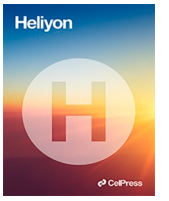
Heliyon 10 (2024) e23147

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



The effect of long-term traditional Chinese medicine treatment on extra-articular lesions of rheumatoid arthritis patients based on propensity score matching: A retrospective cohort study

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ARTICLE INFO

Keywords:
Rheumatoid arthritis
Traditional Chinese medicine
Extra-articular lesions
Propensity score matching

ABSTRACT

Objective: To explore the efficacy of long-term traditional Chinese medicine (TCM) treatment on the occurrence of extra-articular lesions in rheumatoid arthritis (RA) patients.
Methods: Our retrospective cohort study included patients diagnosed with RA between January 2018 to December 2019. Patients were divided into TCM treatment group and control group according to whether they received TCM treatment for more than three months. Propensity score matching (PSM) was used to balance covariates between groups. The occurrence time of extra-articular lesions, including interstitial lung disease, Sjögren's syndrome, and anemia, was calculated for both groups after PSM. Additionally, clinical indicators that may affect the occurrence of extra-articular lesions in RA were included in Cox multivariate regression analysis to explore prognostic factors related to RA.
Results: A total of 883 RA patients were initially included in our study, with 481 in the TCM treatment group and 279 in the control group. TCM treatment improved all clinical indicators of RA patients, and there was a higher degree of support, confidence, and lift between TCM treatment and the improvement of clinical indicators. There was no significant difference in the rate of extra-articular lesions occurrence between the two groups. After PSM, the median occurrence time of interstitial lung disease, Sjögren's syndrome and anemia in the TCM treatment group were 30.767, 21.370 and 31.970 months, respectively. While in the control group, it was 15.911, 14.667 and 11.825 months, respectively. Cox multivariate regression analysis indicated that TCM treatment was a protective factor for the occurrence of extra-articular lesions in RA, while abnormally high level of IgG was an independent factor for interstitial lung disease and C4 was an independent factor for Sjögren's syndrome. Moreover, a longer duration of TCM usage was associated with a later occurrence of extra-articular lesions.

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https://doi.org/10.1016/j.heliyon.2023.e23147
Received 4 January 2023; Received in revised form 27 November 2023; Accepted 27 November 2023
Available online 2 December 2023

Conclusion: Long-term TCM treatment not only positively affects the occurrence time of extra-articular lesions in RA patients, but also helps reduce the risk of extra-articular lesions occurrence. TCM can be applied flexibly throughout the treatment process for RA patients.

Key messages

1. Long-term TCM treatment can reduce the occurrence of extra-articular lesions in RA patients.
2. The longer the TCM usage, the lower the incidence of extra-articular lesions occurrence in RA.

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, and autoimmune disease that can lead to irreversible joint destruction and deformity, seriously affecting people's quality of life [1,2]. The global incidence of RA is 0.5 %–1 %, whereas in China, the incidence is 0.2 %–0.4 %, and the incidence rate demonstrates an increasing trend [3,4]. Apart from destroying the affected joints, RA also has extra-articular effects on the body, including respiratory, cardiovascular, digestive, and neurological systems [5,6]. Patients with RA often have pulmonary involvement, and interstitial lung disease (ILD) is the primary lesions, with rates of ILD reported to be up to 10 %

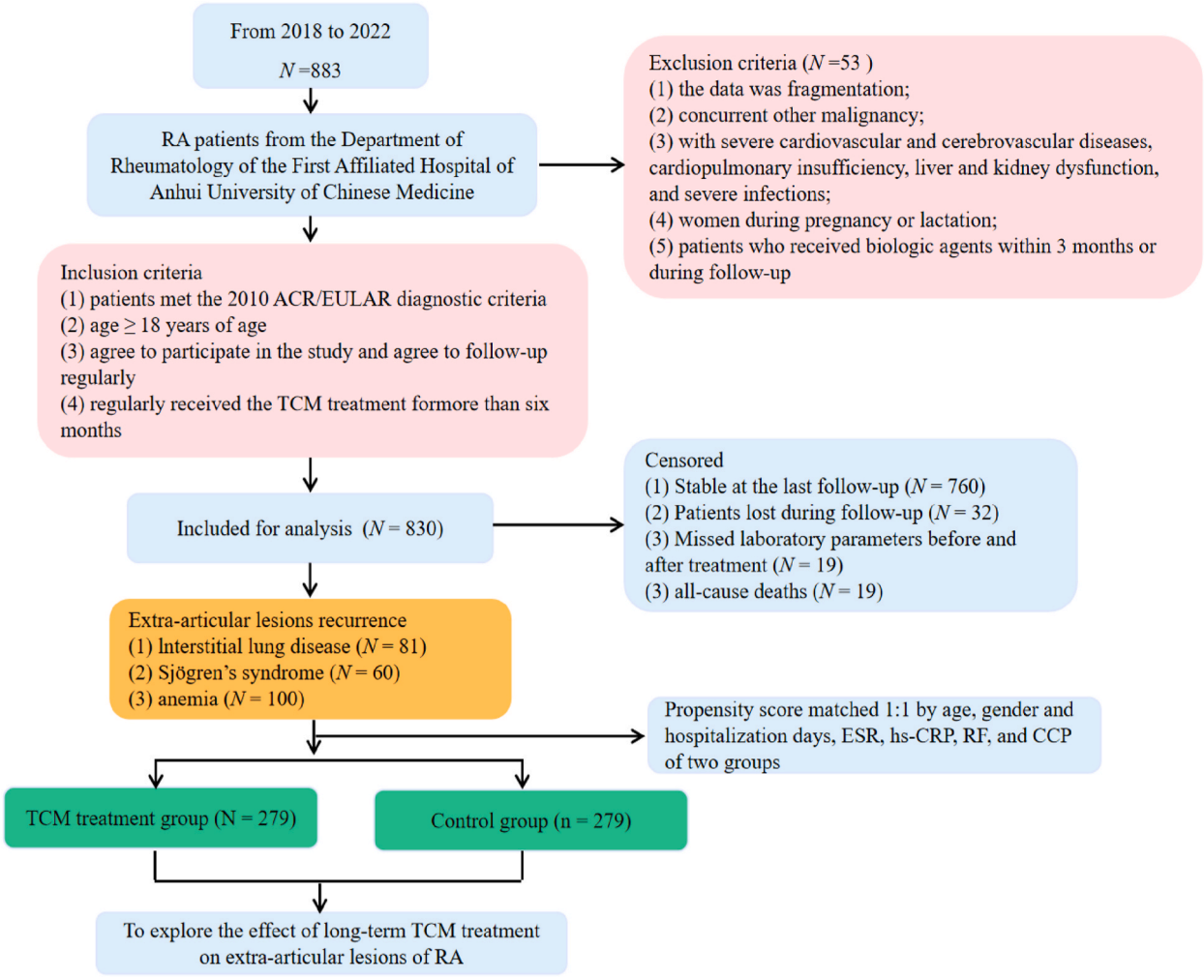

Fig. 1. Flow chart for study participant selection. RA, rheumatoid arthritis; TCM, traditional Chinese medicine; ESR, erythrocyte sedimentation rate; hs-CRP, hypersensitive C-reactive protein; RF, rheumatoid factor; CCP, cyclic citrullinated peptide.

in RA [7,8]. Secondary Sjögren's syndrome is considered one of the most common extra-articular lesions of RA [9]. A recent study found that the cumulative prevalence of Sjögren's syndrome in RA was 17 % and 25 % after 10 and 30 years of disease duration, respectively [10]. Anemia is an another common extra-articular lesions of RA, affecting 30 %–70 % RA patients [11]. Therefore, the prevention and treatment of RA are facing severe challenges.

