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Xin'an Jianpi Tongbi formulation improves self-perception of patient and reduces platelet-to-lymphocyte ratio in rheumatoid arthritis

A cohort study

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Abstract

The aim of this study was to investigate the clinical value of the platelet-to-lymphocyte ratio (PLR) in rheumatoid arthritis (RA) and the effects of Xin'an Jianpi Tongbi Formulation (XAJPF) [containing Xinfeng Capsule (XFC) and Huangqinqingrechubi Capsule (HQC)] on the Self-Perception of Patient (SPP) – a multidimensional construct encompassing patient-reported outcomes and traditional Chinese medicine (TCM) syndrome evaluations – and laboratory indices in patients with RA. A cohort study design was used, and the study data were obtained from RA patients admitted to the Department of Rheumatology of the First Affiliated Hospital of Anhui University of Traditional Chinese Medicine from February 2024 to March 2025. General information (gender, age, BMI, disease duration, co-morbidities), PLR (platelets/Lymphocyte), laboratory indicators [mean platelet volume (MPV), platelet distribution width (PDW), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), hypersensitive C-reactive protein (hs-CRP), alanine aminotransferase (ALT), aspartate transaminase (AST), serum creatinine (Scr), blood urea nitrogen (BUN)], and SPP indicators were collected through the medical record system. The SPP scales included the MOS item short from health survey (SF-36), visual analogue scale (VAS), Self-Rating Anxiety scale (SAS), Self-Rating Depression scale (SDS), Chinese medicine evidence scores (cold-dampness syndrome [CDS], syndrome of dampness-heat [SDH], syndrome of blood stasis [SBS], and syndrome of dampness stagnancy due to spleen deficiency [SDSSD]). Correlation analysis was used to study the correlation between PLR and laboratory indicators and SPP indicators. Binary Logistics regression models were used to assess the risk and protective factors for SPP changes in RA patients. Mediation analysis was used to investigate the mediating role that PLR acted as in the improvement of SPP by XAJPF. Association rule analysis was used to explore the association of PLR reduction with other laboratory indices and SPP improvement, as well as the association of XAJPF treatment with improvement in SPP indices and laboratory indices in RA patients. Finally, subgroup analyses were used to observe the effects of different exposure levels on SPP indicators and laboratory indicators in RA patients. The results of correlation analysis showed a significant negative correlation between PLR and BP, VT, SF, and MH, and a significant positive correlation with VAS, Chinese patient-eported activity index with rheumatoid arthritis (CPRI-RA), SAS, SDS, SDH, and SDSSD. There were 183 and 185 RA patients in the non-exposed (XAJPF Unused) and exposed groups (XAJPF Used), respectively. Compared with pretreatment, the levels of PF, RP, BP, GH, VT, SF, RE and MH increased and the levels of VAS, CPRI-RA, SAS, SDS, CDS, SDH, SDSSD and SBS decreased in both groups after treatment. The levels of PLR, MPV, PDW, ESR, RF and hs-CRP in laboratory indices were decreased. Liver and kidney function parameters remained within the normal range despite transient, statistically significant increases in alanine aminotransferase (ALT) and aspartate transaminase (AST). In addition, the improvements in PF, RP, BP, VT, RE, MH, VAS, CPRI-RA, SAS, SDS, CDS, SDH, SDSSD, and SBS were significantly greater in the exposed group than in the non-exposed group. Inflammatory markers (hs-CRP, ESR, RF, PLR) improved similarly in both groups. Binary logistic regression analysis showed that use of XAJPF was a protective

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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factor for improvement in GH, VT, SF, RE, and SDSSD, and improvement in PLR was a protective factor for improvement in PF, GH, VT, SDS, and SDSSD. In the mediation analysis, PLR and XAJPF played a partial mediating role in improving GH and VT, and a complete mediating role in improving SDSSD. Association rule analysis showed that PLR reduction was associated with improvement in other laboratory indicators and SPP indicators, and the application of XAJPF was associated with improvement in PF, RP, BP, VT, RE, MH, VAS, CPRI-RA, SAS, SDS, CDS, SDH, SDSSD, SBS, PLR, MPV, PDW, ESR, RF, and hs-CRP Highly correlated. Subgroup analyses showed that there were 36 and 149 RA patients in the high-exposure and low-exposure groups, respectively, and that compared with the pretreatment period, both groups had elevated levels of PF, RP, BP, GH, VT, SF, RE, and MH, and increased levels of VAS, CPRI-RA, SAS, SDS, CDS, SDH, SDSSD, SBS, PLR, MPV, PDW, ESR, and RF, hs-CRP were reduced. In addition to this, exploratory analysis suggested that VT, MH, CPRI-RA, SDS, and SDH improved more significantly in the high-exposure group compared to the low-exposure group after treatment. However, the smaller sample size of the high-exposure group (n = 36) necessitates cautious interpretation of these findings. PLR in RA patients is correlated with SPP and laboratory parameters. XAJPF treatment can significantly improve SPP indicators. Inflammatory markers improved similarly in both XAJPF and control groups. XAJPF may improve VT, GH, and SDSSD partly through reducing PLR. Exploratory analysis suggested that high-exposure regimens might offer additional benefits for VT, MH, CPRI-RA, SDS, and SDH, warranting further confirmation.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BP = body pain, BUN = blood urea nitrogen, CDS = cold-dampness syndrome, CREA = creatinine, DMARDs = disease-modifying anti-rheumatic drugs, ESR = erythrocyte sedimentation rate, GH = general health, HQC = Huangqinqingrechubi Capsule, hs-CRP = hypersensitive C-reactive protein, MH = mental health, MPV = mean platelet volume, NSAIDs = nonsteroidal anti-inflammatory drugs, PDW = platelet distribution width, PF = physical functioning, PLR = platelet-lymphocyte ratio, RA = Rheumatoid Arthritis, RE = role-emotional, RF = rheumatoid factor, RP = role-physical, SAS = self-rating anxiety scale, SBS = syndrome of blood stasis, SDH = syndrome of dampness-heat, SDS = self-rating depression scale, SDSSD = syndrome of dampness stagnancy due to spleen deficiency, SF = social functioning, SF-36 = the MOS item short form health survey, SPP = self-perception of patient, TCM = traditional Chinese medicine, VAS = visual analogue scale, VT = vitality, XAJPF = Xin'an Jianpi Tongbi Formulation, XFC = XinFeng Capsule.

Keywords: cohort study, PLR, rheumatoid arthritis, SPP, Xin'an Jianpi Tongbi Formulation

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic, symmetrical polyarticular synovitis, with a core pathological mechanism of joint and systemic inflammatory responses caused by abnormal activation of the immune system, ultimately leading to irreversible bone erosion and dysfunction.[1] Epidemiological data show that the global prevalence of RA is about 0.5% to 1%, the incidence rate of women is 2 to 3 times higher than that of men, and the high incidence rate is in the age group of 40 to 60 years; the incidence rate in Asia has been on the rise in recent years.[2] RA carries a heavy burden of disease, with patients not only facing persistent pain, joint deformity and disability risk, but also often combined with systemic complications such as cardiovascular disease and osteoporosis, leading to a significant decline in quality of life and increased healthcare expenditures.[3] According to the Global Burden of Disease Study 2021, the disability rate of RA is as high as 30–40 per cent, and the risk of unemployment for patients is more than 2 times higher than that of healthy people.[4] Current Western medical treatment is centered on compliance therapy. The combination of nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids, disease-modifying anti-rheumatic drugs and biologics is effective in controlling inflammation and delaying disease progression, but there are still significant shortcomings: long-term glucocorticosteroids are prone to cause osteoporosis and metabolic abnormalities; the biologics are expensive and some patients are resistant to them or at increased risk of infection; and about 30% of patients do not respond well to the existing treatments. About 30% of patients do not respond well to existing treatments and become refractory to RA.[5]Against this background, Chinese medicine has shown unique potential in the treatment of RA. The principles of "holistic view" and "diagnosis and treatment" of traditional Chinese medicine (TCM) provide new ideas for individualized treatment of RA, which is especially valuable in improving the long-term prognosis of patients.

Xin'an Jianpi Tongbi Formulation (XAJPF) includes Xinfeng Capsule (XFC) and Huangqinqingrechubi Capsule (HQC). Both are Chinese medicinal preparations from the First Affiliated Hospital of Anhui University of Traditional Chinese Medicine. Chinese medicine classifies RA as "BiZheng", and believes that its onset is closely related to the attack of wind, cold and dampness, and the internal cause of spleen deficiency and dampness, as well as the stasis of veins and collaterals. XFC and HQC are developed to address this core disease mechanism. XFC (Anhui Pharmaceutical Production Number: Z20050062; Patent Number: ZL 2013 1 0011369.8), composed of Astragalus membranaceus, Coicis semen, Tripterygium wilfordii, and centipede, is mainly used for the spleen deficiency and dampness, and it can be taken into account for phlegm and blood stasis paralysis. XFC has been incorporated into the guidelines of the Chinese Association of Chinese Medicine Rheumatology (Standard No.: T/CACM 1042-2017).[6] HQC (Anhui Pharmaceutical Production Number: Z20200001; Patent Number: ZL 2011 1 0095718.X). It is composed of 5 Chinese medicines, namely, Scutellaria baicalensis, Gardenia jasminoides, Radix clematidis, Semen coix lacryma, and Peach kernel, and is mainly used for the more severe dampness-heat, which can be taken into account with blood stasis. We have conducted systematic research on the preparation process, quality standard, pharmacodynamics, toxicology, metabolomics and clinical efficacy of XAJPF, confirming its safe and controllable quality and significant therapeutic efficacy.[7,8] Mechanisms have also been explored through animal and cellular experiments, confirming its protective effects on RA patients through various pathways.[9–11]

