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Original Article

Data Mining Study on Prescription Patterns of Different Dosage Forms of Chinese Herbal Medicines for Treating and Improving Immune-Inflammatory Indices in Patients with Rheumatoid Arthritis*

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ABSTRACT **Objective:** To explore the prescription patterns of different dosage forms of Chinese herbal medicines (CHMs) for the treatment of rheumatoid arthritis (RA) and their effects on immune-inflammatory indices. **Methods:** Clinical data were collected from patients with RA in 4 hospitals (3 Class A comprehensive hospitals and 1 Class B comprehensive hospital) in Anhui Province, China, from August 2012 to June 2018 via the electronic medical record gathering system. Following extraction of prescription information, each prescribed herb was quantified and standardized according to the knowledge base to establish a database of RA treatment formulae. The medical records were divided into the granules group and decoction pieces group. Core herbs and their combination patterns were obtained from the two groups of cases using Liquorice software. Changes in immune-inflammatory and hepatic and renal function indices were compared between the two groups using SPSS 23.0 software. The Aprior module of SPSS Clementine 11.1 software was applied to analyse the correlation between CHMs and improvement in indices. Finally, the ORACLE 10 g tool was used to evaluate the random walk model of the immune-inflammatory indices between the two groups. **Results:** (1) We retrospectively analysed 35,898 prescriptions for 6,829 patients with RA who received CHM treatment. There were 3,816 patients in the granules group and 3,013 in the decoction pieces group. (2) The core herbs were Pi (Spleen)-strengthening and dampness-resolving drugs, blood-activating and stasis-resolving drugs, wind/dampness-dispelling drugs and heat-clearing and detoxifying drugs. (3) Both dosage forms could improve immune-inflammatory indices in RA patients, with similar efficacy and no influence on hepatic or renal function. (4) *Herba Siegesbeckiae* and *Oldenlandia* had a stronger association with immune-inflammatory indices in the two groups. (5) The immune-inflammatory indices showed obvious improvement after treatment with granules and decoction pieces of CHMs, and there were long range correlations between the comprehensive evaluation indices and interventions. **Conclusions:** The principal CHM treatment methods for RA in four hospitals in Anhui Province are strengthening Pi and resolving dampness, activating blood and resolving stasis, dispelling wind/dampness and clearing heat. Granules and decoction pieces of CHMs have similar efficacy in improving immune-inflammatory indices in RA patients and could be used as treatment options for RA.

KEYWORDS rheumatoid arthritis, Chinese heral medicine, granules, decoction pieces, data mining

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Rheumatoid arthritis (RA) is the most common autoimmune arthritis, with a prevalence of approximately 1% of the worldwide population.[1] Autoimmunity and overall systemic and refractory synovial inflammation can lead to progressive destruction of the joints, causing stiffness, deformity and dysfunction, and this can eventually lead to disabilities, with a serious negative impact on the quality of life of patients.[2,3] In addition to joint damage, other organs may be compromised.[4] The estimated prevalence of extra-articular manifestations among RA patients is as high as 21.5%, and most deaths are attributable to extra-articular manifestations.[5,6]

Currently, treatment for RA mainly involves drug intervention. Over the past decade, the development of biological agents and disease-modifying anti-rheumatic drugs has profoundly enhanced the success of RA treatment.[2,7] However, some patients fail to use these drugs and experience different degrees of adverse reactions.[8-10] Additionally, the complementary effects of alternative and complementary therapies in the treatment of RA have been demonstrated. Among these treatments, Chinese medicine (CM) is considered a powerful option.[11] Indeed, CM has been used in China to treat RA for thousands of years, and based on empirical data, it is a promising alternative or complementary treatment option for patients with RA.[12] CM is widely used as a complementary method for the prevention and treatment of RA.[13] An increasing number of clinical and experimental studies have confirmed that Chinese herbal formulas and extracts can effectively reduce the severity of RA.[14,15] However, the prescription rule of formulae for CM is complicated and remains uncharacterized.