Currently, disease-modifying anti-rheumatic drugs, non-steroidal anti-inflammatory drugs, and glucocorticoid are widely used for the treatment of RA [12]. It is important to note, however, that most of these therapeutic agents are associated with adverse effects that affect the cardiovascular and gastrointestinal systems, kidneys, and liver [12]. As medicine has developed, there is greater interest in alternative and complementary medicine and adjuvant therapies in the treatment of RA [13,14]. As a critical component of complementary and alternative medicine, traditional Chinese medicine (TCM) has become an indispensable treatment method for RA due to its unique treatment based on syndrome differentiation and holistic regulation [15]. Several studies have shown that TCM can reduce the clinical indicators of RA patients, improve their quality of life, morning stiffness, joint pain [16], and prevent or reduce extra-articular lesions occurrence in RA [17]. Experimental studies have revealed that TCM compounds exert an antirheumatic effect by affecting the inflammation [18], apoptosis [19], oxidative stress [20], and other multiple pathways and targets of RA synovial fibroblasts. However, there is almost no research exploring the long-term efficacy of TCM in treating extra-articular lesions in patients with RA.

Therefore, to further explore the influence of long-term TCM treatment on the occurrence of extra-articular lesions in RA, we conducted a single-center, large sample retrospective study.

2. Methods

2.1. Study design and participants

This study was designed as an observational, retrospective single-center study conducted at the First Affiliated Hospital of Anhui University of Chinese Medicine. This study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Anhui University of Chinese Medicine (approval number 2019 AH-12). From 2018 to 2022, 883 patients diagnosed with RA were screened, and 760 were included in the study. All data were collected from the electronic medical record information system. Cases were selected based on clear diagnoses, specifically including patients with RA combined with ILD, Sjögren's syndrome, or anemia. Patients with additional extra-articular manifestations were excluded from this study. The diagnosis of ILD was confirmed through High-Resolution Computed Tomography (HRCT), Sjögren's syndrome was determined based on post-lip biopsy pathology, and anemia was identified by hemoglobin levels.

The inclusion criteria were as follows: (1) patients who met the 2010 ACR/EULAR diagnostic criteria; (2) age $\geq$18 years old; (3) agreement to participate in the study and follow-up regularly; (4) regular receipt of TCM treatment for more than six months. Patients with one or more of the following conditions will be excluded from this study: (1) fragmented data; (2) concurrent other malignancy; (3) severe cardiovascular and cerebrovascular diseases, cardiopulmonary insufficiency, liver and kidney dysfunction, and severe infections; (4) women during pregnancy or lactation; (5) patients who received biologic agents within three months or during follow-up.

The patients who received long-term systematic TCM treatment were assigned to the TCM treatment group (n = 481), while those who were unwilling to take Chinese herbal decoction or could not tolerate it were assigned to the control group (n = 279). Fig. 1 shows the flow chart of the participant selection procedure.

2.2. Long-term systematic TCM treatment

Compared to chemical drugs and biopharmaceuticals, TCM has a unique advantage in treating chronic diseases due to its multi-component and multi-target nature, which causes less adverse reactions. Therefore, it is meaningful to observe the long-term effect of TCM on RA treatment. Patients who received systematic TCM treatment for RA were recommended to receive Chinese herbal decoction continuously for at least three months as part of their long-term treatment. All patients in the TCM treatment group took the modified Jianpi Formula, which consisted of invigorating spleen for eliminating dampness, promoting blood circulation to remove meridian obstruction, dispelling wind and eliminating dampness, and heat-clearing and detoxifying herbs.

In addition, TCM is characterized by syndrome differentiation and individualized treatment, emphasizing a holistic approach to healthcare. Therefore, clinicians can adjust drug dosage or composition to optimize efficacy and prevent adverse effects. The concentrated herbs were decocted into 300 ml and taken orally twice a day, half an hour after meals. The herbs were provided by the Chinese medicine pharmacies of the First Affiliated Hospital of Anhui University of Chinese Medicine to ensure their quality.

2.2.1. Follow up scheme

2.2.1.1. Follow up method. All patients underwent regular follow-up via outpatient clinical visits or telephone interviews by trained researchers routinely each three months. ILD patients are followed up every 6 months with a pulmonary HRCT scan, while SS patients are followed up every 3 months with salivary flow rate measurements.

2.2.1.2. Follow up contents.

(1) General information: first visit time, gender, age, and telephone number.

(2) Past history: osteoarthritis, hypertension, diabetes, chronic gastritis, cerebral infarction, thyroid nodule, and et al.

(3) The use of Chinese herbs: have been taking TCM in the past three months, have experienced any problems or symptoms after taking TCM.

(4) The outcome of interests was extra-articular lesions. This was defined as the time from the beginning of treatment to the observation of interstitial lung disease, Sjögren syndrome, or anemia, whichever occurs first.

2.3. Statistical analysis

We entered the data into an ad hoc created database using Excel software. Statistical analyses were conducted using SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and Stata version 12.0 (StataCorp LLC, College Station, TX, USA). Continuous variables did not satisfy the normality test and are presented as median and 25–75 interquartile range (IQR) and compared using Kruskal-Wallis test. Categorical data were presented as number (percentage) and compared using Pearson χ^2 test. The probability of extra-articular lesions occurrence was analyzed by Kaplan-Meier curve, and the difference in extra-articular lesions between two groups was calculated by Log-rank test. Schoenfeld residuals test was used to assess the proportional hazards assumption. Cox proportional hazard regression model was established to explore the effect of independent factors on the occurrence of extra-articular lesions in RA patients.

Propensity score matching (PSM) is a statistical matching technique that attempts to estimate the effect of a treatment and intervention by accounting for the covariates that predict receiving the treatment. To minimize the selection bias caused by differences in initial conditions between the TCM group and the control group, we first applied PSM method to “balance” the two groups. PSM was used to perform a 1: 1 match on seven factors of the two groups, including age, gender, hospitalization day, erythrocyte sedimentation rate (ESR), hypersensitive C-reactive protein (hs-CRP), rheumatoid factor (RF), and cyclic citrullinated peptide (CCP). The match tolerance of PSM was set at 0.05. Moreover, to systematically verify the associations between TCM treatment and clinical indicators improvement, association rules analysis was used to estimate the strength of the associations. *P* value while was less than 0.05 was considered to be statistically significant.