Self-perception of patient (SPP) is a comprehensive subjective evaluation system formed by patients based on their physiological, psychological and social functioning status, which has attracted a lot of attention in recent years as a key indicator of disease outcome assessment.[12] Its core meaning is to quantify the difference between the individual's expectation and actual experience of health status, which comprehensively reflects the patient's ability to adapt in the 3 dimensions of physical health, psychological health and social adaptation. The greater the discrepancy, the more significant the negative perception of the

patient's state and the lower the quality of life. In this study, the standardized assessment tool recommended by the International Consortium for Health Outcome Measurement (ICHOM) was used.[13] Including the MOS item short from health survey (SF-36),[14] visual analogue scale (VAS),[15] self-rating anxiety scale (SAS),[16] Self-rating depression scale (SDS).[17] This study added the TCM syndrome score, which comprehensively evaluates the integrated sum of 4 syndrome characteristics including cold-dampness syndrome (CDS), syndrome of dampness-heat (SDH), syndrome of blood stasis (SBS), and syndrome of dampness stage due to spleen deficiency (SDSSD). A multidimensional SPP comprehensive evaluation system was constructed. This improved scheme not only strengthens the correlation of disease activity of traditional scales, but also dynamically tracks the effects of different TCM evidence on the overall state of patients, highlighting the advantages of TCM evidence-based treatment. There is a deterioration of SPP in RA patients, as evidenced by increased anxiety and depression and a significant decrease in quality of life, which is significantly correlated with serum inflammatory markers.[18,19] This further demonstrates the necessity of integrating patients' subjective feelings with clinical studies.

Platelet-to-lymphocyte ratio (PLR) is a composite inflammation-related biomarker derived from the routine complete blood count. It quantitatively assesses systemic inflammation and immune imbalance by integrating the counts of platelets (active contributors to inflammation[20]) and lymphocytes (often depleted in chronic inflammatory states[21]). Beyond its convenience, low cost, and high stability, PLR offers a unique pathophysiological rationale for RA. It reflects the interplay between pro-inflammatory drivers and immune dysregulation, core features of RA.[22] Importantly, emerging evidence suggests PLR not only correlates with conventional disease activity measures like DAS-28[23] and is elevated in RA patients compared to controls,[24] but may also provide prognostic value and detect subclinical inflammation even when traditional acute-phase reactants are normal.[25] This makes PLR a promising complementary biomarker for a multidimensional assessment of RA.

Although studies have now begun to explore the value of PLR in RA by linking it to clinical indicators. There are also various studies using SPP indicators such as SF-36, SAS, and SDS to assess the physiological and psychological conditions of patients. However, no study has yet linked PLR with laboratory indicators, SPP, and incorporated TCM evidence points into traditional SPP indicators to explore their correlation with each other. Our study aimed to reveal the potential association between clinical indicators and SPP indicators, and, at the same time, to observe the effects of XAJPF on the above indicators in RA patients.

2. Materials and methods

2.1. Data sources

Clinical data of patients diagnosed with RA were retrieved from the electronic medical record system of the Department of Rheumatology of the First Affiliated Hospital of Anhui University of Traditional Chinese Medicine, Anhui Province, China, The diagnostic criteria for RA refer to the latest classification criteria and scoring system proposed by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) in 2010.[26] That is, RA is diagnosed when at least 1 joint is swollen and painful with synovitis; arthritis caused by other diseases is also excluded, and there are typical radiological manifestations of bone destruction. In addition, RA can also be diagnosed by scoring 4 components, namely, joint involvement, serological indexes, synovitis duration, and acute temporal reactants, with a total score of 6 points or more. Indicators included in the present study included general indicators, laboratory indicators, and SPP indicators. General indicators included: age, gender, BMI (weight/height^2), co-morbidities, duration of disease, and laboratory included: PLR, mean platelet volume (MPV), platelet distribution width (PDW), erythrocyte sedimentation rate (ESR), hs-CRP, rheumatoid factor (RF), ALT, AST, blood urea nitrogen, CERA, UA. SPP indicators included: PF, RP, BP, GH, VT, SF, RE, MH, Chinese patient-eported activity index with rheumatoid arthritis (CPRI-RA), VAS, SAS, SDS, CDS, SDH, SDSSD, SBS.

This study was registered with the International Traditional Medicine Clinical Trial Registry Platform (ITMCTR) on September 20, 2024 (registration number: ITMCTR2024000692). The study followed the Declaration of Helsinki, was approved by the Ethics Committee of the First Affiliated Hospital of Anhui University of Traditional Chinese Medicine (Ethics No. 2024AH-92).

2.2. SPP scale filling and score calculation

Structured interviews, including the TCM syndrome assessment, were conducted by 2 clinical researchers. Prior to the study, both researchers received joint standardized training on the TCM syndrome diagnostic criteria based on the Guiding Principles for Clinical Research of New Chinese Medicines and relevant guidelines.[6,27,28] To ensure consistency, inter-rater reliability was assessed on a subset of 30 patients. The Cohen Kappa for primary syndrome diagnosis was 0.78, and the intraclass correlation coefficient (ICC) for syndrome total scores was 0.82, indicating substantial to excellent agreement. The interviews were conducted on the day of admission and discharge, with the informed consent of the patient or his/her legal guardian. The researcher explained each item of the scale in layman's terms and instructed the participants to select the corresponding option based on their current experience. In order to ensure the quality of data collection, the use of technical terms was strictly avoided during the assessment process, and life analogies were used to assist understanding (e.g., "The pain level can be compared to the classification of daily headache feelings"). After completion of the questionnaire, a 2-person simultaneous review process was carried out, and outliers and missing items were immediately replaced retrospectively. Finally, the results of the survey were entered into the data processing system, which was pre-programmed to automatically generate various scores, avoiding manual calculations that could lead to incorrect estimates.

2.3. Specific content of SPP scale

2.3.1. SF-36. The SF-36 contains 36 entries, Includes 8 dimensions: GH, PF, RE, MH, RP, BP, SF, VT. Total score for the 8 dimensions is the total score of this table.

2.3.2. VAS. The VAS is a standardized subjective instrument based on the principle of visual-to-numerical conversion, using a 10 cm horizontal scale anchored at each end by a score of 0 for "no pain" and 10 for "severe intolerable pain." Two standardized procedures were used: firstly, subjects were asked to mark the position of the vertical line segments on the scale according to their immediate pain experience; secondly, the researcher guided the patient to perform the quantification through a structured question (e.g., 'Which level of pain does your current pain level most closely correspond to that described by the scale?) The patient was guided to quantify his/her assessment. Based on the quantitative results, pain intensity was classified into 4 clinical thresholds: asymptomatic (0), mild (1–3), moderate (4–6) and severe (7–10).

2.3.3. CPRI-RA. CPRI-RA is a Chinese patient-reported clinical outcome scale for RA, which contains a total of 11 items. Each item was scored 0, 1, 2 and 3 points from no symptoms to aggravation of symptoms. Total score calculation

formula = 1.43x item 1 + 0.93x item 2 + 0.40x item 3 + 1.09x Item 4 + 0.11x item 5 + 0.18x item 6 + 0.24x item 7 + 0.04x item 8 + 1.17x item 9 + 0.19x item 10 + 0.02x item 11.

2.3.4. SAS and SDS. Both the SAS and SDS contain 20 entries, each describing 20 states associated with anxiety/depression. Of the 20 entries on the SAS scale, 15 entries used negative statements on a scale of 1 to 4, and the remaining 5 entries used affirmative statements on a scale of 4 to 1. There were 10 affirmative and 10 negative statements in the SDS. The scale total is the sum of the scores of the 20 entries with a cutoff value of 50. The degree of anxiety/depression can be classified into the following categories based on the score: 50 to 59: mild anxiety/mild depression; 60 to 69: moderate anxiety/moderate depression; 70 and above: severe anxiety/depression.

2.3.5. Syndrome of TCM scale. The TCM evidence scale quantifies and grades TCM symptoms and signs based on established diagnostic criteria from Chinese national guidelines, transforming subjective TCM evidence into quantifiable data.[6,27,28] The scoring criteria for the syndromes (CDS, SDH, SDSSD, SBS) used in this study have been applied in previous clinical studies of RA.[29–31] In practical application, we assigned different weights to the primary and secondary symptoms/signs as per the standard criteria, and assessed the syndrome severity by calculating the total score. The higher the score, the more severe the patient's symptoms within that specific syndrome pattern.

2.4. Definition of exposure

In this study, we defined the use of XAJPF as the exposed group, where the use of XFC only was considered as low exposure, the use of both XFC and HQC was considered as high exposure, and the nonuse of any of the above groups of pCms was defined as non-exposed group.

2.5. Correlation analysis

A nonparametric measure of rank correlation, the Spearman correlation, was employed to study the statistical dependence between the rankings of 2 variables. The Spearman correlation coefficient between 2 variables is equivalent to the Pearson correlation coefficient between the rank values of those variables, assessing monotonic relationships (whether linear or not). In this study, Spearman correlation analysis was used to explore the correlation between PLR, immune inflammation indicators and SPP indicators.