Chinese herbal medicines (CHMs) can be prescribed in different forms of medicinal preparations, such as water decoctions or medicinal wine decoctions. In addition to decoctions, plant extracts and granules are available commercially and are widely used in China.[14] With the development and wide application of granules, increasing attention has been paid to their efficacy and safety. A study showed that granules and decoction pieces of Duhuo Jisheng Decoction (独活寄生汤) can relieve clinical symptoms and pain and improve biochemical indices, with no differences between the two groups analysed.[16] Nevertheless, there is no documented real-world study of a large number of samples from multiple centres in a complex clinical environment that compares the efficacy and safety of decoction pieces and granules.

In this study, based on real-world analysis, we analyzed the prescriptions for RA treatment of decoction pieces and granules using frequency analysis and complex networks to explore the conventional CHM prescriptions, the law of medication, and the potential core prescriptions. In addition, we evaluated the changes in immune-inflammatory indices as well as markers of liver and kidney functions.

METHODS

Data Source

All the required clinical information was obtained retrospectively through medical chart review. The data mining system independently developed by the First Affiliated Hospital of Anhui University of Chinese Medicine (patent No. 2017SR422234) was used to collect the in-patient (n=7,099) and out-patient (n=812) medical records of patients with RA in 4 hospitals, including 3 Class A comprehensive hospitals (the First Affiliated Hospital of Anhui University of Chinese Medicine, Bozhou Hospital of Chinese Medicine, Anhui Hospital of Integrated Traditional Chinese and Western Medicine) and 1 Class B comprehensive hospital (Huangshan Hospital of Chinese Medicine), from August 2012 to June 2018. The Western diagnostic criteria applied referred to the American College of Rheumatology (ACR) and the European Union of Rheumatology (EULAR) 2010 RA classification criteria and scoring system, with a total score of 6 or more diagnosed as RA.[17] The diagnostic criteria of CM referred to the "Guidelines for the Diagnosis and Treatment of Rheumatoid Arthritis" from the Rheumatology Branch, Chinese Society of Traditional Chinese Medicine.[18] The following conditions were excluded: (1) incomplete prescription composition, (2) not receiving CHMs, and (3) lack of laboratory examinations before or after treatment.

Data Extraction and Processing

According to the clinical databases of the hospitals, all data from outpatient medical records for the selected patients were extracted and transformed to establish a new database by using ORACLE 10 g tools (Oracle Corporation, USA). Noise was removed, and the data were used after checking for errors in logic. According to the Pharmacopoeia of the People's Republic of China (2015 edition)[19] and the textbook of CM (new century edition 2),[20] the correct name

of CHMs should be determined to prevent the use of the same drug with different names. The CHMs were listed according to the selected medicinal formulae and organized to establish a database to analyse the frequency of herbs used. An initial statistical analysis of the database was carried out to categorize the herbs according to their functions. The frequencies of occurrence and use were then computed based on the categorization.

Complex Network Analysis

We regarded the constituent herbs for RA therapy as nodes and the connections between two herbs as edges. All medical record data were rationalized into a network of drug nodes and edges using Liquorice software[21] (a complex network analysis tool) and the multiscale backbone algorithm (http://jung.sourceforge.net/). By establishing the aggregation system, the network automatically divides the community structure, and the nodes of the same community are closely connected, which can be considered to indicate the compatibility of common CHMs.[21]

Observation of Changes in Laboratory Indices

The medical records were divided into the granules group and decoction pieces group. The granules group was treated with CHM granules from Anhui Jiren Pharmaceutical Co., Bozhou, China. The decoction piece group was treated with decoction pieces of CHMs from Anhui Bozhou Zhewan Chinese Medicine Co., Bozhou, China. The therapeutic method of CM referred to the "Guidelines for the Diagnosis and Treatment of Rheumatoid Arthritis" from the Rheumatology Branch, Traditional Chinese Society of Chinese Medicine.[18] The following laboratory indicators were collected before and after treatment: indices for assessing therapeutic effects included rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (CCP), immunoglobulin A (IgA), immunoglobulin G (IgG), complement (C3, C4), erythrocyte sedimentation rate (ESR), and C-reactive protein (hs-CRP). Indices for determining function (including hepatic and renal function) included alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and serum creatinine (CREA).

