





Traditional Chinese Medicine is Associated with the Reduction in Endpoint Events in Patients with Gouty Arthritis: Cohort Study and Association Rule Analysis

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Objective: This study aimed to evaluate the effect of traditional Chinese medicine (TCM) on endpoint events in patients with gouty arthritis (GA).

Methods and Materials: A total of 2091 hospitalized GA patients were followed up by telephone, and propensity score matching (PSM) was used to reduce potential bias in the study design. Cox proportional risk model and Kaplan-Meier survival curve were utilized to analyze the impact and time effect of factors on the readmission of GA patients. The differences of laboratory indexes before and after treatment between the low and high exposure groups were compared, and the types and frequencies of medicines in all patients were counted. Association rule analysis was performed to investigate the association between TCM and test indexes or endpoint events.

Results: After 1:1 PSM, 187 patients were enrolled in the TCM group and 187 patients in the non-TCM group. The incidence of readmission, new tophus, and all-cause death was lower in the TCM group than that in the non-TCM group ($P < 0.05$). Cox proportional risk regression analysis showed that TCM, NSAIDs and uric acid lowering drug were independent protective factors for GA readmission. The protective effect was enhanced by the prolongation of TCM treatment and the drug combinations. Kaplan-Meier survival curves indicated a significantly lower readmission rate in the high exposure group than in the low exposure group ($P < 0.01$). Compared with before treatment, NLR, hs-CRP, UA, TC and other laboratory indexes of the low and high exposure groups were improved after treatment ($P < 0.01$); The improvement of TG and TC in the high exposure group was more significant than the low exposure group ($P < 0.01$). The analysis of medicines used by all patients identified the top 20 Chinese herbal medicines and the top 20 Chinese patent medicines. The core drugs identified through association rule analysis that can improve test index and reduce the incidence of endpoint events include Yiyiren, Danshen, and HQC, among others. The network diagram of association rule analysis intuitively shows the relationship between core drugs and “improvement of indicators” and “the absence of endpoint events”.

Conclusion: TCM is associated with a reduced incidence of endpoint events in patients with GA.

Keywords: gouty arthritis, cohort study, traditional Chinese medicine, Chinese patent medicine, neutrophil to lymphocyte ratio

Introduction

Gouty arthritis (GA) is the most common form of Crystal arthritis associated with diet, obesity, and genetics. Pathologically, GA is triggered by the deposition of sodium urate crystals in joints due to excessive production or impaired excretion of uric acid (UA).^{1,2} GA typically presents with painful redness, swelling, and even restricted movement of joints.³ The incidence of GA is on the rise in the past 10 years and shows a younger trend, and men are more prone to GA onset than women.^{4,5} Moreover, GA patients at the advanced stage are vulnerable to severe complications such as cardio-cerebrovascular disease, kidney disease, and liver disease, which significantly compromise the quality of life and pose heavy economic burdens.⁶

Encouragingly, traditional Chinese medicine (TCM) has shown promising efficacy in alleviating the clinical symptoms of GA. A randomized controlled trial of Qingre Lishi Decoction (QLRD)⁷ demonstrated that the QLRD group was outperformed the control group (basic treatment and colchicine tablets) in improving joint symptom, effective rate, uric acid (UA), erythrocyte sedimentation rate (ESR), interleukin-1 β (IL-1 β), NALP3. Some researchers⁸ have found that GA patients receiving the external application of compound Qingbi granules combined with basic medicine exhibited better joint pain and swelling relief, CRP and UA level, onset time, and efficacy duration than those treated with basic medicine alone, and no significant difference was found in the incidence of adverse events between the groups. Many scholars believe that the application of TCM can inhibit inflammatory responses, promote the dissolution and excretion of urate crystals, and prevent liver and kidney damage in GA patients.^{9–11} Since long-term use of Western medicine alone may cause damage to liver and kidney function, it is of great practical significance to explore the advantages of TCM application in GA and seek the possibility of TCM as a complementary or even alternative therapy for GA.