2.6. Logistic regression analysis

Logistic regression models were used to predict protective factors and risk factors for SPP indicators. Models were adjusted for age, gender, disease duration, and baseline values of the respective outcome variable to control for potential confounding. In binary logistic regression analyses, a P-value <.05 indicated a statistically significant relationship. An odds ratio (OR) > 1 suggests a risk factor, and an OR < 1 suggests a protective factor. The specific formula is as follows[32]:

$$\log itP = \ln\left[\frac{P}{1-P}\right] = a + b_1 x_1 + b_2 x_2 + \cdots + b_n x_n$$

$$OR = \frac{[P_1/(1-P_1)]}{[P_0/(1-P_0)]}$$

Where $P_1/(1 - P_1)$ is the ratio of the exposed group and $P_0/(1 - P_0)$ is the ratio of the non-exposed group.

2.7. Mediation analysis

Mediation analysis is a statistical method used to study how the independent variable (X) affects the dependent variable (Y) through one or more intermediate variables (called mediators, M) (Fig. 1). It helps the researcher to understand the underlying mechanism or process by which X affects Y. To test whether PLR plays a role in XAJPF-mediated SPP outcomes, causal mediator analyses were conducted according to the method proposed by VanderWeele,[33] adjusting for age, gender, and disease duration.

2.8. Association rule analysis

Association rule analysis was performed using the Apriori algorithm in IBM SPSS Modeler 18.0 software. The minimum Support of the association is set to 20%, the minimum Confidence is set to 60%, and the Lift is >1. Support and confidence thresholds were set based on common practices in clinical association rule mining to identify sufficiently frequent and strong rules, while lift > 1 indicates associations greater than chance. In the analysis of the association rule between PLR and other laboratory indicators and SPP indicators, the improvement of PLR and other laboratory indicators and SPP indicators is denoted as T, and the non-improvement is denoted as F. In the analysis of the association rule between the use of XAJPF and the improvement of laboratory indicators and SPP ind icators, the improvement of JQP use or SPP indicators is assigned as T, and the improvement of JQP use or SPP indicators is assigned as F. In the correlation rule analysis of XAJPF usage and improvement of laboratory indicators and SPP indicators, the use of XAJPF and improvement of indicators is recorded as T, and the nonuse of XAJPF and non-improvement of indicators is recorded as F. The formula of Apriori algorithm in the correlation rule is as follows[34]:

$$support\,(X \to Y) = \sigma\frac{(X \bigcup Y)}{N}$$

$$confidence\ \ (X \to Y) = \sigma\frac{(X \bigcup Y)}{\sigma\,(X)}$$

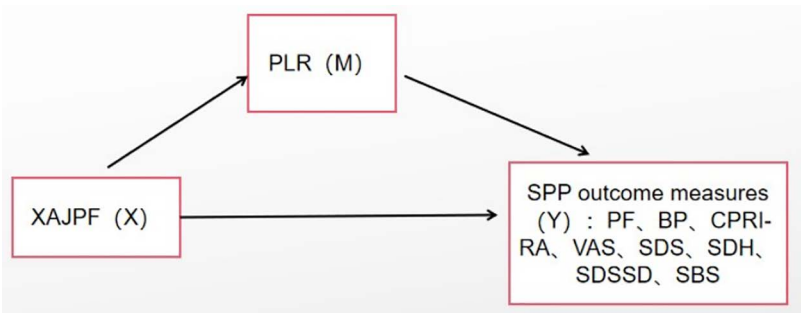

Figure 1. Mediation analysis effect plots.

$$lift\,(X \to Y) = confidence\frac{(X \to Y)}{\sigma\,(Y)}$$

2.9. Statistical analysis

IBM SPSS statistics 23 software was used for statistical analysis. For data description, mean ± standard deviation was used for normal distribution and quartiles were used for non-normal distribution. Two independent sample t test was used to compare the measurement data between the 2 groups, and the Kruskal–Wallis nonparametric test was used for any group of data that did not conform to the normal distribution. For intra-group comparison of measurement data, paired t test was used for the difference in accordance with normal distribution, and Wilcoxon signed average rank test was used for the difference in non-normal distribution. Chi-square test was used to compare count data. GraphPad Prism 8.0.2 software was used for image delineation. $P < .05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics of RA patients

As shown in Table 1. A total of 368 patients with RA were included in this study (median age: 59 years [IQR 52–70]; median disease duration 9 years (3–19 years), median BMI 22.3 kg/m^2 (19.9–24.5 kg/m^2). Co-morbidities included hypertension (25.3%), osteoporosis (32.4%), cerebral infarction (15.2%), osteoarthritis (20.8%), Sjogren syndrome (9.5%), and chronic gastritis (11.3%). The SF-36 quality of life assessment revealed significant impairment in several domains: PF (35 [25–50]), RP (25 [0–50]), BP (41 [31–62]), GH (30 [25–38]), VT (45 [40–55]), SF (50 [38–75]), RE (33 [33–67]) and MH (52 [40–60]). Psychological assessment revealed elevated anxiety [SAS: 51 (46–55) points] and depression [SDS: 59 (53–64) points], with a median pain intensity of 4.25 (VAS: 2.00–5.80) and a median CPRI-RA score of 7.23 (4.02–9.99). The main TCM patterns were CDS[10.0 (9.0–17.0)], SDH[11.0 (7.0–15.0)], SDSSD[9.0 (6.0–12.0)] and SBS[5.00 (4.00–7.00)]. Laboratory indices suggested systemic inflammation (ESR: 24 mm/h [11–43]; RF: 99 IU/mL [34–235]; hs-CRP: 6 mg/L[2–23]), PLR:165 [119–229]; MPV: 10.50 (9.89–11.20); PDW:11.70 [10.40–13.33]). These findings characterize female RA patients with long-term disease, multimorbidity, reduced quality of life, active inflammation and a unique TCM evidence pattern.

Table 1

Baseline data of RA patients.

Characteristics	Indicators	RA (n = 368)
Baseline characteristics	Age	59 (52, 70)
	BMI	22.3 (19.9, 24.5)
	Course of disease	9 (3, 19)
	Gender	
	Female	310 (84.2%)
	Male	58 (15.8%)
	Comorbidity	260 (70.7%)
	hypertension	93 (25.3%)
	Cerebral infarction	56 (15.2%)
	Osteoarthritis	76 (20.8%)
	Sjogren syndrome	35 (9.5%)
	Osteoporosis	119 (32.4%)
	Chronic gastritis	42 (11.4%)
SF-36	PF	35 (25, 50)
	RP	25 (0, 50)
	BP	41 (31, 62)
	GH	30 (25, 38)
	VT	45 (40, 55)
	SF	50 (38, 75)
	RE	33 (33, 67)
	MH	52 (40, 60)
	VAS	4.25 (2.00, 5.80)
	CPRI-RA	7.23 (4.02, 9.99)
	SAS	51 (46, 55)
	SDS	59 (53, 64)
TCM syndrome score	CDS	10.0 (9.0, 17.0)
	SDH	11.0 (7.0, 15.0)
	SDSSD	9.0 (6.0, 12.0)
	SBS	5.00 (4.00, 7.00)
Laboratory indicators	PLR	165 (119, 229)
	MPV	10.50 (9.89, 11.20)
	PDW	11.70 (10.40, 13.33)
	ESR	24 (11, 43)
	RF	99 (34, 235)
	hs-CRP	6 (2, 23)

BMI = body mass index, BP = body pain, CDS = cold-dampness syndrome, ESR = erythrocyte sedimentation rate, GH = general health, hs-CRP = hypersensitive C-reactive protein, MH = mental health, MPV = mean platelet volume, PDW = platelet distribution width, PF = physical functioning, PLR = platelet-lymphocyte ratio, RE = role-emotional, RF = rheumatoid factor, RP = role-physical, SAS = self-rating anxiety scale, SBS = syndrome of blood stasis, SDH = syndrome of dampness-heat, SDS = self-rating depression scale, SDSSD = syndrome of dampness stagnancy due to spleen deficiency, SF = social functioning, SF-36 = the MOS item short form health survey, TCM = traditional Chinese medicine, VAS = visual analogue scale, VT = vitality.

3.2. Correlation analysis of PLR with SPP and laboratory indicators with SPP

Correlation analyses revealed different patterns between clinical parameters and SPP, especially with respect to the PLR. Strong associations were found between SF-36 and inflammatory markers: the BP was strongly correlated with SDH ($R = 0.84$), CPRI-RA ($R = 0.81$) and hs-CRP ($R = 0.54$), whereas PF was moderately correlated with ESR ($R = 0.58$) and RF ($R = 0.55$). In psychological scales, SAS ($R = 0.78$) and SDS ($R = 0.87$) were significantly correlated with SF impairment, while SDS was significantly correlated with CPRI-RA: ($R = 0.70$) SDSSD: ($R = 0.93$). TCM evidence showed different correlations: the CDS was significantly correlated with inflammatory indicators (ESR: $R = 0.58$; RF: $R = 0.41$), whereas the SBS correlated more strongly with VAS ($R = 0.66$) than with laboratory parameters. Notably, PLR showed a unique pattern of correlation, exhibiting weak but recognizable correlations with systemic inflammation (ESR: $R = 0.30$; hs-CRP: $R = 0.27$) as well as minimal associations with CPRI-RA ($R = 0.15$) or functional outcome (SF-36 domains: $R = 0.06$–0.15), whereas there was a strong intrinsic associations (MPV-PDW: $R = 0.95$) (Fig. 2). These results underline the potential of PLR as an independent marker of inflammation and highlight the complex interdependence between inflammatory status and patient perceptual manifestations, providing avenues for multidimensional assessment of RA.