3. Results

3.1. PSM balance test

As shown in Table 1, the normalized bias values of all seven variables are less than 10. Additionally, the t-statistics following the matching did not reach significance. Therefore, we can conclude that there are no systematic differences between the TCM and control groups, and our matching estimation results are efficient and reliable.

3.2. Baseline characteristics

As of the last follow-up date (February 28, 2022), a total of 760 patients met the study criteria and were included in the

Table 1
PSM balance test.

Variable	Before and after matching	Mean		% reduct		*t*-test	
		TCM group	Control group	%bias	bias	t	p > t
Gender	Unmatched	0.2	0.2	4.6	0.5	0.6	–
	Matched	0.2	0.	4.3	7.5	0.3	0.74
Age	Unmatched	59.2	55.7	31.4	3.1	0.0	0.96
	Matched	59.2	59.2	−0.5	98.5	−0.0	0.97
Hospitalization day	Unmatched	22.6	22.5	11.4	6.5	0.9	0.39
	Matched	22.6	22.5	−5.1	3.0	−2.3	0.77
ESR (mm/h)	Unmatched	34.6	33.0	7.8	8.1	0.3	0.93
	Matched	34.6	33.0	6.1	3.1	0.0	0.23
hs-CRP (mg/L)	Unmatched	15.8	10.3	5.1	1.1	0.2	0.14
	Matched	15.8	14.7	3.2	6.0	0.2	0.62
RF (U/ml)	Unmatched	33.1	31.8	6.2	11.4	−1.4	0.87
	Matched	33.1	32.9	0.4	−4.1	0.2	0.41
CCP (U/ml)	Unmatched	47.0	42.7	24.0	2.7	−2.3	0.77
	Matched	47.0	46.0	−2.0	12.6	0.1	0.43

Abbreviation: ESR, erythrocyte sedimentation rate; hs-CRP, hypersensitive C-reactive protein; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; PSM, propensity score matching; TCM, traditional Chinese medicine.
T test used for p-value calculation.

retrospective cohort study. Before PSM, there were 481 patients in the TCM group and 279 patients in the control group. There were statistically significant differences between the two groups in factors such as hospitalization days, immunoglobulin (Ig) G, and complement (C) 4 ($p < 0.05$). However, after PSM, 279 patients in each group were matched, leading to the equilibrium of covariates between the two groups. As a result, there were no statistically significant differences between the two groups in factors such as age, gender, hospitalization days, ESR, hs-CRP, RF, CCP, IgA, IgG, IgM, C3, C4, comorbidities, and Western medicine ($P < 0.05$). The baseline characteristics and clinical features are displayed in Table 2.

3.3. Comparison of extra-articular lesions between the two groups

Before PSM, 36 patients in the TCM group had interstitial lung disease (7.5 %), 33 patients had Sjögren's syndrome (6.9 %), and 43 patients (8.9 %) had anemia. While in the control group, 45 patients had interstitial lung disease (16.1 %), 27 patients had Sjögren's syndrome (9.7 %), and 57 patients (20.4 %) had anemia. After PSM, 28 patients in the TCM group had interstitial lung disease (10.0 %), 23 patients had Sjögren's syndrome (8.2 %), and 32 patients (11.5 %) had anemia. While in the control group, 45 patients had interstitial lung disease (16.1 %), 27 patients had Sjögren's syndrome (9.7 %), and 57 patients (20.4 %) had anemia. The difference between the two groups is statistically significant before and after PSM, as shown in Table 3.

Table 2
Baseline characteristics and clinical features of TCM group and the control group before and after PSM.

Characteristics	Befor PSM					After PSM				
	Total cohort (n = 760)	TCM group (n = 481)	Control group (n = 279)	Z/ χ2	P value	Total cohort (n = 558)	TCM group (n = 279)	Control group (n = 279)	Z/ χ2	P value
Gender, n (%)										
Female	618 (81.3)	389 (80.9)	229 (82.1)	0.2	0.69	111 (19.9)	218 (78.1)	229 (82.1)	1.4	0.24
Male	142 (18.7)	92 (19.1)	50 (17.9)			447 (80.1)	61 (21.9)	50 (17.9)		
Age (year), n (%)	55.0 (48.0, 65.0)	55.0 (48.0, 65.0)	54.0 (49.0, 65.0)	0.3	0.74	55.0 (49.0, 69.0)	55.0 (49.0, 65.0)	54.0 (49.0, 65.0)	0.6	0.54
≤60 years	475 (62.5)	294 (61.1)	181 (64.9)	1.1	0.30	352 (63.1)	171 (61.3)	181 (64.9)	0.8	0.38
> 60 years	285 (37.5)	187 (38.9)	98 (35.1)			206 (36.9)	108 (38.71)	98 (35.1)		
Hospitalization days, n (%)	13.37 (10.4, 17.0)	13.4 (9.9, 16.4)	14.0 (11.0, 18.4)	3.0	0.00	14.0 (11.0, 18.0)	14.0 (11.0, 18.0)	14.0 (11.0, 18.4)	0.4	0.72
≤12 days	310 (40.8)	207 (43.0)	103 (36.9)	2.7	0.10	174 (31.2)	87 (31.2)	87 (31.2)	0.0	1.00
> 12 days	450 (59.2)	274 (57.0)	176 (63.1)			384 (68.8)	192 (68.8)	192 (68.8)		
ESR (mm/h)	36.0 (19.0, 57.0)	38.0 (18.5, 59.0)	34.0 (19.0, 56.0)	0.9	0.37	34.0 (19.0, 56.0)	36.0 (18.0, 56.0)	34.0 (19.0, 56.0)	0.2	0.83
hs-CRP (mg/L)	12.5 (2.9, 36.0)	13.0 (3.0, 35.1)	11.0 (2,5, 36.8)	0.3	0.80	12.9 (2.8, 37.1)	14.7 (3.3, 37.2)	11.0 (2.5, 36.8)	0.8	0.40
RF (U/ml), n (%)	84.8 (18.9, 251.2)	94.7 (19.6, 251.0)	71.5 (18.8, 257.7)	0.9	0.39	77.7 (17.7, 229.5)	83.1 (16.5, 211.4)	71.5 (18.8, 257.7)	0.2	0.83
RF negative	164 (21.6)	102 (21.2)	62 (22.2)	0.1	0.74	128 (22.9)	66 (23.7)	62 (22.2)	0.2	0.69
RF positive	596 (78.4)	379 (78.8)	217 (77.8)			430 (77.1)	213 (76.3)	217 (77.8)		
CCP (U/ml), n (%)	59.5 (5.7, 249.0)	54.2 (6.7, 246.5)	71.1 (4.5, 253.6)	0.3	0.76	54.4 (3.4, 236.1)	41.2 (3.3, 213.0)	71.1 (4.5, 253.6)	0.4	0.86
CCP negative	182 (24.0)	113 (23.5)	69 (24.7)	0.1	0.70	141 (25.3)	72 (25.8)	69 (24.7)	0.1	0.77
CCP positive	578 (76.1)	368 (76.5)	210 (75.3)			417 (74.7)	207 (74.2)	210 (75.3)		
IgA (g/L)	2.3 (1.8, 3.0)	2.3 (1.7, 3.1)	2.3 (1.9, 3.0)	0.5	0.65	2.3 (1.8, 3.06)	2.4 (1.7, 3.1)	2.3 (1.9, 3.0)	0.1	0.92
IgG (g/L)	12.8 (10.1, 15.8)	13.0 (10.2, 15.9)	12.3 (9.8, 15.2)	2.2	0.03	12.5 (9.9, 15.6)	12.9 (9.9, 15.9)	12.3 (9.8, 15.2)	1.4	0.17
IgM (g/L)	1.3 (0.9, 1.7)	1.3 (0.9, 1.7)	1.2 (0.9, 1.7)	1.0	0.30	1.2 (0.9, 1.6)	1.2 (0.9, 1.6)	1.2 (0.9, 1.7)	1.1	0.25
C3 (g/L)	1.1 (0.9, 1.2)	1.1 (0.9, 1.2)	1.1 (1.0, 1.2)	1.6	0.12	0.9 (0.3, 1.1)	0.3 (0.2, 0.3)	0.3 (0.2, 0.3)	1.0	0.26
C4 (g/L)	0.3 (0.2, 0.3)	0.3 (0.2, 0.3)	0.2 (0.2, 0.3)	2.9	0.00	0.3 (0.2, 0.3)	0.3 (0.2, 0.3)	0.3 (0.2, 0.3)	0.1	0.91
HGB (g/L)	116.0 (105.0, 127.8)	116.0 (104.0, 127.0)	116.0 (106.0, 129.0)	0.1	0.95	116.0 (106.0, 128.0)	117.0 (106.0, 128.0)	116.0 (106.0, 129.0)	0.5	0.64
Osteoarthritis	195 (25.7)	114 (23.7)	45 (16.1)	5.2	0.27	88 (15.8)	43 (15.4)	45 (16.1)	0.2	1.00
Hypertension	114 (15.0)	78 (16.2)	36 (12.9)			70 (12.5)	34 (12.2)	36 (12.9)		
T2DM	92 (12.1)	67 (13.9)	25 (9.0)			47 (8.4)	22 (7.9)	25 (9.0)		
Chronic gastritis	73 (9.6)	56 (11.6)	17 (6.1)			31 (5.6)	14 (5.0)	17 (6.1)		
CHD	57 (7.5)	34 (7.1)	23 (8.2)			44 (7.9)	21 (7.5)	23 (8.2)		
Glucocorticoids	398 (52.4)	189 (39.3)	209 (74.9)	1.1	0.57	361 (64.7)	152 (54.5)	209 (74.9)	1.3	0.51
NSAIDs	491 (64.6)	221 (46.0)	270 (96.8)			197 (35.3)	227 (81.4)	270 (96.8)		
DMARDs	384 (50.5)	186 (38.7)	198 (71.0)			365 (65.4)	167 (59.9)	198 (71.0)		

