Many studies on cold and heat patterns have been conducted in various fields including pattern questionnaires, Chinese medicine textbooks, the literature and the doctors' experience [8,9]. Nevertheless, there were few reports on the classification of cold and heat patterns with cluster analysis. Herein, we classified cold and heat patterns with cluster analysis from the symptoms of RA patients and analyzed RA characteristics between these two patterns.

2. Methods and design

2.1. Study design

The study was a cross-sectional study. Three hundred RA patients were recruited in the Second Affiliated Hospital of Zhejiang Chinese Medical University in Hangzhou in China between October 2019 to October 2021. All participants provided informed consent, and the trial was approved by the Ethics Committees of the Second Affiliated Hospital of Zhejiang Chinese Medical University. The approval number was 2019 KL-125-01. RA Patients met the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria were included [10]. The diagnosis of TCM syndrome is based on the Chinese medicine industry standard of the People's Republic of China, the Therapeutic Effect Standard of TCM Syndrome Diagnosis (2012) issued by the State Administration of Traditional Chinese Medicine [11]. General demographic information about the age, gender, joint condition, pain condition, symptoms (fever, sweating, color of face and skin, diet, urination and defecation characteristics, and mental consciousness), tongue and pulse conditions associated with RA were collected. In addition, interventions and treatments for RA were also collected.

2.2. Sample size

Based on our former research [12], we set our parameters as $P = 0.5$, $d = 0.1$, and $\alpha = 0.05$. Therefore, approximately 300 cases of RA patients would fulfill the analysis.

2.3. TCM terminology

Terminology was based on the World Health Organization International Standard Terminologies on Traditional Medicine in the Western Pacific Region and the International Standard Chinese-English Basic Nomenclature of Chinese Medicine [13].

2.4. Quality control

The doctors participating in the clinical diagnoses were all senior physicians of the rheumatology department and had a full understanding of the diagnosis and treatment guidelines. Symptoms were determined by two physicians of rheumatology especially tongue and pulse conditions. All the recordings of data were strictly monitored to ensure the integrity, authenticity and credibility of information.

2.5. Statistical analysis

The statistical analysis was performed with SPSS 22.0 (IBM SPSS, Armonk, NY, USA). Variables with less discrimination in symptoms and tongue and pulse conditions were removed to reduce the number of variables and reduce errors (e.g., variables with a frequency of less than 15% were eliminated). In addition, the R-type clustering (i.e., the system connection-Pearson correlation coefficient method) systematic clustering method was selected. Kaiser-Meyer-Olkin (KMO) test and Bartlett sphericity test were used for the factor analysis. Results are presented as mean ± SEM. Comparisons between groups were assessed using the *t*-test. Results were corrected for multiple testing using the Bonferroni-correction. $P < 0.05/2 = 0.025$ was considered as statistically significant.