3.3. Effects of exposure on experimental indices and SPP outcomes

The comparative analysis of treatment outcomes between the exposed (n = 185) and non-exposed (n = 183) groups revealed significant improvements across multiple domains. In the exposed group, all SF-36 subscales demonstrated marked posttreatment enhancements (all P1 < .01), with particularly notable increases in PF, RP, and BP. Similarly, the non-exposed group showed significant within-group improvements in most SF-36 subscales, though posttreatment between-group comparisons (P3) indicated superior outcomes in the exposed group for PF, RP, BP, VT, RE, MH, and VAS (all P3 < .01). However, GH: (P3 = .251) and SF (P3 = .537) did not differ significantly posttreatment. For instance, the exposed group achieved significantly lower posttreatment pain scores (VAS and CPRI-RA, P3 < .01). Psychological and TCM syndrome scores were significantly improved. The SAS and SDS scores of the exposure group decreased more significantly after treatment than before treatment ($P < .01$), and the CDS, SDH, SDSSD and SBS scores decreased more, and all $P < .01$Laboratory indicators

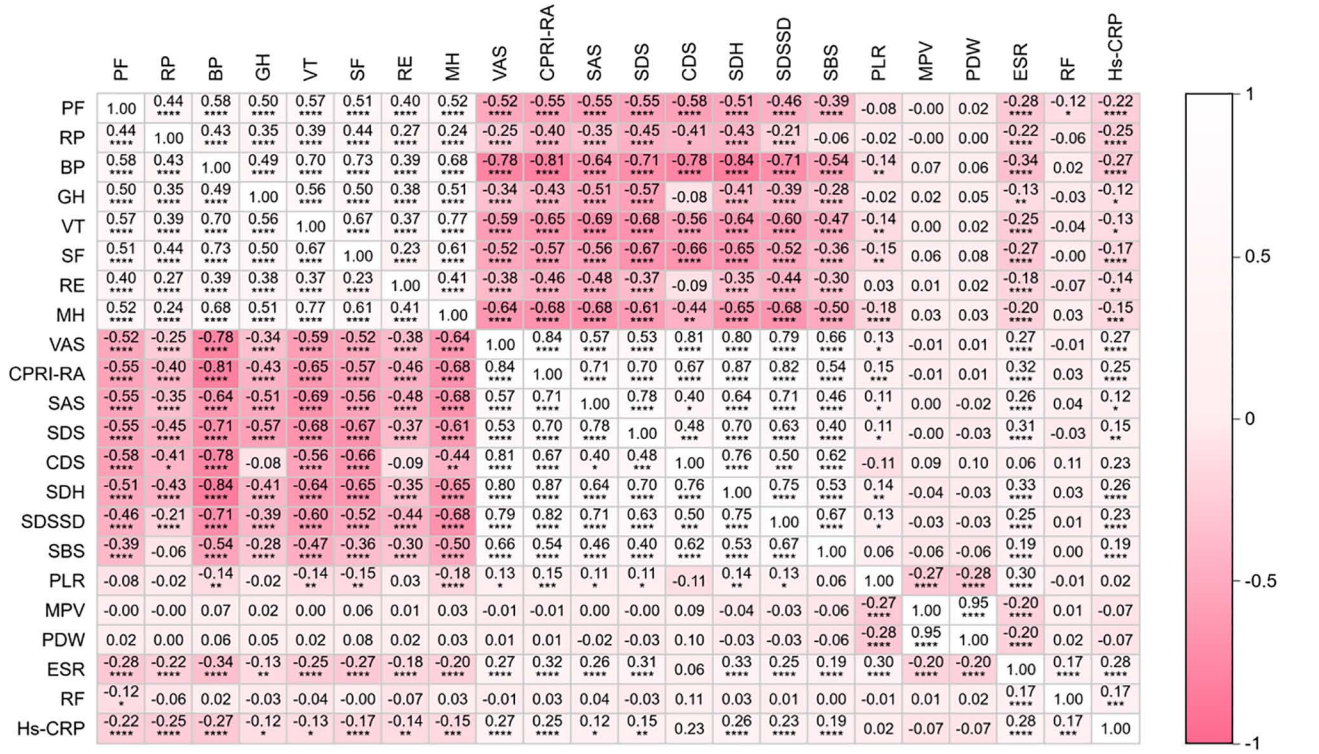

Figure 2. Correlation analysis between laboratory indicators and outcome indicators of SPP. * $P < .05$; ** $P < .01$; *** $P < .05$; **** $P < .05$. SPP = self-perception of patient.

PLR, hs-CRP, ESR, and RF were improved after exposure and non-exposure treatment, but their results were not statistically significant. And liver and kidney function parameters remained within the normal range before and after treatment, despite statistically significant increases in ALT and AST (Table 2). These results suggest that the intervention elicited robust within-group improvements in both cohorts, but the exposed group achieved significantly greater benefits in physical function, pain relief, and psychological outcomes, underscoring a potential treatment-specific effect.

3.4. Logistic regression analysis: Protective factors for improvement of SPP

Multivariable logistic regression analyses identified key predictors of improvement of SPP. XAJPF intervention use significantly increased the likelihood of improvement in GH (aOR = 4.17, $P < .001$), VT (aOR = 6.26, $P < .001$), SF (aOR = 3.93, $P < .001$), RE (aOR = 3.49, $P < .001$), and SDS (aOR = 7.31, $P < .001$). PLR improvement independently predicted better PF (aOR = 1.59, $P = .037$), VT (aOR = 2.81, $P < .001$), and reduced SDS (aOR = 2.81, $P < .001$). Inflammatory markers showed domain-specific effects: ESR improvement was associated with reduced BP (aOR = 2.42, $P = .019$) and better SF (aOR = 1.92, $P = .024$), while hs-CRP improvement predicted lower pain intensity (VAS: aOR = 3.46, $P = .019$) and improved SDH (aOR = 3.60, $P = .002$). For CPRI-RA, failure to improve ESR/hs-CRP substantially reduced improvement likelihood (ESR: aOR = 0.12, $P < .001$; hs-CRP: aOR = 0.28, $P = .020$). MPV and RF showed no significant associations with any outcome after adjustment (Fig. 3).

3.5. Mediating factors for XAJPF to improve SPP

As shown in Table 3, mediation analysis showed that XAJPF intervention had a significant indirect effect on some indicators of SPP through the PLR pathway. For GH, a positive indirect effect was observed (GH: ab = 0.12, 95% BootCI [0.07, 0.18], *p* < measures). The direct effect was significant, suggesting a partial mediating effect. In contrast, VT and SDSSD had significant negative indirect effects (VT: ab = –0.13, 95% BootCI [-0.22, –0.04], *p* =.009; SDSSD: ab = 0.16, 95% BootCI [0.24, 0.09], * * (p.001). VT played a partial mediating role through the continuous direct effect (c "= –0.47), For SDSSD, the direct effect of XAJPF was not statistically significant (c" = –0.24, $P = .12$), suggesting that the effect of XAJPF on alleviating SDSSD may operate primarily through reducing PLR. These findings together demonstrate the role of PLR as an important regulator, and a complete regulatory role is observed in SDSSD.

3.6. Association rule analysis between PLR and laboratory indicators, SPP and the improvement effect of XAJPF

The association rule mining revealed robust linkages between reduced PLR and improvements in laboratory parameters, symptom scores, and functional outcomes. As can be seen from Table 4 and Figure 4, with a consistent support of 61.7%, PLR demonstrated strong directional associations (lift > 1) across 16 clinical variables. Notably, PLR exhibited the highest confidence for alleviating pain severity (VAS: 96.0% confidence, lift = 1.01) and reducing disease activity (CPRI-RA: 95.6% confidence, lift = 1.01). Significant correlations were also observed with inflammatory markers, including ESR (79.7% confidence, lift = 1.10) and hs-CRP (74.0%confidence, lift = 1.04). Concurrently, PLR was associated with enhanced MH (81.1% confidence) and PF (80.6% confidence), alongside reductions in psychological distress (SAS: 88.5% confidence; SDS:88.5% confidence) (Table 4 and Fig. 4).

Another association rule tapped the degree of association between the XAJPF intervention and improvements in laboratory indicators and SPP indicators. High confidence intervals (CONFIDENCE ≥ 90%) were associated with the core

Table 2

Changes of indexes before and after exposure and non-exposure treatment.