Abbreviation: ESR, erythrocyte sedimentation rate; hs-CRP, hypersensitive C-reactive protein; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; Ig, immunoglobulin; C, complement; PSM, propensity score matching; TCM, traditional Chinese medicine.
Pearson χ2 test used for p-value calculation.

Table 3
Comparison of extra-articular lesions of the two groups.

Extra-articular lesions	Before PSM					After PSM				
	Total cohort (n = 760)	TCM group (n = 481)	Control group (n = 279)	χ2	*P* value	Total cohort (n = 558)	TCM group (n = 279)	Control group (n = 279)	χ2	*P* value
Interstitial lung disease	81 (10.7)	36 (7.5)	45 (16.1)	2.4	0.31	73 (13.1)	28 (10.0)	45 (16.1)	1.4	0.50
Sjögren's syndrome	60 (7.9)	33 (6.9)	27 (9.7)			50 (9.0)	23 (8.2)	27 (9.7)		
Anemia	100 (13.2)	43 (8.9)	57 (20.4)			89 (16.0)	32 (11.5)	57 (20.4)		

Abbreviation: PSM, propensity score matching; TCM, traditional Chinese medicine.
Pearson χ2 test used for p-value calculation.

3.4. Analysis of traditional Chinese medicine

These formulae consisted of a total of 158 types of herbs, with the highest frequency of use being 509. Table 4 shows the top 20 most frequently used TCM, which are categorized as follows: invigorate spleen for eliminating dampness, promote blood circulation to remove meridian obstruction, dispel wind and eliminate dampness, and clear away heat and toxic materials. In addition, widely used Chinese patent medicines include Xinfeng capsule, Huangqin Qingre Chubi capsule, Wuwei Wentong Chubi capsule, Furong Gao, and Xiaoyu Jiegu San.

Table 4
Application of Chinese herbal medicine in RA treatment.

TCM	TCM group (n = 481)		
Chinese herbal medicine	Frequency (%)	Nature and taste	Meridian tropism
PORIA (Fuling)	394 (81.8 %)	Sweet, light and flat	Heart, lung, spleen and kidney
COICIS SEMEN (Yiyiren)	367 (76.7 %)	Sweet, light and cool	Spleen, stomach and lung
HORDEI FRUCTUS GERMINATUS (Maiya)	160 (33.3 %)	Sweet and flat	Spleen and stomach
PINELLIAE RHIZOMA (Banxia)	194 (40.4 %)	Spicy and warm	Spleen, stomach and lung
SETARIAE FRUCTUS GERMINATUS (Guya)	159 (33.6 %)	Sweet and warm	Spleen and stomach
CITRI RETICULATAE PERICARPIUM (Chenpi)	349 (72.5 %)	Bitter, pungent and warm	Lung and spleen
DIOSCOREAE RHIZOMA (Shanyao)	272 (56.6 %)	Sweet and flat	Spleen, lung and kidney
ASTRAGALI RADIX (Huangqi)	113 (23.5 %)	Sweet and mild	Lung and spleen
ANGELICAE SINENSIS RADIX (Danggui)	159 (33.1 %)	Sweet, pungent and warm	Liver, heart and spleen
SPATHOLOBI CAULIS (Jixueteng)	276 (57.4 %)	Bitter, sweet and warm	Liver and kidney
SALVIAE MILTIORRHIZAE RADIX ET RHIZOMA (Danshen)	339 (70.6 %)	Bitter and slightly cold	Heart and liver
PERSICAE SEMEN (Taoren)	315 (65.4 %)	Bitter, sweet and flat	Heart, liver and large intestine
CARTHAMI FLOS (Honghua)	393 (81.7 %)	Spicy and warm	Heart and liver
CHUANXIONG RHIZOMA (Chuanxiong)	192 (39.9 %)	Spicy and warm	Liver, gallbladder and pericardial
TARAXACI HERBA (Pugongying)	349 (72.5 %)	Bitter, sweet and cold	Liver and stomach
HERBA HEDYOTIS DIFFUSAE (Baihuasheshecao)	233 (48.4 %)	Slightly bitter and cold	Stomach, large intestine and small intestine
ANGELICAE PUBESCENTIS RADIX (Duhuo)	133 (27.7 %)	Pungent, bitter and mild	Kidney and bladder
LYCOPODII HERBA (Shenjincao)	210 (43.6 %)	Slightly bitter, pungent and warm	Liver, spleen and kidney
CLEMATIDIS RADIX ET RHIZOMA (Weilingxian)	310 (64.5 %)	Spicy, salty and warm	Bladder
SIEGESBECKIAE HERBA (Xixiancao)	279 (58.0 %)	Pungent, bitter and cold	Liver and kidney
Chinese patent medicine (n = 760)			
Xinfeng Capsule	144 (19.0 %)	NA	NA
Huangqin Qingre Chubi Capsule	78 (10.3 %)	NA	NA
Wuwei Wentong Chubi Capsule	13 (1.8 %)	NA	NA
Jingzhui Huoxue Capsule	59 (7.7 %)	NA	NA
Yaotong Huoxue Capsule	22 (2.9 %)	NA	NA
Furong Gao	391 (51.5 %)	NA	NA
Xiaoyu Jiegu San	314 (41.3 %)	NA	NA
Wuwei Guju Badu San	137 (18.1 %)	NA	NA