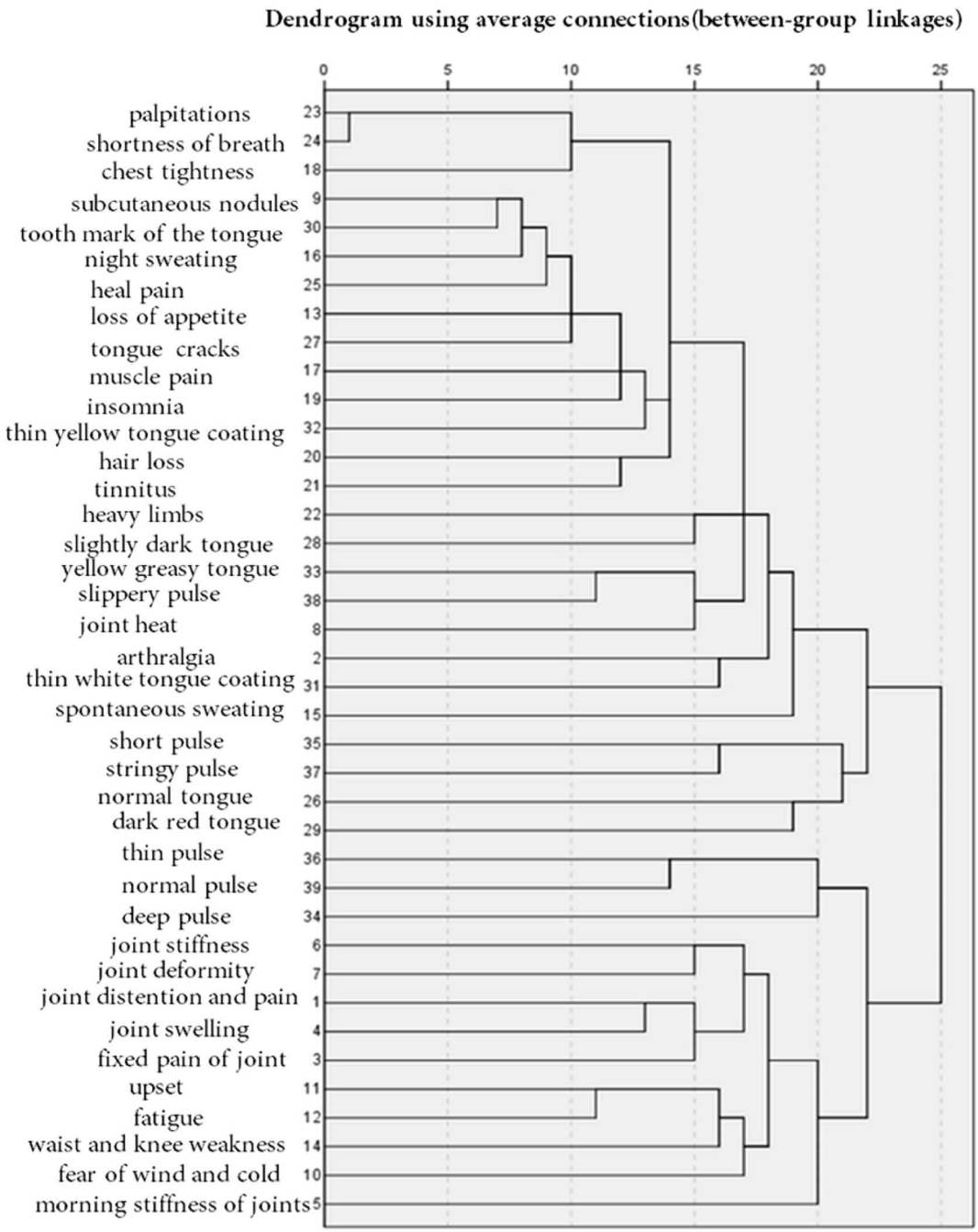

Fig. 1. Pattern cluster analysis of symptoms of RA patients.

3. Results

3.1. Cluster analysis of RA syndromes

In the present study, we tried all the combinations of clustering methods and distance calculation methods given by SPSS. At last, it is meaningful to connect a correlation coefficient with a clustering graph in the selected group. In the cluster analysis, the symptoms and tongue manifestations with a frequency of less than 15% were deleted, then the remaining main symptoms, and tongue and pulse conditions were clustered, and the following results were obtained (Fig. 1).

According to the results obtained by clustering, the symptoms can be divided into two categories. The symptoms in the first category were palpitations, shortness of breath, hair loss, chest tightness, tinnitus, spontaneous sweating, tooth mark of the tongue, loss of appetite, night sweating, insomnia, muscle pain, heel pain, subcutaneous nodules, heavy limbs, joint pain, joint heat, tongue cracks, red tongue, dark red tongue, yellow greasy tongue, and slippery pulse. Most of them were heat pattern RA patients with dampness, heat, phlegm, and blood stasis. The heat pattern could be comprised by two subgroups, including phlegm and blood stasis heat syndrome and dampness and heat syndrome. Palpitations, shortness of breath, and chest tightness were usually caused by the phlegm and blood stasis obstructive in the chest and heart. Subcutaneous nodules were always presented in the RA patients' joint with phlegm and blood stasis. Meanwhile, symptoms of heavy limbs, joint pain, joint heat, and slippery pulse were usually demonstrated in the RA patients with dampness and heat syndrome. Thus, the accumulation of phlegm, blood stasis, heat and dampness were main pathological products of heat pattern. The second category of symptoms were fear of wind and cold, joint deformity, joint distension and pain, fixed pain of joint, upset, fatigue, waist and knee weakness, joint stiffness, light red tongue, thin white coating and thin pulse. They were more common in cold pattern RA patients. The cold pattern could be comprised by two subgroups, qi and blood deficiency causing cold syndrome and kidney and liver deficiency causing cold syndrome. The symptoms of arthralgia, thin white tongue coating, spontaneous sweating, short pulse were usually caused by the qi and blood deficiency. Meanwhile, the fatigue, waist and knee weakness, joint stiffness and thin pulse were often presented in the RA patients with kidney and liver deficiency.