	Exposure (XAJPF, n = 185)			Non-exposed (non-XAJPF, n = 183)			
	Pretreatment	Posttreatment	P1	Pretreatment	Posttreatment	P2	P3
SF-36							
PF	30.00 (20.00, 35.00)	55.00 (40.00, 65.00)	<.01	35.00 (25.00, 45.00)	45 (30, 45)	<.01	<.01
RP	25.00 (0.00, 25.00)	50.00 (25.00, 75.00)	<.01	25.00 (0.00, 25.00)	25 (25, 50)	<.01	<.05
BP	31.00 (22.00, 41.00)	64.00 (52.00, 74.00)	<.01	31.00 (31.00, 41.00)	52 (52, 62)	<.01	<.01
GH	30.00 (20.00, 35.00)	35.00 (25.00, 42.00)	<.01	25.00 (20.00, 35.00)	35 (25, 40)	<.01	.251
VT	40.00 (30.00, 45.00)	60.00 (50.00, 70.00)	<.01	40.00 (35.00, 45.00)	50 (45, 60)	<.01	<.01
SF	50.00 (25.00, 50.00)	75.00 (56.00, 75.00)	<.01	50.00 (50.00, 62.50)	75 (50, 75)	<.01	.537
RE	33.33 (33.33, 33.33)	66.67 (66.67, 100)	<.01	33.00 (0.00, 66.00)	67 (33, 67)	<.01	<.01
MH	40.00 (36.00, 52.00)	64.00 (56.00, 72.00)	<.01	44.00 (36.00, 52.00)	56 (48, 64)	<.01	<.01
VAS	5.70 (5.20, 6.50)	1.70 (1.40, 2.30)	<.01	5.50 (5.00, 6.20)	2 (1.6, 2.5)	<.01	<.01
CPRI-RA	9.95 (8.48, 10.95)	3.02 (2.57, 4.18)	<.01	9.71 (7.96, 10.83)	4.2 (3.1, 5.8)	<.01	<.01
SAS	53.75 (51.25, 57.5)	42.50 (38.75, 45.00)	<.01	53.75 (51.25, 56.25)	47.5 (43.75, 52.5)	<.01	<.01
SDS	61.25 (58.75, 67.5)	50.00 (46.25, 55.00)	<.01	60.00 (56.25, 63.75)	53.75 (48.75, 58.75)	<.01	<.01
TCM syndrome score							
CDS	16.5 (13.00, 18.00)	5.00 (4.00, 7.00)	<.01	16.00 (13.00, 17.00)	9.00 (7.00, 10.00)	<.01	<.01
SDH	15.00 (13.00, 18.00)	5.00 (4.00, 7.00)	<.01	13.00 (11.00, 16.00)	7.00 (5.00, 9.00)	<.01	<.01
SDSSD	12.00 (10.00, 16.00)	5.00 (3.00, 7.00)	<.01	11.00 (8.00, 14)	6.00 (5.00, 8.00)	<.01	<.01
SBS	7.00 (5.00, 8.00)	3.00 (2.00, 4.00)	<.01	7.00 (5.00, 8.00)	4.00 (3.00, 5.00)	<.01	<.01
PLR	173.21 (123.92, 247.39)	152.42 (115.22, 203.76)	<.01	179.57 (137.81, 236.98)	159..34 (116.27, 214.55)	<.01	.354
Laboratory indicators							
MPV	10.45 (9.80, 11.40)	10.40 (9.70, 11.10)	<.05	10.50 (9.90, 11.10)	10.10 (9.40, 10.20)	<.05	.542
PDW	11.65 (10.40, 13.60)	11.60 (10.40, 13.20)	<.05	11.85 (10.50, 13.35)	11.70 (10.40, 13.10)	<.05	.875
ESR	31.50 (16.00, 54.50)	17.50 (8.00, 35.00)	<.01	34.00 (16.00, 52.00)	18.00 (8.00, 35.00)	<.01	.893
RF	109.25 (39.55, 235.80)	98.80 (32.40, 230.00)	<.01	145.90 (41.60, 292.50)	100.20 (35.70, 234.60)	<.01	.061
hs-CRP	14.67 (2.68, 35.66)	1.94 (0.84, 7.80)	<.01	14.86 (3.45, 36.47)	2.89 (0.91, 11.21)	<.01	.371
Security indicators							
ALT (U/L)	13.70 (10.05, 18.60)	13.75 (12.20, 25.30)	<.01	15.10 (10.90, 22.75)	18.50 (12.30, 27.30)	<.01	.372
AST (U/L)	18.35 (15.65, 21.85)	19.55 (16.40, 23.90)	<.01	18.90 (15.30, 25.55)	19.40 (15.00, 25.40)	.687	.587
BUN	4.90 (3.98, 6.03)	5.06 (4.12, 6.30)	.285	4.88 (3.85, 6.21)	4.87 (3.87, 6.16)	.725	.419
CERA	51.95 (45.10, 63.65)	53.85 (45.40, 64.00)	.988	53.90 (46.50, 63.40)	51.80 (46.10, 59.60)	<.01	.567

P1: Exposure: pretreatment vs posttreatment; P2: non-exposed: pretreatment vs posttreatment; P3: Exposure posttreatment vs non-exposed posttreatment.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BP = body pain, BUN = blood urea nitrogen, CDS = cold-dampness syndrome, CREA = creatinine, ESR = erythrocyte sedimentation rate, GH = general health, hs-CRP = hypersensitive C-reactive protein, MH = mental health, MPV = mean platelet volume, PDW = platelet distribution width, PF = physical functioning, PLR = Platelet-lymphocyte ratio, RE = role-emotional, RF = rheumatoid factor, RP = role-physical, SAS = self-rating anxiety scale, SBS = syndrome of blood stasis, SDH = syndrome of dampness-heat, SDS = self-rating depression scale, SDSSD = syndrome of dampness stagnancy due to spleen deficiency, SF = social functioning, SF-36 = the MOS item short form health survey, TCM = traditional Chinese medicine, VAS = visual analogue scale, VT = vitality.

treatment outcomes of pain reduction (VAS: 94.59%), control of disease activity (CPRI-RA: 94.59%), and Chinese medicine evidence remission (SDSSD: 94.05%; SDH: 90.81%). Psychological improvement showed the same mechanistic strength, with reductions in anxiety (SAS: 91.35%) and depression (SDS: 91.35%) showing the same level of confidence. Functional recovery showed moderate but clinically meaningful associations including VT enhancement (VT: 90.27%, lift = 1.12), SF improvement (SF: 88.11%, lift = 1.16) and RE recovery (RE: 79.46%, lift = 1.20). Systemic inflammatory modulation was demonstrated by reduced ESR (78.38%), hs-CRP suppression (75.68%) and PLR reduction (61.62%). Notably, the reduction in autoimmune markers (RF: 61.08%) paralleled patient-reported overall health improvement (GH: 61.62%), suggesting an overall treatment effect. The above information can be found in Table 5 and Figure 5. This suggests that XAJPF is a multifactorial intervention in the management of RA targeting the inflammatory cascade response, functional recovery and psychosomatic balance.

3.7. Improvement in indicators with different exposure interventions

In Table 6, stratified analyses of the low-exposure (n = 149) and high-exposure (n = 36) interventions revealed different treatment effects in the functional, psychological, and biomarker domains. Both groups showed significant improvements in the SF-36 subscales (P1 and P2 < .01 for PF, RP, BP, VT, RE, and MH) and in TCM symptoms scores (e.g., CDS: low exposure $\Delta = 11.00$, P1 < .01). However, posttreatment between-group comparisons (P3) showed that the high-exposure group showed significant improvements in VT, MH and CPRI-RA were superior to those in the high-exposure group (Fig. 6). The high-exposure group had greater decreases in SDS, SDH (P3 < .05). Notably, inflammatory indices showed comparable decreases in both groups (hs-CRP: high-exposure $\Delta = 14.15$ vs low-exposure $\Delta = 12.76$, P3 = .058; ESR: P3 = .961), whereas no significant changes were observed before and after treatment for PLR, MPV, and PDW (P3 > .05). Although the smaller sample size of the high-dose exposure group may have limited statistical efficacy, its consistent superiority in multidimensional outcomes (especially psychological and functional indicators) suggests a dose–response relationship. These findings underscore the potential benefits of intensive intervention programs, while highlighting the need for larger trials to confirm scalability and address nonsignificant between-group differences in VAS and SF.

4. Discussion

RA is a chronic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction and systemic complications leading to severe disability and reduced quality of life.[35] In addition to its pathophysiological manifestations, RA