Abbreviation:RA, rheumatoid arthritis; propensity score matching; TCM, traditional Chinese medicine.
Xinfeng Capsule is a kind of compound preparation of TCM, contains 4 herbs: Astragalus membranaceus, Coixol, Scutigeromorpha, and Tripterygium wilfordii.
Huangqin Qingre Chubi Capsule is a kind of compound preparation of TCM, contains 5 herbs: Scutellaria baicalensis, Semen pruni persicae, Gardenia jasminoides Ellis, Coixol and Radix Clematidis.
Wuwei Wentong Chubi Capsule is a kind of compound preparation of TCM, contains 5 herbs: Poria, Epimedii Folium, Zingiberis Rhizoma Recens, Cinnamomi Ramulus, and Scutellaria baicalensis.

3.5. Changes of clinical indicators before and after treatment

Compared to before treatment, levels of ESR, hs-CRP, RF, CCP, IgA, IgG, IgM, C3 and C4 were reduced after treatment in both the TCM group and control group ($P < 0.05$), as shown in Table 5. TCM treatment lead to a recognized improved of microindicators through the application of association rules. The results of association rule analysis showed a strong correlation between TCM treatment and clinical indicator improvement, with a support degree was greater than 30 %, confidence degree was greater than 80 %, and improvement degree greater than 1 (Table 6).

3.6. Comparison of extra-articular lesions occurrence probability between the two groups

Fig. 2 presents the Kaplan–Meier curves for the probability of occurrence of extra-articular lesions in the two groups. Before PSM, the median interstitial lung disease occurrence time was 29.2 months and 15.9 months in the two groups, respectively (hazard ratio, HR: 0.43, 95%CI: 0.30 to 0.63, log-rank $p < 0.001$), as shown in Fig. 2A. The median occurrence time of Sjögren's syndrome was 23.4 months and 14.7 months in the two groups, respectively (HR: 0.31, 0.21 to 0.45, log-rank $p < 0.001$), as shown in Fig. 2B. The median occurrence time of anemia was 29.8 months and 11.8 months in the two groups, respectively (HR: 0.70, 0.53 to 0.91, log-rank $p = 0.01$), as shown in Fig. 2C. After PSM, the median occurrence time of interstitial lung disease was 30.8 months and 15.9 months in the two groups, respectively (HR: 0.37, 95%CI: 0.24 to 0.56, log-rank $p < 0.001$), as shown in Fig. 2D. The median occurrence time of Sjögren's syndrome was 21.4 months and 14.7 months in the two groups, respectively (HR: 0.23, 0.14 to 0.38, log-rank $p < 0.001$), as shown in Fig. 2E. The median occurrence time of anemia was 32.0 months and 11.8 months in the two groups, respectively (HR: 0.65, 0.48 to 0.88, log-rank $p = 0.01$), as shown in Fig. 2F.

3.6.1. Cox regression and subgroups analysis of hazard ratio

Cox regression was used to analyze the potential factors that could influence the occurrence time of extra-articular lesions in RA patients, with the outcome defined as the occurrence of extra-articular lesions. All clinical features that may impact the occurrence time of extra-articular lesions in RA patients were included in the analysis.

The results of the Cox regression analysis indicated that taking TCM decoction was a protective factor for the occurrence of extra-articular lesions (interstitial lung disease, Sjögren's syndrome, and anemia) in RA patients. However, abnormally high level of IgG was an independent risk factor for interstitial lung disease, while abnormally high level of C4 was an independent risk factor for Sjögren's syndrome. Therefore, abnormal level of immune-inflammation indicators influenced the occurrence of extra-articular lesions in RA patients. Higher levels of abnormal clinical indicators corresponded to increased symptom severity, which is consistent with clinical practice, as shown in Fig. 3.

3.7. Influence of TCM on extra-articular aesions occurrence of RA for the duration of TCM usage

Based on the above analysis of the occurrence probability of extra-articular lesions in RA patients, we further explored the effect of TCM treatment duration on the occurrence of extra-articular lesions in RA patients.

To assess whether the occurrence of extra-articular lesions varied with the duration of TCM usage, we estimated the effect of TCM usage for less than and more than six months on the occurrence of extra-articular lesions. For patients who used TCM less than six months, we found that the occurrence time of extra-articular lesions in the TCM group was longer than that in the control group. The occurrence probability rates (95%CI) of interstitial lung disease was 0.23 (0.07–0.74; Fig. 4A), Sjögren's syndrome was 0.13 (0.03–0.57; Fig. 4B), and anemia was 0.25 (0.09–0.70; Fig. 4C), ($p < 0.05$). For patients who used TCM for more than six months, we found that the occurrence time of extra-articular lesions in the TCM group was significantly longer than that in the control group. The occurrence probability rates (95%CI) of interstitial lung disease was 0.27 (0.16–0.44; Fig. 4D), Sjögren's syndrome was 0.25

Table 5
Changes of clinical indicators before and after treatment.