Association Rules

The value of "Yes" for treatment with CHMs was set to 1, and the value of "None" was set to 0. SPSS Clementine 11.1 (Sun Microsystems InC., USA) was used to analyse the drug association rules of the top 15 CHMs. The most common association rule is the Apriori algorithm, which aims to determine the relationship between items in a data set, also known as shopping blue analysis. In our data, each drug was treated as a variable. The formulae were as follows:

$$\text{support}(X\rightarrow Y) = \sigma\frac{X\cup Y}{N}$$

$$\text{confidence}(X\rightarrow Y) = \sigma\frac{X\rightarrow Y}{\sigma(X)}$$

$$\text{lift}(X\rightarrow Y) = \text{confidence}\frac{X\rightarrow Y}{\sigma(Y)}$$

An association rule has the form left-hand side (LHS)→right-hand side (RHS), where LHS and RHS are sets of items and the RHS set is likely to occur whenever the LHS set occurs. Two parameters (support and confidence) are essential in association rule mining. Support has the form Support (A→B)=P(A∪B), which reveals the probability that A and B occur simultaneously. Confidence has the form Confidence (A→B)=P(B|A), which reveals the conditional probability of B given A.[22]

Random Walk Model

This study was referred to Peng's random walk model.[23] The evaluation of the random walk model in the laboratory indices was performed with ORACLE 10g. For the conventional one-dimensional random walk model, a walker moves either up (u(i)= +1) or down (u(i)=–1) one unit length (u) for each step i of walk[2]. For the case of an uncorrelated walk, the direction of each step is independent of the previous steps. For the case of a correlated random walk, the direction of each step is independent of the history ('memory') of the walker. A random walk naturally motivates quantification of this correlation by calculating the 'net displacement' (y) of the walker after l step, which is the sum of the unit steps u(i) for each step i,

$$y(l)=\sum_{i=1}^{l}u(i) \quad (1)$$

An important statistical quantity characterizing any walk[2] is the root mean square fluctuation F(l) about the average of the displacement; F(l) is defined in terms of the difference between the average of the square and the square of the average,

$$F^2(l)=[\overline{\triangle y(l)-\overline{\triangle y(l)}]^2}=[\overline{\triangle y(l)]^2}-\left[\overline{\triangle y(l)}\right]^2, \quad (2a)$$

of a quantity $\triangle y(l)$ defined by $\triangle y(l)= y(l_0+l) - y(l_0)$. (2b)

Operationally, this is equivalent to (1) taking a

set of calipers set for a fixed distance l, (2) moving the beginning point sequentially from l_0=1 to l_0=2 and so on, (3) calculating the quantity $\triangle y(l)$ (and its square) for each value of l_0, and (4) averaging all of the calculated quantities to obtain equation (2a).

$$F^2(l) \sim l^{\alpha} \quad (3)$$

where $\alpha \neq \frac{1}{2}$.

Statistical Analysis

SPSS 23.0 software (USA) was used for statistical analysis. The Chi-square test was used for counting data. A *t* test was employed for data with a normal distribution and the *Wilcoxon* rank sum test for data that did not conform to a normal distribution. The differences between groups were significant if the *P*-value was less than 0.05.

RESULTS

Patient Characteristics

In total, 35,898 prescriptions from 6,829 patients were enrolled in this study. There were 19,617 prescriptions from 3,816 patients in the granules group, including 3,277 (85.9%) female patients and 539 (14.1%) male patients, and 16,281 prescriptions from 3,013 patients in the decoction pieces group, including 2,548 (84.6%) female patients and 465 (15.43%) male patients. Before treatment, there was no statistically significant difference in gender, age or course of treatment between the two groups (*P*>0.05, Appendix 1).