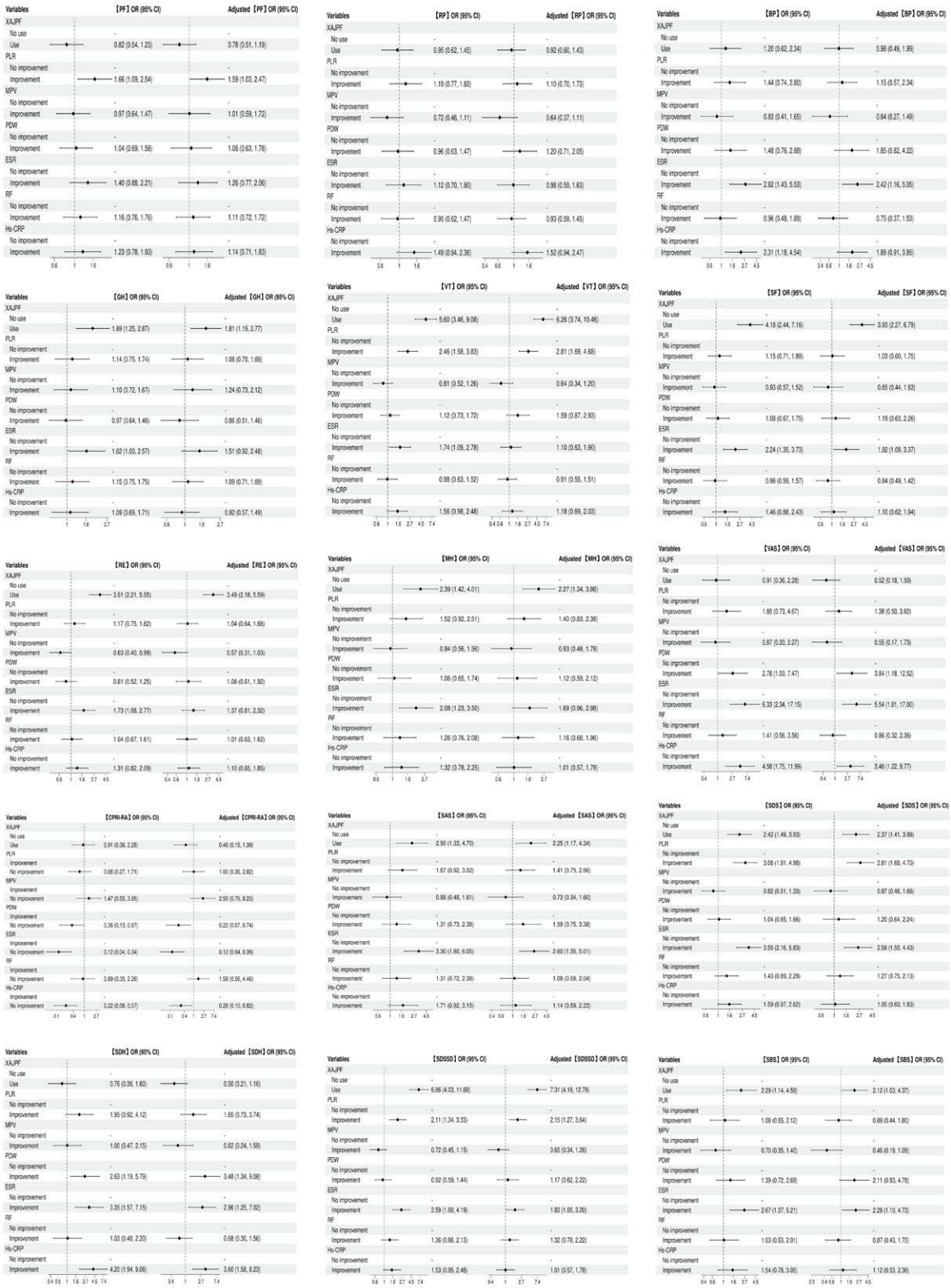

Figure 3. Logistic regression analysis of SPP indicators. SPP = self-perception of patient.

profoundly affects SPP, e.g., the SF-36 Health Survey captures impairment of PF, role limitations due to RP and BP, which are strongly correlated with RA disease activity.[36] The CPRI-RA is a culturally adapted tool that further quantifies the burden of the disease by including symptom severity, functional limitations, and treatment-related distress, further quantifies disease burden. RA patients treated with TCM show the joint improvement of DAS-28 and CPRI-RA, which provides an objective and quantitative basis for the evaluation of the efficacy of TCM on RA. Psychological distress, as measured by the SAS and the SDS, exacerbates RA-associated fatigue and functional decline, creating a bidirectional cycle between inflammation and mental

Table 3

Mediating factors for XAJPF to improve SPP.

X–M–Y	c Total effect	a	b	a*b Intermediary effect value	a*b (Boot SE)	a*b (*z* value)	a*b (*P* value)	a*b (95% BootCI)	c' Direct effect	Inspection conclusion
XAJPF–PLR–GH	0.67	−0.32	−0.38	0.12	0.03	4	<.001	[0.07, 0.18]	0.55	Partial mediation
XAJPF–PLR–VT	−0.6	−0.25	0.5	−0.13	0.05	−2.6	.009	[−0.22, −0.04]	−0.47	Partial mediation
XAJPF–PLR–SDSSD	−0.4	−0.35	0.45	−0.16	0.04	−4	<.001	[−0.24, −0.09]	−0.24	Complete mediation

GH = general health, PLR = Platelet-lymphocyte ratio, SDSSD = syndrome of dampness stagnancy due to spleen deficiency, SPP = self-perception of patient, VT = vitality, XAJPF = Xin'an Jianpi Tongbi Formulation.

Table 4

Association rules between PLR reduction and other laboratory indicators, SPP.

Antecedent	Consequent	Support (%)	Confidence (%)	Lift
PLR↓				
SF-36	PF↑	61.68478261	80.61674009	1.01
	RE↑	61.68478261	67.40088106	1.02
	MH↑	61.68478261	81.05726872	1.04
	RP↑	61.68478261	64.31718062	1.02
	BP↑	61.68478261	90.74889868	1.02
	SF↑	61.68478261	77.09251101	1.01
	VT↑	61.68478261	82.37885463	1.02
	VAS↓	61.68478261	96.03524229	1.01
	CPRI-RA↓	61.68478261	95.59471366	1.01
	SAS↓	61.68478261	88.54625551	1.03
	SDS↓	61.68478261	88.54625551	1.02
TCM syndrome score	SDH↓	61.68478261	93.83259912	1.02
	SDSSD↓	61.68478261	93.83259912	1.01
Laboratory indicators	MPV↓	61.68478261	77.53303965	1.24
	ESR↓	61.68478261	79.73568282	1.10
	hs-CRP↓	61.68478261	74.00881057	1.04

BP = body pain, ESR = erythrocyte sedimentation rate, hs-CRP = hypersensitive C-reactive protein, MH = mental health, MPV = mean platelet volume, PF = physical functioning, PLR = platelet-lymphocyte ratio, RE = role-emotional, RP = role-physical, SAS = self-rating anxiety scale, SDH = syndrome of dampness-heat, SDS = self-rating depression scale, SDSSD = syndrome of dampness stagnancy due to spleen deficiency, SF = social functioning, SF-36 = the MOS item short form health survey, SPP = self-perception of patient, TCM = traditional Chinese medicine, VAS = visual analogue scale, VT = vitality.

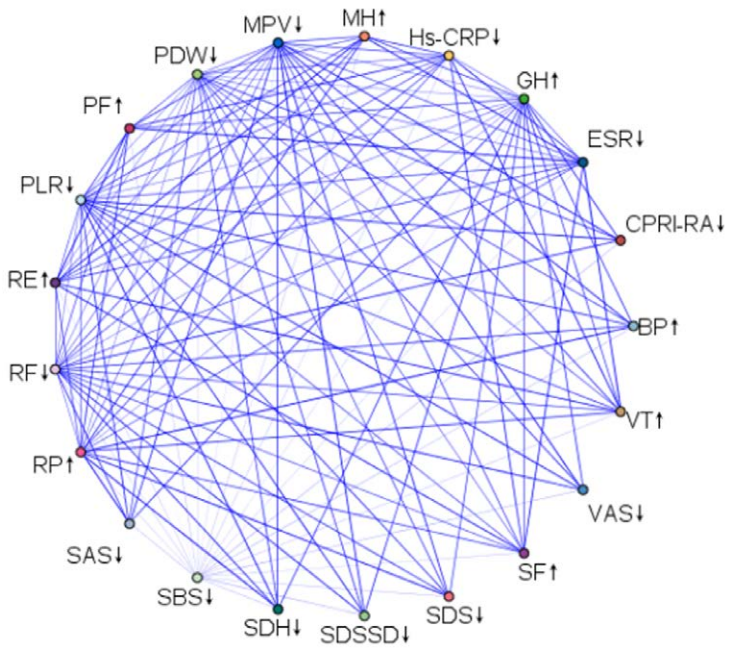

Figure 4. Association rules between PLR reduction and other laboratory indicators, SPP. PLR = platelet-lymphocyte ratio, SPP = self-perception of patient.

Table 5

Association rule analysis between XAJPF and S laboratory indicators, SPP improvement.

Antecedent	Consequent	Support (%)	Confidence (%)	Lift
XAJPF				
SF-36	GH↑	50.27173913	61.62162162	1.15
	PF↑	50.27173913	89.18918919	1.12
	RE↑	50.27173913	79.45945946	1.20
	MH↑	50.27173913	85.40540541	1.09
	RP↑	50.27173913	62.16216216	1.01
	BP↑	50.27173913	90.27027027	1.01
	SF↑	50.27173913	88.10810811	1.16
	VT↑	50.27173913	90.27027027	1.12
	VAS↓	50.27173913	94.59459459	1.01
	CPRI-RA↓	50.27173913	94.59459459	1.01
	SAS↓	50.27173913	91.35135135	1.06
	SDS↓	50.27173913	91.35135135	1.05
TCM syndrome score	SDH↓	50.27173913	90.81081081	1.01
	SDSSD↓	50.27173913	94.05405405	1.01
	PLR↓	50.27173913	61.62162162	1.01
Laboratory indicators	ESR↓	50.27173913	78.37837838	1.08
	hs-CRP↓	50.27173913	75.67567568	1.06
	RF↓	50.27173913	61.08108108	1.01

BP = body pain, ESR = erythrocyte sedimentation rate, GH = general health, hs-CRP = hypersensitive C-reactive protein, MH = mental health, PF = physical functioning, PLR = platelet-lymphocyte ratio, RE = role-emotional, RF = rheumatoid factor, RP = role-physical, SAS = self-rating anxiety scale, SDH = syndrome of dampness-heat, SDS = self-rating depression scale, SDSSD = syndrome of dampness stagnancy due to spleen deficiency, SF = social functioning, SF-36 = the MOS item short form health survey, SPP = self-perception of patient, TCM = traditional Chinese medicine, VAS = visual analogue scale, VT = vitality, XAJPF = Xin'an Jianpi Tongbi Formulation.