3.2. Factor analysis of the heat pattern and cold pattern from RA patient clustering

3.2.1. KMO and Bartlett sphericity test

KMO test is always used to compare the value of observed correlation coefficient with the value of lopsided relationship. The value is required to be larger than 0.3. As for Bartlett sphericity test, $P < 0.001$ indicates that the variables are highly correlated.

3.2.2. Hot pattern

The KMO statistic value was 0.544, indicating that there was no significant difference in the correlation between the variables. In

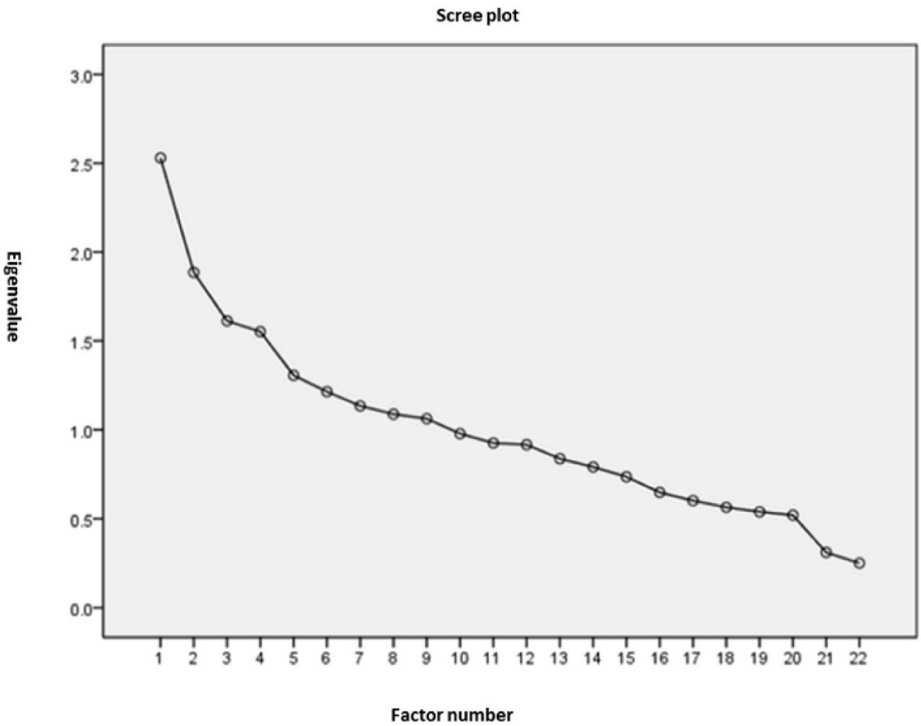

Fig. 2. Scree plot of the main components of heat pattern from the cluster analysis of RA patients.

the Bartlett sphericity test: $\chi 2 = 888.630$, df = 231, and $P = 0.000$, with larger values, it was suitable for factor analysis.

3.2.3. Cold pattern

The KMO statistic value was 0.662. In the Bartlett sphericity test, $\chi 2 = 209.145$, df = 45 and $P = 0.000$.

3.2.4. Scree plot

From the scree plot, according to the steepness of the slope of lines connecting the points, the importance of the factor can be clearly seen.

Nine main components (with eigenvalues of 1 or more) were closely related to the first category from the RA cluster analysis according to the scree plot (Fig. 2).