Core Prescription Analysis in Treatment of RA

To further analyse the roles of various herbs and their combinations in RA treatment, we adopted the complex network method and found that the core herbs of the two groups in RA treatment were *Poria Cocos*, *Flos Carthami*, *Salvia Miltiorrhiza*, *Pericarpium Citri Reticulatae*, *Coix Seed*, *Glycyrrhiza uralensis Fisch*, *Herba Taraxaci*, *Semen Pruni Persicae*, *Rhizoma Dioscoreae*, *Radix Clematidis*, *Herba Siegesbeckiae*, *Caulis Spatholobi*, *Fructus Hordei Germinatus*, and *Rhizoma Alismatis* (Figure 1).

Frequency and Analysis of Top 15 Oral Herbs in Treatment of RA

Appendix 2 shows the top 15 oral herbs in the two groups of RA patients. The first 15 CHMs are divided into 4 categories according to their effects, namely, principal function in strengthening Pi (Spleen) and resolving dampness, activating blood and resolving stasis, clearing heat and detoxifying, and dispelling wind/dampness.

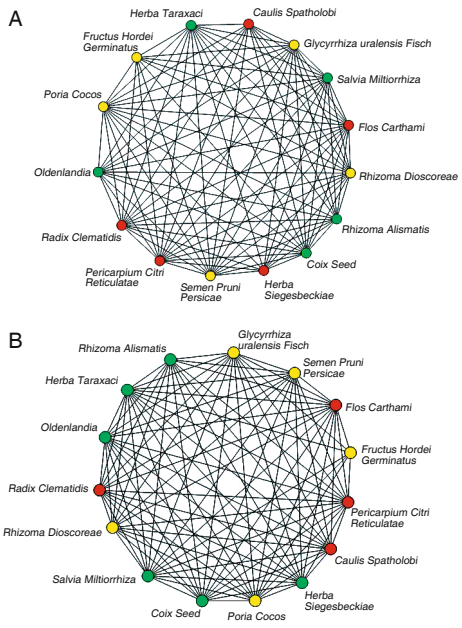

Figure 1. Core Prescription Chart of Two Groups
Notes: (A) granules group; (B) decoction pieces group

Changes in Laboratory Indices in Treatment of RA

No significant difference was detected between the two groups at baseline (*P*>0.05). Comparison of the initial laboratory indices after treatment with the values before treatment revealed that RF, CCP, ESR, hs-CRP, IgA, IgG, C3 and C4 were significantly reduced in the two groups (*P*<0.01). There was no difference between the two groups after treatment (*P*>0.05, Table 1). ALT, AST, BUN and CREA were all in normal ranges after treatment in the two groups (Appendix 3).

Association Rule Analysis of CHMs and Immune-Inflammatory Indices in Treatment of RA

To identify the effective core herbs in the two groups, we performed association rule analysis with single herbs and immune-inflammatory indices. We obtained 6 correlations between the single herbs and indices. There were no correlations between the herbs and RF, IgA and C4. In the pieces group, *Oldenlandia* had a strong correlation with CCP, ESR, hs-CRP, IgA and C3, *Herba Siegesbeckiae* had a strong correlation with IgG. In the decoction pieces group, *Oldenlandia* had a strong correlation with CCP, hs-CRP and C3, *Herba Siegesbeckiae* had a strong correlation with IgG, *Rhizoma Alismatis* had a strong correlation with ESR, and *Caulis Spatholobi* had a strong correlation

Table 1. Changes in Immune-Inflammatory Indices in Two Groups before and after Treatment [M (P25, P75)]