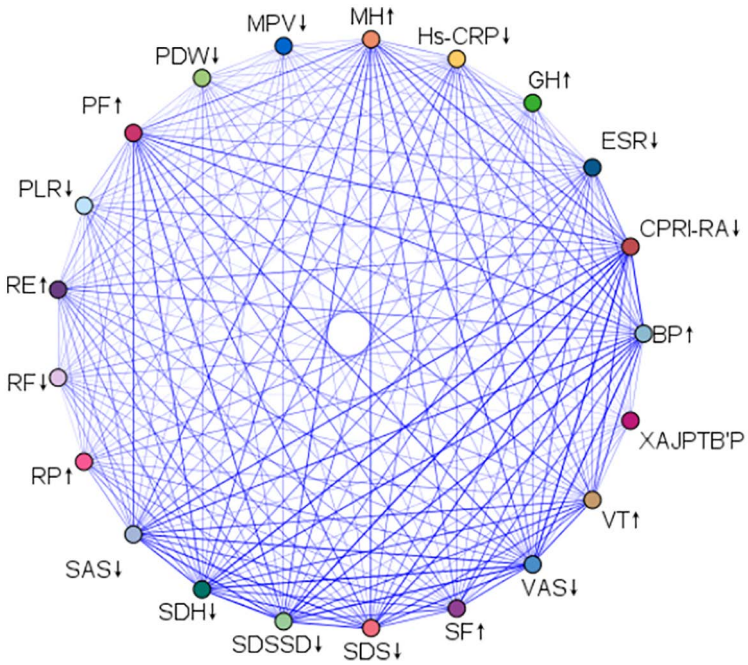

Figure 5. Association rule analysis between XAJPF and S laboratory indicators, SPP improvement. SPP = self-perception of patient, XAJPF = Xin'an Jianpi Tongbi Formulation.

health.[37]In addition, the integration of the Chinese medicine syndrome score, which incorporates patterns such as "SDSSD" and "SBS," provides complementary insights into disease progression and treatment response, bridging the gap between biomedical and holistic health perspectives.

Cost-effective biomarkers have become valuable tools in RA treatment. In active RA, significant increases in PLR levels have been observed in multiple studies,[24,38] the study found that Inflammatory cytokines such as IL-1β, IL-6 and TNF-α were released, and thrombopoietin (TPO) and granulocyte colony-stimulating factor (granulocyte colony-stimulating factor) were also released Factors, G-CSF) can cause an increase in platelets, while lymphopenia may be related to the inflammatory environment promoting lymphocyte programmed death, the inhibition of lymphocyte production, the migration of lymphocytes from the blood circulation to the synovial membrane of the inflamed joint or other inflammatory sites, and immune senescence/exhaustion. At the same time, the increase of PLR and joint erosion severity.[25]and patient reports pain. Clinically, the reduction in PLR after treatment can predict the treatment effect. These findings position PLR as a prognostic marker and a potential mediator of inflammation-driven deterioration of SPP, highlighting its dual role in objective disease monitoring and patient-centered therapy.

Table 6

Changes of indexes before and after low and high exposure treatment.

	Low exposure (XFC, n = 149)			High exposure (XFC + HQC, n = 36)			
	Pretreatment	Posttreatment	P1	Pretreatment	Posttreatment	P2	P3
SF-36							
PF	30.00 (20.00, 35.00)	50.00 (35.00, 65.00)	<.01	30.00 (20.00, 40.00)	60.00 (47.50, 65.00)	<.01	<.029
RP	25.00 (0.00, 25.00)	50.00 (25.00, 50.00)	<.01	25.00 (0.00, 25.00)	50.00 (25.00, 75.00)	<.01	<.285
BP	31.00 (31.00, 41.00)	64.00 (52.00, 74.00)	<.01	31.00 (22.00, 41.00)	62.00 (57.00, 74.00)	<.01	<.879
GH	30.00 (20.00, 35.00)	35.00 (25.00, 42.00)	<.01	30.00 (20.00, 35.00)	35.00 (30.00, 45.00)	<.01	<.403
VT	40.00 (35.00, 45.00)	60.00 (50.00, 65.00)	<.01	40.00 (30.00, 45.00)	65.00 (60.00, 72.50)	<.01	<.01
SF	50.00 (25.00, 62.50)	75.00 (60.00, 75.00)	<.01	50.00 (25.00, 50.00)	75.00 (50.00, 75.00)	<.01	<.609
RE	33.33 (33.33, 50.00)	66.67 (66.67, 100)	<.01	33.33 (33.33, 33.33)	66.67 (66.67, 100)	<.01	<.267
MH	44.00 (36.00, 52.00)	64.00 (56.00, 68.00)	<.01	40.00 (36.00, 52.00)	64.00 (56.00, 68.00)	<.01	<.01
VAS	5.60 (5.15, 6.50)	1.70 (1.30, 2.30)	<.01	5.70 (5.20, 6.50)	1.75 (1.50, 2.25)	<.01	<.573
CPRI-RA	9.99 (7.99, 10.90)	3.08 (2.57, 4.31)	<.01	9.99 (8.63, 11.07)	2.59 (2.38, 3.34)	<.01	<.05
SAS	53.75 (51.25, 57.5)	42.50 (40.00, 46.25)	<.01	53.75 (51.25, 57.5)	41.88 (37.50, 45.00)	<.01	<.098
SDS	61.25 (58.75, 66.25)	50.00 (46.25, 56.25)	<.01	61.25 (58.75, 66.25)	48.75 (43.75, 51.25)	<.01	<.05
TCM syndrome score							
CDS	16.00 (13.00, 18.00)	5.00 (3.50, 7.00)	<.01	–	–	–	–
SDH	14.00 (12.00, 18.00)	6.00 (4.00, 7.00)	<.01	16.00 (14.00, 21.5)	5.00 (4.00, 6.00)	<.01	<.05
SDSSD	12.00 (9.00, 16.00)	5.00 (3.00, 7.00)	<.01	12.00 (10.00, 16.00)	6.00 (3.50, 6.00)	<.01	<.857
SBS	6.00 (5.00, 8.00)	3.00 (2.00, 4.00)	<.01	6.00 (5.00, 8.00)	2.00 (1.00, 4.00)	<.01	<.071
PLR	170.12 (124.52, 247.39)	151.06 (115.22, 208.00)	<.05	174.51 (124.71, 259.16)	164.66 (118.16, 189.23)	<.05	<.858
Laboratory indicators							
MPV	10.50 (9.89, 11.55)	10.50 (9.70, 11.20)	.052	10.50 (9.80, 11.40)	10.25 (9.70, 10.85)	<.886	<.161
PDW	11.80 (10.50, 13.90)	11.70 (10.50, 13.30)	.086	11.80 (10.40, 13.55)	11.45 (9.95, 12.90)	<.604	<.178
ESR	31.50 (14.00, 53.50)	16.00 (9.00, 35.00)	<.01	33.00 (16.00, 57.00)	19.5 (7.00, 35.50)	<.01	<.961
RF	102.10 (36.50, 267.72)	142.60 (43.10, 281.50)	.895	113.15 (38.30, 267.72)	150.30 (45.80, 321.00)	<.148	<.957
hs-CRP	15.28 (3.09, 35.66)	2.52 (1.01, 8.80)	<.01	15.38 (3.35, 36.47)	1.23 (0.47, 7.46)	<.01	<.058
Security indicators							
ALT	13.45 (10.00, 18.45)	17.40 (12.20, 24.40)	<.01	13.95 (10.00, 19.55)	17.40 (12.20, 24.40)	<.01	<.500
AST	18.45 (15.55, 22.05)	19.90 (16.50, 23.90)	<.05	18.60 (15.85, 22.05)	18.45 (15.40, 23.85)	<.083	<.466
BUN	4.86 (3.97, 6.06)	4.99 (4.01, 6.27)	.678	4.84 (3.98, 6.03)	5.22 (4.59, 6.30)	<.528	<.260
CERA	52.30 (45.20, 64.00)	54.50 (45.80, 63.70)	.678	51.55 (44.90, 63.20)	51.10 (43.55, 62.10)	<.825	<.336

P1: low exposure: pretreatment vs posttreatment; P2: high exposure: pretreatment vs posttreatment; P3: low exposure posttreatment vs high exposure posttreatment.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BP = body pain, BUN = blood urea nitrogen, CDS = cold-dampness syndrome, CREA = creatinine, ESR = erythrocyte sedimentation rate, GH = general health, HQC = Huangqinqingrechubi Capsule, hs-CRP = hypersensitive C-reactive protein, MH = mental health, MPV = mean platelet volume, PDW = platelet distribution width, PF = physical functioning, PLR = Platelet-lymphocyte ratio, RE = role-emotional, RF = rheumatoid factor, RP = role-physical, SAS = self-rating anxiety scale, SBS = syndrome of blood stasis, SDH = syndrome of dampness-heat, SDS = self-rating depression scale, SDSSD = syndrome of dampness stagnancy due to spleen deficiency, SF = social functioning, SF-36 = the MOS item short form health survey, TCM = traditional Chinese medicine, VAS = visual analogue scale, VT = vitality, XFC = XinFeng Capsule.