Indicators	TCM group (n = 279)		Z	*P*	Control group (n = 279)		Z	*P*
	Before treatment	After treatment			Before treatment	After treatment		
ESR (mm/h)	36.0 (18.0, 56.0)	23.0 (13.0, 38.0)	27.1	0.00	34.0 (19.0, 56.0)	23.0 (13.0, 38.0)	32.2	0.00
hs-CRP (mg/L)	14.7 (3.3, 37.2)	2.2 (0.7, 6.1)	9.3	0.00	11.0 (2.5, 36.8)	2.1 (0.6, 8.6)	13.3	0.00
RF (U/ml)	83.1 (16.5, 211.4)	67.9 (16.5, 192.9)	12.0	0.00	71.5 (18.8, 257.7)	79.3 (17.1, 235.1)	14.5	0.00
CCP (U/ml)	41.2 (3.3, 213.0)	38.6 (2.5, 200.0)	15.8	0.00	71.1 (4.5, 253.6)	48.1 (1.8, 186.0)	16.7	0.00
IgA (g/L)	2.4 (1.73, 3.1)	2.2 (1.7, 2.9)	19.0	0.00	2.3 (1.9, 3.0)	2.3 (1.7, 3.0)	19.8	0.00
IgG (g/L)	12.9 (9.9, 15.9)	11.7 (9.5, 14.7)	65.1	0.00	12.3 (9.8, 15.16)	11.7 (9.6, 14.4)	64.6	0.00
IgM (g/L)	1.2 (0.9, 1.6)	1.2 (0.8, 1.6)	4.3	0.00	1.2 (0.9, 1.7)	1.3 (0.9, 1.7)	4.6	0.00
C3 (g/L)	0.3 (0.2, 0.3)	0.2 (0.2, 0.3)	22.3	0.00	0.3 (0.2, 0.2)	1.1 (1.0, 1.2)	17.5	0.00
C4 (g/L)	0.3 (0.2, 0.3)	0.2 (0.2, 0.3)	58.5	0.00	0.3 (0.2, 0.3)	0.2 (0.2, 0.3)	56.2	0.00
HGB (g/L)	117.0 (106.0, 128.0)	119.0 (110.0, 129.0)	161.3	0.00	116.0 (106.0, 129.0)	118.0 (107.0, 129.0)	151.0	0.00

Abbreviation: ESR, erythrocyte sedimentation rate; hs-CRP, hypersensitive C-reactive protein; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; Ig, immunoglobulin; C, complement; TCM, traditional Chinese medicine; HGB, hemoglobin.
data are presented as median and interquartile range. Kruskal-Wallis test used for p-value calculation.

Table 6
Analysis of association rules between TCM treatment and clinical indicators improvement.

The antecedent	The consequent	Support (%)	Confidence (%)	Lift	*P* value
COICIS SEMEN	CRP↓	41.78	90.1	1.0	≤0.001
PORIA	CRP↓	40.9	89.9	1.0	≤0.001
TARAXACI HERBA	CRP↓	51.1	89.8	1.0	≤0.001
COICIS SEMEN	CCP↓	41.8	82.5	1.1	≤0.001
PORIA	CCP↓	40.9	82.4	1.1	≤0.001
SALVIAE MILTIORRHIZAE RADIX ET RHIZOMA	CCP↓	41.2	82.2	1.1	≤0.001
CITRI RETICULATAE PERICARPIUM	CCP↓	40.9	81.1	1.1	≤0.001
PORIA	C4↓	40.9	81.1	1.0	≤0.001
SPATHOLOBI CAULIS	C4↓	41.6	81.0	1.0	≤0.001
DIOSCOREAE RHIZOMA	C4↓	50.0	81.0	1.0	≤0.001
TARAXACI HERBA	ESR↓	51.1	80.9	1.1	≤0.001
SALVIAE MILTIORRHIZAE RADIX ET RHIZOMA	ESR↓	41.2	80.9	1.1	≤0.001
Wuwei Wentong Chubi Capsule	CRP↓	32.6	90.1	1.0	≤0.001
Huangqin Qingre Chubi Capsule	CRP↓	40.9	89.9	1.0	≤0.001
Xiaoyu Jiegu San	CRP↓	86.2	87.9	1.0	≤0.001
Furong Gao	CRP↓	81.2	87.9	1.0	≤0.001

Abbreviation: CRP, C-reactive protein; TCM, traditional Chinese medicine.
Pearson $\chi 2$ test used for p-value calculation.

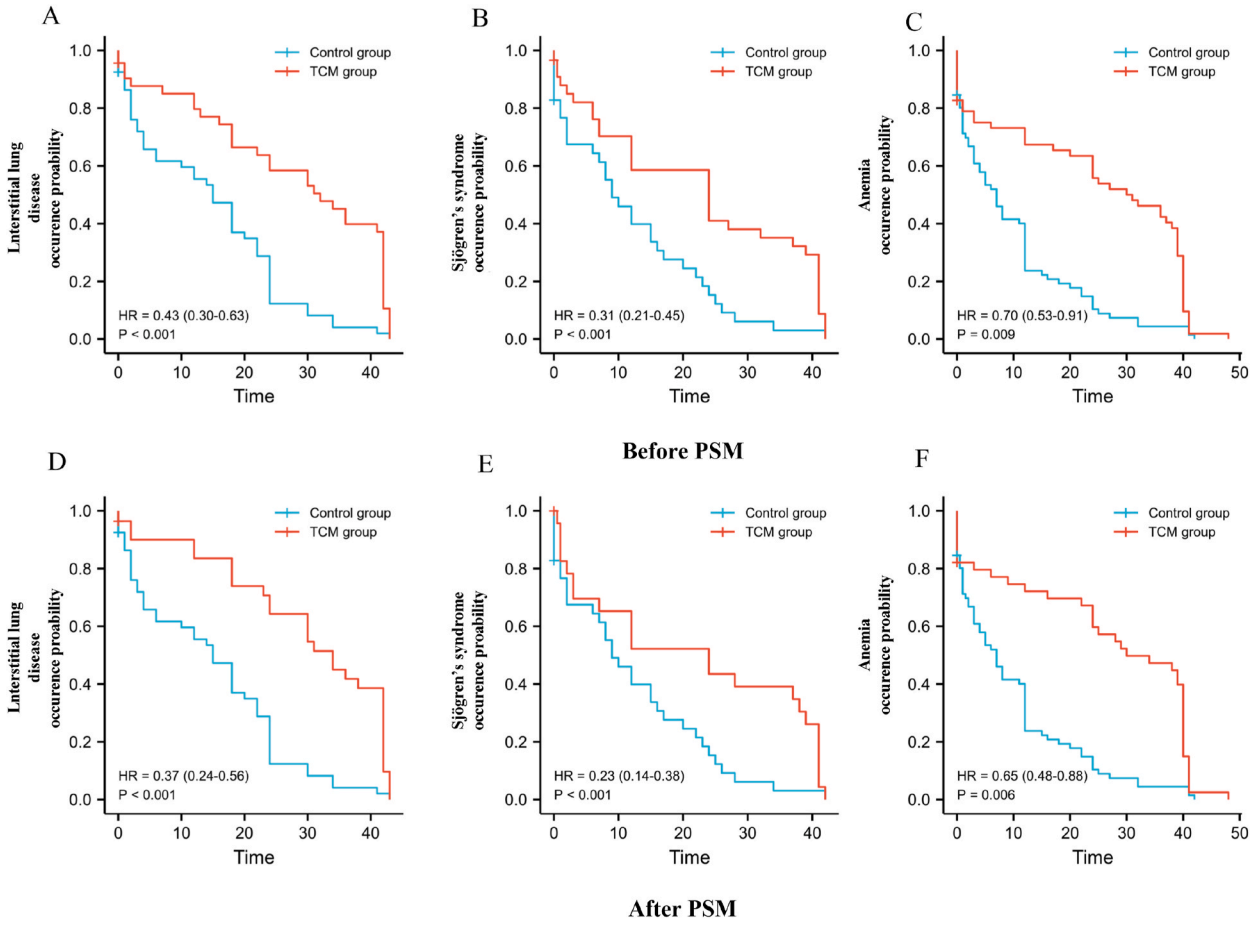

Fig. 2. Kaplan-Meier curve of extra-articular lesions occurrence probability of RA patients. A-C, K-M curve of interstitial lung disease, Sjögren's syndrome, and anemia before PSM; D-F, K-M curve of interstitial lung disease, Sjögren's syndrome, and anemia after PSM. RA, rheumatoid arthritis; TCM, traditional Chinese medicine; PSM, propensity score matching; HR, hazard ratio.