Four main components (with eigenvalues of 1 or more) were closely related to the second category from the RA cluster analysis (Fig. 3).

3.2.5. Total variance explained

Data extraction was performed according to the principal component analysis method, and the default feature value was 1. Among the 22 symptoms from the first category of RA cluster analysis, nine principal components were extracted (Initial eigenvalues>1) (Table 1). The component with the highest eigenvalue (2.530) were mainly contributed by shortness of breath, palpitation, heavy limbs, chest tightness and yellow greasy tongue with high factor loading values (0.765, 0.703, 0.504, 0.429 and 0.402, respectively). (Supplementary Table 1). Among the ten symptoms of the second category of RA cluster analysis, four principal components were extracted (Table 2). The component with the highest eigenvalue (2.089) was mainly contributed by joint distension and pain, joint stiffness, fatigue and upset with high factor loading values (0.597, 0.590, 0.491 and 0.481, respectively). (Supplementary Table 2).

Thus, the first main component of heat pattern of RA patients mainly focused on the systemic symptoms such as palpitations, shortness of breath, chest tightness, and heavy limbs. In contrast, the first main component of cold pattern of RA patients mainly focused on the joint symptoms such as joint stiffness, joint distention and pain.

3.2.6. Demographic characteristics and treatment of the RA participants

After cluster analysis and factor analysis, 119 RA participants belonged to heat pattern and 181 patients attributed to cold pattern. There were approximately 70% of RA patients female in both heat and cold patterns (Table 3). Although there were no statistical differences with the levels of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP), the levels of C-reaction protein (CRP)($P = 0.0019$), platelet (PLT) ($P = 0.0055$) and the disease activity score using 28 joint counts ($DAS28\text{-}_{ESR}$) ($P = 0.0022$) were significantly higher in the heat pattern RA patients compared to the ones in cold patten. Moreover, the health assessment questionnaire (HAQ) score was also slightly higher in the heat pattern (Fig. 4).

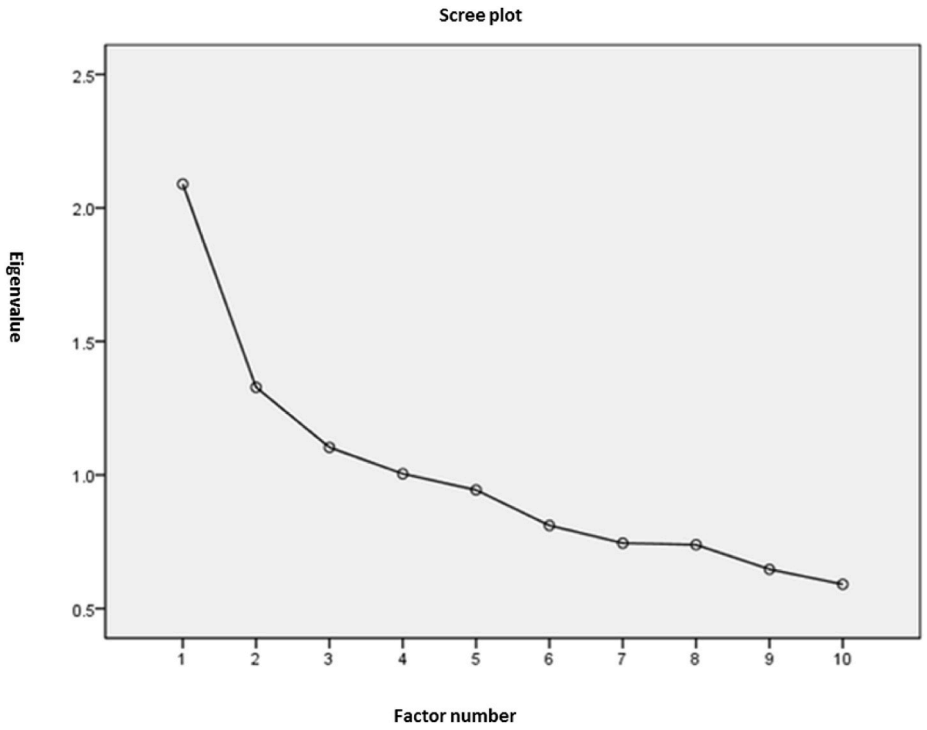

Fig. 3. Scree plot of the main components of cold pattern from the cluster analysis of RA patients.