Indices	Decoction pieces group (*n*=3013)		Granules group (*n*=3816)		*P* value (Decoction pieces group *vs.* Granule group after treatment)	Normal range
	Before treatment	After treatment	Before treatment	After treatment		
RF (U/mL)	106.60 (37.8, 241.90)	96.70 (37.70, 218.25)*	106.30 (40.60, 232.28)	96.85 (36.30, 207.60)*	0.511	0–14
hs-CRP (mg/L)	18.00 (4.57, 41.71)	2.29 (0.52, 9.66)*	18.54 (4.54, 43.86)	2.32 (0.48, 10.70)*	0.975	0–5
ESR (mm/h)	42.00 (24.00, 66.00)	27.00 (16.00, 44.00)*	44.00 (25.00, 67.00)	28.00 (16.00, 46.00)*	0.161	2–6
CCP (RU/mL)	205.42 (56.28, 492.27)	199.96 (49.13, 477.64)*	222.40 (73.48, 484.28)	207.97 (59.53, 465.39)*	0.065	<25.0
IgA (g/L)	2.51 (1.90, 3.28)	2.40 (1.84, 3.13)	2.53 (1.91, 3.35)	2.44 (1.86, 3.20)*	0.116	0.7–4.06
IgG (g/L)	13.20 (10.60, 16.11)	12.60 (10.30, 15.28)*	13.33 (10.70, 16.30)	12.80 (10.40, 15.60)*	0.079	6.8–14.5
C3 (mg/dL)	113.80 (99.85, 129.50)	108.20 (95.40, 122.30)*	114.00 (99.40, 130.30)	108.50 (94.90, 122.80)*	0.773	75–135
C4 (mg/dL)	24.80 (20.00, 30.30)	22.60 (17.60, 27.70)*	24.50 (19.43, 30.00)	22.30 (17.40, 27.50)*	0.119	9–36

Note: *$P<0.05$ *vs.* before treatment in the same group

Table 2. Association Rule Analysis of CHMs and Immune-Inflammatory Indices in Two Groups

Indices (LHS,X)	Granules group				Decoction pieces group			
	Herbs (RHS,Y)	Support (X)(%)	Confidence (X=>Y)(%)	Lift	Herbs (RHS,Y)	Support (X)(%)	Confidence (X=>Y)(%)	Lift
CCP ↓	*Oldenlandia*	42.17	41.99	1.09	*Oldenlandia*	49.23	41.03	1.04
ESR ↓	*Oldenlandia*	43.08	66.48	1.06	*rhizoma alismatis*	49.90	73.93	1.14
hs-CRP ↓	*Oldenlandia*	43.27	78.77	1.06	*Oldenlandia*	50.39	78.21	1.02
IgA ↓	*Oldenlandia*	43.54	40.86	1.09	*Caulis Spatholobi*	56.63	40.41	1.07
IgG ↓	*Herba Siegesbeckiae*	41.95	42.40	1.12	*Herba Siegesbeckiae*	57.84	40.10	1.03
C3 ↓	*Oldenlandia*	43.54	44.85	1.11	*Oldenlandia*	30.39	44.19	1.05

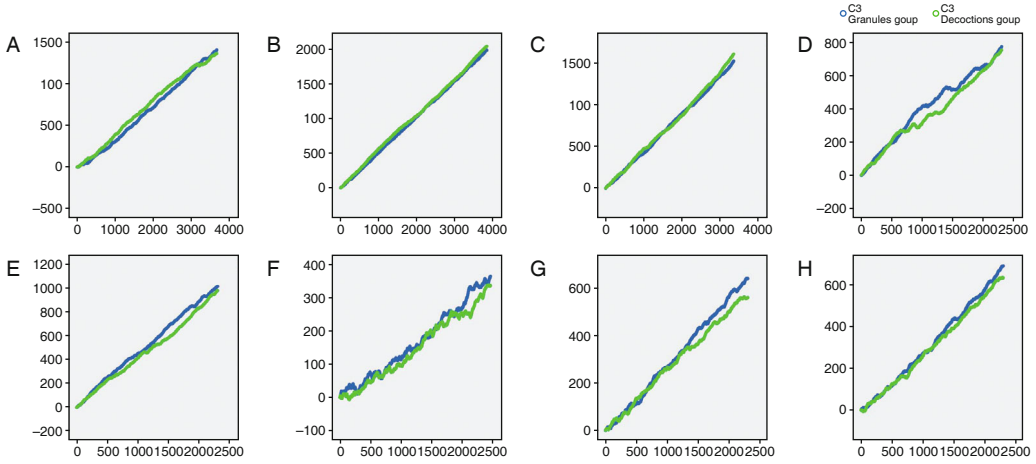

Figure 2. Evaluation Indicators of Immune-Inflammatory Indices Random Walk Model in Two Groups