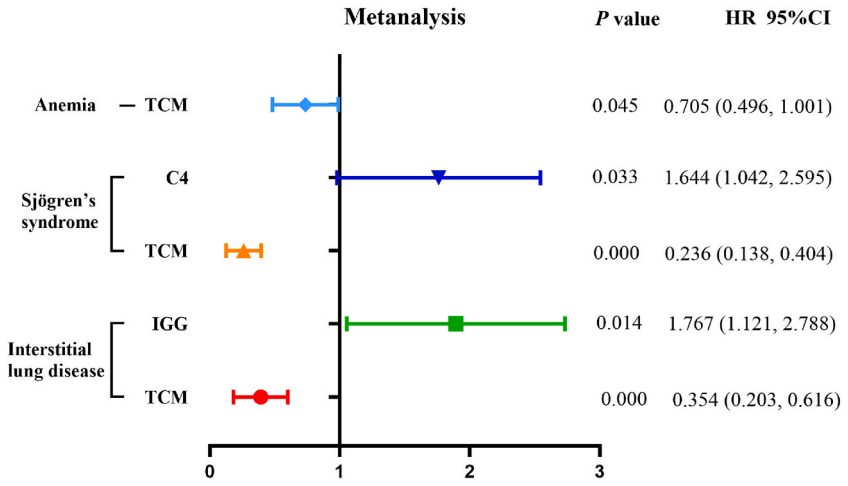

Fig. 3. Cox regression results of RA patients. TCM, traditional Chinese medicine; HR, hazard ratio.

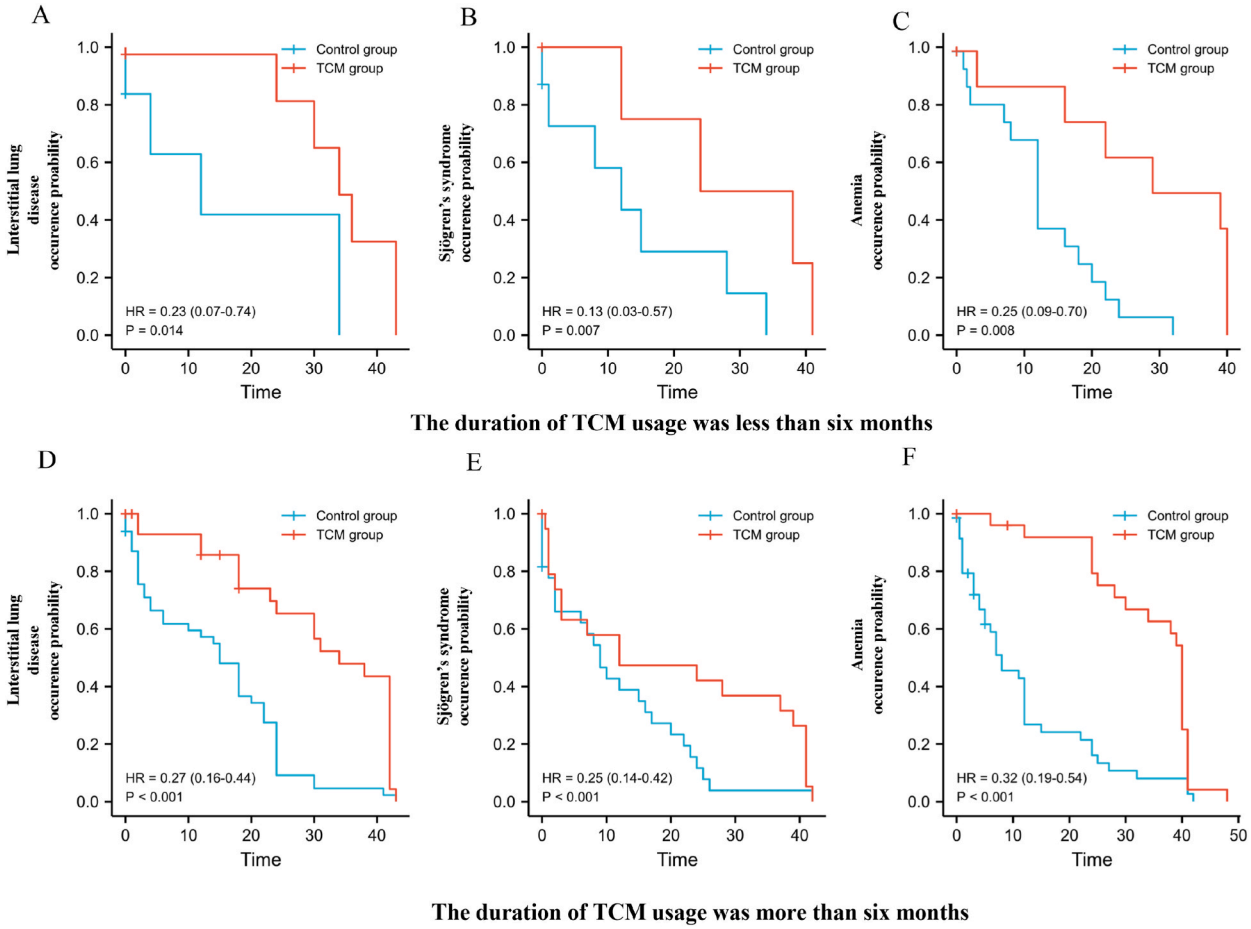

Fig. 4. Influence of TCM on extra-articular aesions occurrence of RA for the duration of TCM usage. A-C, K-M curve of interstitial lung disease, Sjögren's syndrome, and anemia when the duration of TCM usage less than six months; D-F, K-M curve of interstitial lung disease, Sjögren's syndrome, and anemia when the duration of TCM usage more than six months. TCM, traditional Chinese medicine; HR, hazard ratio.

(0.14–0.42; Fig. 4E), and anemia was 0.32 (0.19–0.54; Fig. 4F), ($p < 0.001$).

In conclusion, compared to patients in the control group, the TCM group showed certain advantages in prolonging the occurrence time of extra-articular lesions. Moreover, the longer the duration of TCM usage, the later the occurrence of extra-articular lesions.