Table 1
Cluster analysis of RA patients with the total variance explained by the principal components of the heat pattern.

Component	Initial eigenvalues			Extracted sum of squared loadings		
	Total	% of variance	cumulative%	Total	% of variance	cumulative%
1	2.530	11.499	11.499	2.530	11.499	11.499
2	1.885	8.570	20.069	1.885	8.570	20.069
3	1.612	7.327	27.396	1.612	7.327	27.396
4	1.552	7.053	34.449	1.552	7.053	34.449
5	1.306	5.935	40.384	1.306	5.935	40.384
6	1.214	5.518	45.902	1.214	5.518	45.902
7	1.134	5.155	51.057	1.134	5.155	51.057
8	1.087	4.943	56.000	1.087	4.943	56.000
9	1.062	4.827	60.827	1.062	4.827	60.827
10	.978	4.446	65.272			
11	.926	4.208	69.480			
12	.916	4.164	73.644			
13	.837	3.805	77.449			
14	.791	3.594	81.043			
15	.735	3.342	84.385			
16	.648	2.946	87.331			
17	.602	2.736	90.068			
18	.564	2.565	92.633			
19	.539	2.450	95.083			
20	.520	2.365	97.447			
21	.311	1.413	98.861			
22	.251	1.139	100.000			

Extraction method: Principal Component Analysis.

Table 2
Cluster analysis of RA patients with the total variance explained by the principal components of the cold pattern.

Component	Initial eigenvalues			Extracted sum of squared loadings		
	Total	% of variance	cumulative%	Total	% of variance	cumulative%
1	2.089	20.893	20.893	2.089	20.893	20.893
2	1.328	13.279	34.172	1.328	13.279	34.172
3	1.103	11.030	45.202	1.103	11.030	45.202
4	1.004	10.042	55.244	1.004	10.042	55.244
5	.944	9.437	64.681			
6	.811	8.109	72.790			
7	.745	7.447	80.237			
8	.739	7.388	87.625			
9	.647	6.468	94.093			
10	.591	5.907	100.000			

Extraction method: Principal Component Analysis.

Table 3
Demographic characteristics and treatment of the RA participants.

	Heat pattern	Cold pattern	P
number	119	181	NA
Age (years), Mean ± SEM	52.25 ± 1.33	62.54 ± 6.947	0.2388
Female, freq (%)	86(72.26)	129(71.27)	0.851
Education > high school degree, freq (%)	65(54.6)	93(51.38)	0.0582
Symptom duration (years), Mean ± SEM	9.126 ± 0.70	9.114 ± 0.6188	0.9901
RA treatment			
MTX, freq (%)	95(79.80)	135(74.59)	0.293
MTX combo, freq (%)	84(70.59)	90(49.72)	0.000***
Biologics, freq (%)	36(30.25)	36(19.89)	0.040
Oral Glucocorticoid use, freq (%)	33(27.7)	48(26.52)	0.817
Chinese herbal medicine, freq (%)	96(80.67)	145(80.11)	0.905

RA: rheumatoid arthritis, MTX: Methotrexate.NA: None applicable.

Among those RA patients, most of them received the methotrexate (MTX) treatment. Notably, heat pattern RA patients were more significantly likely to be prescribed two more DMARDs combined with MTX (70.59% versus 49.72%; $P = 0.000$) (Table 3). In addition, more than 80% of RA patients received the Chinese herbal medicine treatment.