Notes: Blue indicates granule group; green indicates decoction pieces group. (A) RF; (B) hs-CRP; (C) ESR; (D) C3; (E) C4; (F) CCP; (G) IgA; (H) IgG

with IgA (Table 2).

Evaluation of Immune-Inflammatory Indices with A Random Walk Model in Treatment of RA

We used a random walk model to analyse the influence of different treatments on each index (Figure 2). Appendix 4 shows the model parameters of the two groups. We found that immune-inflammatory indices were improved in the two groups, the therapeutic evaluation can be regarded as a long-term correlation, and the results showed the treatments were effective.

DISCUSSION

CM treatment of RA is a comprehensive multi-level, multi-target and multi-channel treatment method, and it differs from Western medicine, which adopts anti-inflammatory and immunosuppression methods targeting a particular process. CM uses comprehensive

treatment to improve the patient's immune system and enhance the body's ability to fight the disease on its own. At the same time, CM aims to reduce the side effects of Western medicines and improve patients' quality of life and survival. Therefore, these unique advantages have gradually made CM treatment of RA become the focus of scholars worldwide.[24]

The basic characteristics of CM include holistic concepts and syndrome differentiation. Ancient doctors identified herbal treatments for RA and recorded a 'trial' that was then repeatedly tested by successors for hundreds or even thousands of years.[25] CM treatment of RA based on CM theories, such as deficiency of Pi qi, failure of transport in Pi, deficiency of qi and blood, frequent production of phlegm dampness, and excess phlegm dampness, are believed to be the main mechanisms responsible for the development of RA.[26]

Anhui Province is located in the Jianghuai River basin, the warm temperate zone and the subtropical transition area, with a humid monsoon climate. The humid and sultry climate leads to the pathogenic factors wind, dampness and heat, which easily attack the body and are important factors in RA. These pathogenic factors remain in the body and aggravate the deficiency of Pi and depletion of qi-blood. They can also lead to heat toxins and blood stasis. Pi is the organ that produces qi and blood and enhances immunity. Therefore, herbs not only for strengthening Pi and resolving dampness but also for activating the blood and resolving stasis, dispelling wind/dampness, clearing heat and detoxifying are essential for the treatment of RA. Based on association rule mining, herbs such as *Poria Cocos*, *Coix Seed*, *Pericarpium Citri Reticulatae*, *Rhizoma Dioscoreae*, *Glycyrrhiza uralensis Fisch* and *Rhizoma Alismatis* were used to strengthen Pi and resolve dampness. *Herba Taraxaci* and *Oldenlandia* were used for clearing heat and detoxification. *Semen Pruni Persicae*, *Flos Carthami*, *Salvia Miltiorrhiza*, and *Caulis Spatholobi* were used for blood activation and stasis resolution. *Herba Siegesbeckiae* and *Radix Clematidis* were used to dispel wind/dampness in the treatment of RA.

RA is a disease characterized by inflammatory autoantibodies, and RF and CCP are closely related to the occurrence and development of RA.[27] In 2010, ACR/EULAR added CCP detection to the classification criteria for RA and emphasized its role in RA diagnosis along with RF, with acute increases in hs-CRP and ESR as one of the reference conditions.[17] Complement activation and immune complex secretion are involved in the development of RA and are related to the course and severity of the disease.[28,29] In our study, we selected certain laboratory indices, including immunologic indices(RF, CCP, IgA, IgG, C3 and C4) and inflammatory indices (hs-CRP and ESR), to evaluate the effect of decoction pieces and granules of CHMs. These indicators are typically used by doctors to judge the activity of the disease and the clinical effect of the treatment regimen in the clinic. In this study, we found that RF, CCP, IgA, IgG, C3, C4, hs-CRP and ESR were significantly decreased in both groups with insignificant difference between them. Furthermore, ALT, AST, BUN, and CREA were all in the normal ranges after treatment in the two groups; thus, the decoction pieces and granules of CHMs were safe with regard to liver and kidney functions.