4. Discussion

The present study is a retrospective cohort study conducted at a single center, which observed that long-term TCM treatment not only has a positive effect on the occurrence time of extra-articular lesions in RA patients but also helps reduce the probability of extra-articular lesions occurring in RA. TCM prescriptions have been used to combat diseases in ancient China, and continue to be used today based on the theories of TCM, which are the characteristics of Chinese medicine and embody the dialectical thought of Chinese medicine and the holistic view of medication. In comparison with modern medicine's precision treatment, TCM has become an increasingly important strategy for the treatment of RA in China due to its good therapeutic effect and low toxic side effects [21].

RA is a chronic autoimmune disease that can result in joint destruction and extra-articular lesions [22]. According to the theory of TCM, RA can be defined as a Bi syndrome, which is associated with wind, cold, and dampness invading the human body and causing poor circulation of Qi and blood. In clinical treatment of RA, TCM and its modification have shown efficacy and safety [23,24].

Many studies have showed that TCM is effective in treating RA, not only in reducing joint pain or swelling, but also in improving extra-articular lesions. In a large multicenter randomized controlled trial, it was found that the TCM compound Xinfeng capsule (XFC), which is composed of radix astragali, coix, tripterygium wilfordii and centipede, can effectively reduce RA joint inflammation, enhance physical function, and improve the quality of life for RA patients [25]. Furthermore, XFC was found to improve lung function and respiratory symptoms [26]. Through clinical data mining research on 10,000 cases of RA, Fang et al. found that there was a positive correlation between TCM treatment and the improvement of immune inflammatory indicators in RA patients; the longer TCM was used, the better the treatment effects were observed [27]. A recent study has shown that TCM compound XFC capsule has many therapeutic targets in RA and exerts multi-component, multi-target and multi-network anti-inflammatory and anticoagulant effects through immune regulation, inflammation, and other pathways [28]. In addition, when studying the risk of readmissions in 893 RA patients with anemia, TCM was found to be a protective factor associated with a reduced risk of readmissions in RA patients with anemia [29]. In their latest published study, Sun et al. found that the TCM compound significantly inhibited immune inflammation, oxidative stress, synovial hyperplasia, and cartilage destruction by upregulating LINC00638 and activating the Nrf2/HO-1 pathway while improving the ultrastructure of synovial cells in adjuvant arthritis rats. These literatures, from different perspectives, demonstrated that TCM is an important component of RA treatment that has prominent advantages in reducing adverse reactions and improving RA joint symptoms [20]. However, most studies are observational studies with small samples size that lack relevant evidence-based medicine. Therefore, our study attempts to deeply explore and demonstrate the efficacy of TCM in the treatment of RA and its extra-articular lesions based on a relatively large retrospective study.

The results of our study showed that TCM treatment for extra-articular lesions in RA can be classified into four main categories of drugs: invigorating the spleen to eliminate dampness, promoting blood circulation to remove meridian obstruction, dispelling wind and eliminating dampness, and clearing away heat and toxic materials. These treatments had a positive effect on patients with RA and effectively reduced the risk of extra-articular lesions in RA. We balanced the covariates by PSM between the two groups regarding the imbalanced baseline clinical data. Long-term TCM treatment still improved laboratory indicators in RA patients with extra-articular lesions after PSM. Cox multivariate regression analysis also showed that taking TCM was an independent protective factor that affected the prognosis of RA patients with extra-articular lesions. Moreover, C4 was identified as an independent risk factor for RA patients with Sjögren's syndrome, and abnormally high levels of IgG were identified as independent risk factors for RA patients with interstitial lung disease.

Through further study on the effect of TCM treatment on the occurrence of extra-articular lesions in RA over the duration of TCM usage, we found that the occurrence time of extra-articular lesions in RA for TCM usage less than six months was longer than for TCM usage greater than six months. Nonetheless, our findings suggest a tendency to decrease the occurrence of extra-articular lesions in RA with TCM treatment. However, these results need to be verified by more rigorous clinical trials in the future. Additionally, the median occurrence time of Sjögren's syndrome in both the TCM and control groups appeared to be much shorter compared to a previous report. The previous report stated that the median time for the development of Sjögren's syndrome among patients with RA was approximately 8–14 years [30,31]. We speculate that the differences in the occurrence time of Sjögren's syndrome may be attributed to the fact that our study primarily focused on patients from Anhui province, located in central China. Anhui experiences a humid climate during summer and dry conditions during winter, and the local population tends to have a dietary preference for spicy and stimulating foods. These demographic, climatic, and dietary factors could potentially contribute to the observed variations in the occurrence time of Sjögren's syndrome.

However, there were some limitations to this study. For instance, the number of cases was relatively small, and the long follow-up time may have resulted in lost to follow-up bias, poor compliance, or insufficient data. Furthermore, the majority of patients included in this study were from Anhui, China, which may limit generalizability of our findings and necessitates further verification through large multicenter studies. In addition, indicators of disease severity are important measures in the management and assessment of rheumatoid arthritis, and information like the exposure time of TCM preceding the cohort entry is needed to adjust. Unfortunately, they were not available in the data set used for the current study. Despite these limitations, the study involved a large cohort, and the clinical follow-up was lengthy, which required a substantial investment of manpower, materials, and financial resources. Consequently, the evidence level of our research results was not particularly high. Therefore, the next essential step is to conduct a multicenter, randomized, controlled, double-blind trial, which is expected to provide a higher level of evidence-based medical support

for the TCM treatment of RA.

5. Conclusion

We conducted a retrospective cohort study that demonstrated the positive effects of long-term TCM treatment on reducing the occurrence time and probability of extra-articular lesions in RA patients. These findings suggest that TCM treatment can be flexibly applied throughout the entire process of RA treatment.

Fundings

This work was supported by grants from Anhui Province Major and Intractable Diseases Collaborative Research Project of Traditional Chinese and Western Medicine (Anhui Traditional Chinese Medicine Development [2021] No. 70); Ministry of Science and Technology National Key Research and Development Program Chinese Medicine Modernization Research Key Project (2018YFC1705204); National Nature Fund Program (82074373); The University Synergy Innovation Program of Anhui Province (GXXT-2020-025); Anhui Famous Traditional Chinese Medicine Liu Jian Studio Construction Project (Traditional Chinese Medicine Development Secret [2018] No. 11); 12th batch of "115" Innovation team of Anhui Province (Anhui Talent Office [2019] No. 1).

Data availability statement

All data are available. We provide data in the Mendeley Data repository according to Elsevier policy. Research data of this article can be found online at https://data.mendeley.com/datasets/wcbwzv2hb4/1.

CRediT authorship contribution statement

Jianting Wen: Writing – original draft, Supervision. **Jian Liu:** Writing – review & editing, Funding acquisition, Data curation, Conceptualization. **Lei Wan:** Validation, Formal analysis. **Ling Xin:** Software, Formal analysis, Data curation. **Yue Sun:** Supervision, Resources, Methodology. **Fanfan Wang:** Visualization, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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