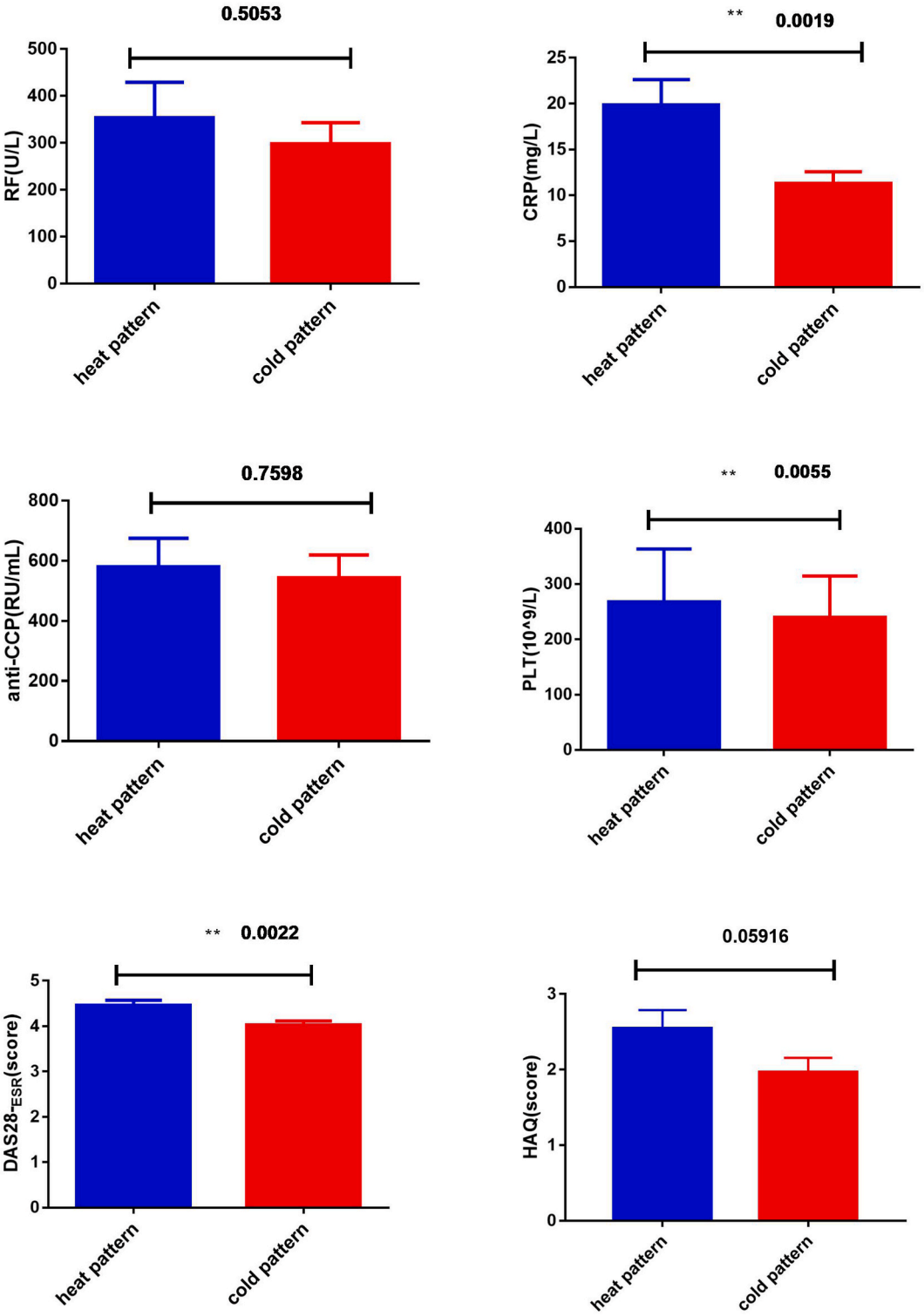

Fig. 4. The comparison of RA characteristics between Heat pattern and cold pattern. Note: RF: rheumatoid factor, anti-CCP: anti-cyclic cirullinated peptide antibodies, CRP: the levels of C-reaction protein, PLT: platelet, DAS28: the disease activity score using 28 joint counts, ESR: Erythrocyte Sedimentation Rate, HAQ: health assessment questionnaire.