Correlation analysis revealed different patterns of association between laboratory indicators and SPP, such as BP with SDH, CPRI-RA, and hs-CRP, underscoring the interaction between subjective pain perception and systemic inflammation. Psychological assessments further highlighted the impact of mental health on social functioning, as SAS and SDS scores were significantly associated with impaired social functioning. Interestingly, we found that the TCM evidence pattern showed different associations: CDS was associated with elevated ESR and RF, in line with its traditional features of chronic inflammation. PLR was associated with systemic inflammation (ESR: $R = 0.30$; hs-CRP: $R = 0.27$), and also correlated with functional outcome (all SF-36 domains: $R = 0.06$–0.15) or CPRI-RA ($R = 0.15$). These findings highlight the need for multidimensional assessment of RA, combining inflammatory markers, psychological status, and TCM evidence-based treatment to develop treatment strategies. Comparisons of results between the exposed and unexposed groups highlight differential treatment benefits. After treatment, the SPP indexes (except GH and SF) and laboratory indexes of the 2 groups were significantly improved, but the improvement of the exposure group was more obvious, and the difference between the 2 groups was statistically significant (P3 < .05). Of note, our intervention maintained hepatorenal safety and improved the tolerability of the intervention. Mediation effect and logistic regression analysis showed that XAJPF showed a strong protective effect in multiple dimensions of SPP, with reduced PLR as a key mediator. Although elevated inflammatory markers (PLR, ESR, hs-CRP) consistently predicted worse outcomes, the fully mediated effect of PLR in SDSSD (SDSSD: ab = –0.16, 95% BootCI [-0.24, –0.09], $P < .001$) underscore its unique mechanistic contribution to this outcome. Unlike the partial mediation observed in other domains, a nonsignificant direct effect (c ‘= –0.24, $P = .12$) suggests that XAJPF alleviates SDSSD only by reducing PLR. This specificity underscores the dual utility of PLR: as a prognostic marker of inflammation severity and as a dynamic indicator of treatment response. These findings with previous link of PLR and RA disease activity study of consistent,[23] and through the quantitative PLR in ending the mediation role of patients report to extend the knowledge. Association rule analysis further described the multifactorial treatment of XAJPF and found that XAJPF correlated well with the improvement of laboratory indexes and SPP. Stratified analysis further showed that the high-exposure group had better results in VT, MH, CPRI-RA, SDS and SDH than other exposure groups, but comparable results in the improvement of laboratory indexes. This may be related to the small sample size in the high-exposure subgroup (n = 36), limiting the statistical power to detect subtle differences in results. These results highlight the need for larger trials to verify the significant effects of XAJPF.

It is noteworthy that while XAJPF significantly improved patient-reported outcomes and TCM syndromes, the improvements in laboratory inflammatory markers (PLR, ESR, RF) were comparable between the XAJPF and control groups. This suggests that the benefits of XAJPF may extend beyond mere anti-inflammatory effects, potentially involving modulation of

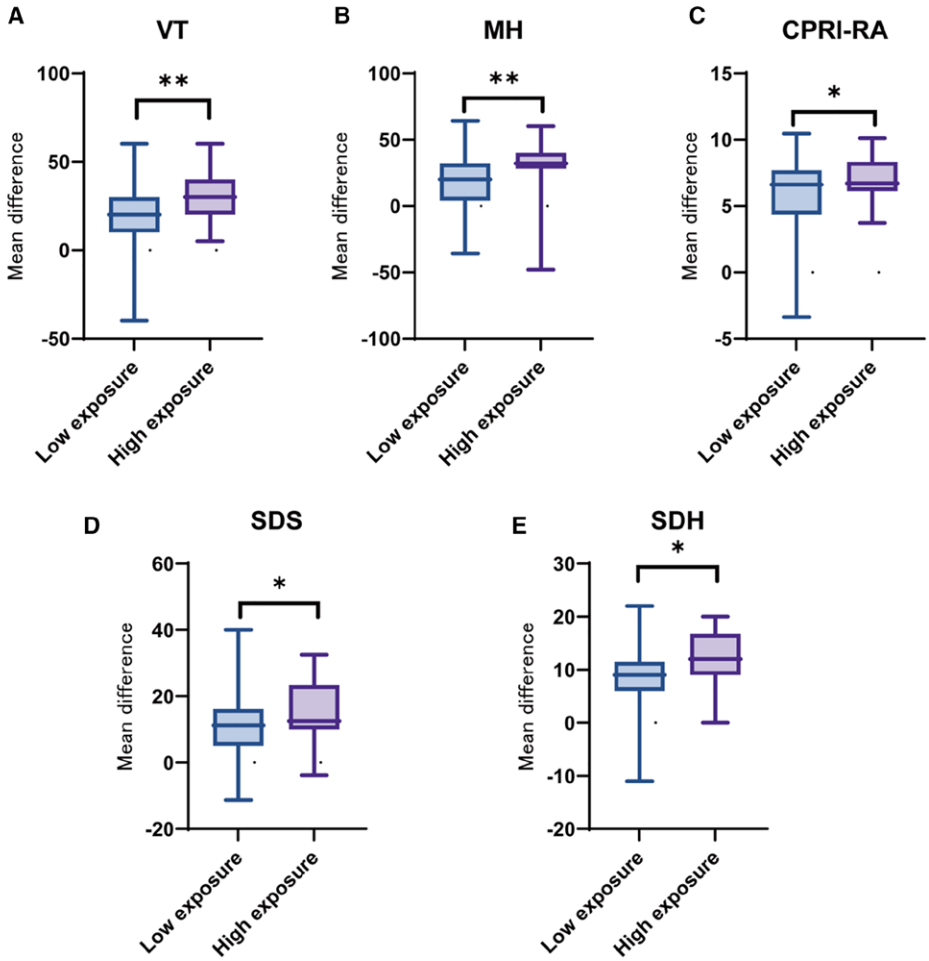

Figure 6. Violin plot of SPP indicators with differences in improvement at admission and at discharge after different exposure treatments. (A) Difference in VT improvement between high and low exposure groups. (B) Difference in MH improvement between high and low exposure groups. (C) Difference in CPRI-RA improvement between high and low exposure groups. (D) Difference in SDS improvement between high and low exposure groups. (E) Difference in SDH improvement between high and low exposure groups.* $P < .05$; ** < .01. MH = mental health, SDH = syndrome of dampness-heat, SDS = self-rating depression scale, SPP = self-perception of patient, VT = vitality.

central perception, psychological distress, and TCM-defined pathological states. Furthermore, although statistically significant increases in ALT and AST were observed posttreatment, values remained within the normal range, suggesting no clinical hepatotoxicity and supporting the safety profile of XAJPF. The exploratory subgroup analysis suggested potential enhanced benefits on VT, MH, and SDH with high-exposure treatment. However, the small sample size of the high-exposure subgroup (n = 36) limits the statistical power to detect subtle differences, and these findings require confirmation in larger, specifically designed studies. The mediating role of PLR suggests a potential link between the formula's effect on systemic inflammation/immunity (as reflected by PLR) and the improvement in certain patient-perceived outcomes, particularly GH and syndrome of dampness stagnancy due to SDSSD. The precise biological pathways connecting XAJPF components to PLR modulation warrant further investigation.

Combined with TCM theory and clinical observation, we found that RA patients often present the characteristics of spleen deficiency and dampness excess, dampness and blood stasis during hospitalization. Based on this, our team developed a Chinese patent medicine compound XAJPF, including XFC and HQC, aiming at the above pathological characteristics. XFC, consisting of Astragalus membranaceus, Coicis semen, Tripterygium wilfordii, and centipede, is mainly used in RA patients with spleen deficiency and dampness excess. HQC is composed of Scutellaria baicalensis, Gardenia jasminoides, Radix clematidis, Semen coix lacryma, and Peach kernel, which is mainly used in RA patients with damp heat and blood stasis. Astragalus membranaceus has been found to have anti-inflammatory and immunostimulatory activities.[39] Coicis by can improve inflammation and oxidative stress in RA.[40] Tripterygium wilfordii can inhibit the growth of RA FLS – and inflammation reaction.[41] centipede neutrophils LPS stimulation can inhibit the mice caused by inflammatory cytokine levels.[42] Wogonin, the active ingredient in Scutellaria baicalensis, inhibits the migration and invasion of Scutellaria baicalensis fibroblast-like synoviocytes by targeting PI3K/AKT/NF-κB pathway in RA.[43] Geniposide's VEGF-induced angiogenesis by inhibiting VEGFR2/PKC/ERK1/2-mediated SphK1 translocation.[44] Total Saponins of Radix Clematis Regulate Fibroblast-Like Synoviocyte Proliferation in Rheumatoid Arthritis via the LncRNA OIP5-AS1/MiR-410-3p/Wnt7b Signaling Pathway,[45]indicating that XAJPF has multi-component and multi-target synergistic effects in the treatment of RA.

This study has the following 3 significant advantages: firstly, at the methodological level, it innovatively combines the international common research methodology with the TCM evidence evaluation system, which not only conforms to the norms of evidence-based medical research, but also significantly improves the scientific connotation of the study through the localized improvement, and constructs the evaluation framework with

the characteristics of combining Chinese and Western medicines. Secondly, the study design adopts the internationally accepted diagnosis and treatment model of combining disease and evidence, takes RA as the research object, and strictly selects the standardized proprietary Chinese medicine preparations that have been approved by the Anhui Provincial Drug Administration and the invention patents, and has strict quality control standards. Thirdly, the whole process of the study follows the international standards for clinical research in Chinese medicine and is registered through the International Traditional Medicine Clinical Trial Registry Platform and strictly fulfills the ethical review procedures for biomedical research, which fully guarantees the standardization and ethical compliance of the study. At the same time, there are some shortcomings in our study. For example, our study was only a single-center study, and the number of cases was not large enough, which needs to be further strengthened, with the exception of further feedback on the dosage, duration and adverse effects of the nosocomial agents used in this study.

5. Conclusion

In conclusion, the present study demonstrated the presence of SPP deterioration in RA patients. XAJPF significantly improved multidimensional SPP compared to controls, while its effects on laboratory inflammatory markers were comparable between groups. Reduction in PLR mediated part of the improvement in certain SPP domains. These findings highlight the clinical value of assessing SPP and PLR in RA management and provide support for the use of XAJPF to enhance patient-perceived outcomes. The role of PLR as a mediator and the mechanisms underlying XAJPF's effects require further investigation.

Author contributions

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Visualization: Shengfeng Liu.
Writing – original draft: Shengfeng Liu.
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