To identify associations between herbs and improved key laboratory indices, association rule learning was applied in this study. Based on association rules mining, the confidence of the correlation between *Oldenlandia* and *Herba Siegesbeckiae* and improved CCP, ESR, hs-CRP, IgA and C3 showed a strong association. *Oldenlandia* is a heat-clearing and detoxifying drug that has anti-inflammatory, antitumour and immunomodulatory activities. Treatment of RA with *Oldenlandia* mainly includes the regulation of immunity, downregulation of inflammatory factors, and inhibition of angiogenesis and other effects, with an inhibitory effect on the proliferation of synovial cells *in vitro* in patients with RA.[30,31] *Herba Siegesbeckiae* was used for dispelling wind/dampness and easing joint movement in the treatment of RA in *Newly Revised Materia Medica* (Xin Xiu Ben Cao) during the Song dynasty. It is now recorded in the Pharmacopoeia of the People's Republic of China.[19] The effectiveness of *Herba Siegesbeckiae in* modifying the body's immune function, inhibiting local tissue inflammation and reducing joint local inflammatory reactions has also been proven by recent studies.[32,33]

The baseline data analysis showed no statistically significant difference in the patients' general condition, frequency of CHM use or core prescriptions. The random walk model analysis suggested that changes

in immune-inflammatory indicices (including RF, CCP, ESR, CCP, IgA, IgG, C3 and C4) were correlated with the interventions received by patients in the long term; that is, the treatment measures received by patients affected the changes in immune-inflammatory indicices. On the basis of confirming this long-term association, the ratio of the cumulative fluctuation value of the random walk and the random walk point (we call it the random positive increase rate) can be calculated to measure the efficacy. The improvement in RF, CCP, ESR, CCP, IgA, IgG, C3 and C4 was very similar in the two groups. Therefore, the long-term effect of clinical intervention for chronic diseases can be objectively evaluated by using a random walk model.[34]

The data mining method used in this study has many advantages. Firstly, there are no requirements for data structures. This is very practical for data mining of CHMs because the data structure of most CHMs is not uniform. Secondly, we used a variety of data mining methods for comprehensive analysis, and the reliability of the results is guaranteed. Thirdly, we verified the clinical efficacy of the investigated CHMs to ensure the accuracy of the conclusion. The main aim was to assess the main treatment methods and uses of CHM through data mining technology, which is an effective approach to learning about CM treatment. Our research also has some limitations. We collected only prescription information but not diagnostic information; thus, our conclusions cannot be completely confirmed. We also examined only objective laboratory indicators and not the symptoms and signs of the patients; therefore, clinical efficacy cannot be evaluated. Our study cannot completely rule out the influence of other factors, such as taking other drugs or taking medicine regularly, on the results. Finally, the safety and efficacy of the core prescriptions should be investigated in a future randomized controlled trial.

In conclusion, prescriptions of decoction pieces and granules of these CHMs mainly involved herbs for strengthening Pi and resolving dampness, activating blood and resolving stasis, dispelling wind/dampness, clearing heat and detoxifying. Granules of CHMs can significantly improve immune-inflammatory indices in RA patients, and their efficacy is comparable to that of the decoction pieces group.

Conflict of Interest

The authors declare that there are no conflicts of interest associated with this work.

Author Contributions

Liu J conceived of and designed the study; Huang D wrote the manuscript; Xin L provided technical support for the data mining; Huang D and Xin L extracted and analysed the data; Xie JG provided guidance on the analysis and writing; and Zhu Q, Chen PS, Shen ZB, Meng QH, and Wang HY identified subjects and the collected clinical data.

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