4. Discussion

In a cross-sectional observational cohort of RA patients, we classified the heat pattern and cold pattern by using cluster analysis and factor analysis. We found that the nine symptoms: subcutaneous nodules, heavy limbs, joint pain, joint heat, red tongue, dark red tongue, dark tongue, yellow greasy tongue and string pulse could be the main symptoms to classify heat pattern. In contrary, fear of cold and wind, fatigue, weakness of the waist and knees, and a thin pulse are the primary ones to classify cold pattern. Additionally, we provide evidence that the levels of CRP, PLT and DAS28-ESR score were significantly higher in the heat pattern RA patients compared to the ones in cold pattern. Moreover, heat pattern RA patients were more significantly likely to be prescribed two more DMARDs combined with MTX and biologics.

The standardization of TCM patterns has always been the challenge TCM pattern research. Cluster analysis is a statistical method to study the classification of things. The use of sample clustering can classify cases with the same symptoms or signs into the same category (that is, the same syndrome type). Specifically, it is the use of "objects to cluster", that is, the principle of aggregation of similar samples [14]. The concept of "class" is similar to the concept of TCM patterns. Factor analysis is a multivariate approach that starts by analyzing the correlation of multiple original indicators, finds a finite number of unobservable latent variables that govern this correlation, and uses these latent variables to explain the correlation or covariance of the original indicators using mathematical and statistical analysis methods [15].

In the present study, the heat pattern was comprised by two subgroups, including phlegm and blood stasis heat syndrome and dampness and heat syndrome. The result revealed that the accumulation of phlegm, blood stasis, heat and dampness were main pathological products of heat pattern. Thus, apart from the cooling herbs, some Chinese herbs with the function of reducing phlegm, activating blood, and resolving dampness also need to be prescribed according to syndrome differentiation. The cold pattern was comprised by two subgroups, qi and blood deficiency causing cold syndrome and kidney and liver deficiency causing cold syndrome. As recoded by *Inner Canon of Huangdi* “Evil-qi would gather together when the vital-qi was in deficiency.”, some Chinese herbs which can invigorate qi and blood and tonify liver and kidney could enhance the vital-qi to protect the human body from the cold evil-qi.

Given heat pattern and cold pattern were the main TCM patterns in RA, several studies investigated the relationship of cold and heat patterns with RA by gene expression [16–19] and metabolic profiling [20,21]. ESR, platelets, and C-reactive protein are used as reaction indicators in the acute phase of inflammation [22], which are significantly increased in patients with active rheumatoid arthritis. In our present study, the levels of ESR, PLT, CRP and DAS28-ESR were significantly higher in the heat pattern RA patients compared to the ones in cold pattern. These results demonstrated that most of RA patients with heat pattern were active and may need more treatment therapies for treat-to-target. The treatment analysis also revealed that heat pattern RA patients were more likely to be prescribed two more DMARDs combined with MTX. Moreover, cooling Chinese herbs were prescribed to heat pattern RA patients and hot and pungent herbs were for cold pattern patients.

Although there were no statistical differences with the levels of RF, anti-CCP and HAQ score, they were still higher in heat pattern compared to cold pattern. Longer follow-up studies need to be done in the future for the prognosis of the heat pattern and cold pattern.

There are study limitations to note. First, this was a single center cross-sectional study in the southeast of China which maybe not be universal for all RA patients. Secondly, the duration of most of the RA patients was at a mean of 9 years. As a result, most RA patients were in the active or late period of the disease. RA patients in the early stage may be another bias. Finally, we would like to witness the pattern studies with larger samples and longer follow-ups with national and even international multi-centers in the near future.

5. Conclusions

In conclusion, heat and cold patterns in RA patients could classified well using cluster analysis and factor analysis. Most of RA patients with heat pattern were active and likely to be prescribed two more DMARDs combined with MTX.

Author contribution statement

Weijie Wang: Conceived and designed the experiments; Wrote the paper; Performed the experiments.
Jintao Guan: Wrote the paper; Performed the experiments; Analyzed and interpreted the data.
Zhengfu Li: Analyzed and interpreted the data.
Xinchang Wang: Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no competing interests.

Ethics approval and consent to participate

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration. It was approved by the Human Ethics Committee of the Second Affiliated Hospital of Zhejiang Chinese Medical University. The approval number was 2019 KL-125-01. Written informed consent was obtained from individual or guardian participants.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e13439.

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