The real-world observational cohort study is particularly suitable for exploring the effects of TCM in managing chronic refractory diseases in the clinic.^{12–14} Therefore, we employed a cohort study to obtain evidence-based medical proof of TCM for GA. This cohort study followed up 2091 GA patients at the First Affiliated Hospital of Anhui University of Chinese Medicine and statistically analyzed the occurrence of endpoint events and medication. We then used association rule analysis to find the core drugs of TCM in the treatment of GA and confirm the relationship between TCM and the occurrence of GA endpoint events.

Methods and Materials

Data Collection

Diagnostic Criteria

The diagnostic criteria of GA referred to the gout classification criteria developed by the American College of Rheumatology and the European League Against Rheumatism in collaboration in 2015 and the guidelines for the combined diagnosis and treatment of gout and hyperuricemia developed by the Chinese Academy of Traditional Chinese Medicine in 2021.^{15,16} All patients with GA were admitted by a senior rheumatologist in our hospital according to the above two guidelines.

Inclusion Criteria

- (1) Inpatients eligible for GA diagnosis between May 2012 and October 2022 at the First Affiliated Hospital of Anhui University of Chinese Medicine;
- (2) Age of 18–85 years old.

Exclusion Criteria

- (1) Patients requiring frequent use of high-dose hormone for combined diseases;
- (2) Patients complicated with severe primary diseases involving the respiratory system and hematopoietic system;
- (3) Patients unable to cooperate (eg, suffering from mental illness);
- (4) Patients with important items missing or massive items missing from the medical case data.

Therapeutic Drugs

Referring to the guidelines for diagnosis and treatment of gout and hyperuricemia with integrated traditional Chinese and Western medicine, the drugs used were recorded during the follow-up period.¹⁷ The conventional Western medicine included colchicine, diclofenac sodium, celecoxib, febuxostat, allopurinol, etc. The commonly used TCM included Chinese patent medicine (CPM) and Chinese herbal medicine decoction (TCM decoction). (1) CPM: Huangqin Qingre Chubi Capsule (HQC), Xinfeng Capsule (XFC), Xinhuang Tablet, etc.; (2) TCM decoction: Simiao San, Dangguiniantong Decoction, Guizhi Shaoyao Zhimu Decoction, Shuanghe Decoction, Xuanbi Decoction, Qinpi Gout Formula, etc.; (3) Drugs for treating other diseases.

Collection of Data

A questionnaire was designed for the GA patient. The patients discharged with a primary diagnosis of GA were retrieved through the medical case information management system of the hospital and strictly screened according to inclusion and

exclusion criteria. The general information of eligible cases was entered into the questionnaire, including name, gender, age, and telephone number.

Through telephone follow-up, the patient's concurrent diseases (including the disease name, onset time, and change of condition), other diseases, drug use after discharge (including the drug name, dosage, and time), and occurrence of endpoint events (including the type, time and frequency) were inquired and recorded. Subsequently, the test indexes of all patients with successful follow-up at the time of admission and during the follow-up period were retrieved from the case information management system, including erythrocyte sedimentation rate (ESR), platelet count (PLT), neutrophil-to-lymphocyte ratio (NLR), white blood cell (WBC), complement C3, complement C4, high sensitive C-reactive protein (hs-CRP), uric acid (UA), creatinine (Cr), blood urea nitrogen (BUN), triglycerides (TG), and total cholesterol (TC). If a patient's hs-CRP exceeded 20mg/L, the corresponding value was supplemented using that patient's CRP.

All follow-up visits were done by our specialized physicians, and at least two physicians were involved in the supervision and verification of the data. The following flowchart depicts the screening and grouping process of GA patients (Figure 1).

Data Processing

Definition

Patients who did not receive TCM decoction and CPM during the follow-up period were defined as the non-TCM group, while patients who received TCM decoction or CPM as the TCM group. Further, the patients with a duration of TCM decoction or CPM for ≤ 3 months were assigned to the low exposure group, while those with a duration of TCM decoction or CPM for > 3 months were assigned to the high exposure group.

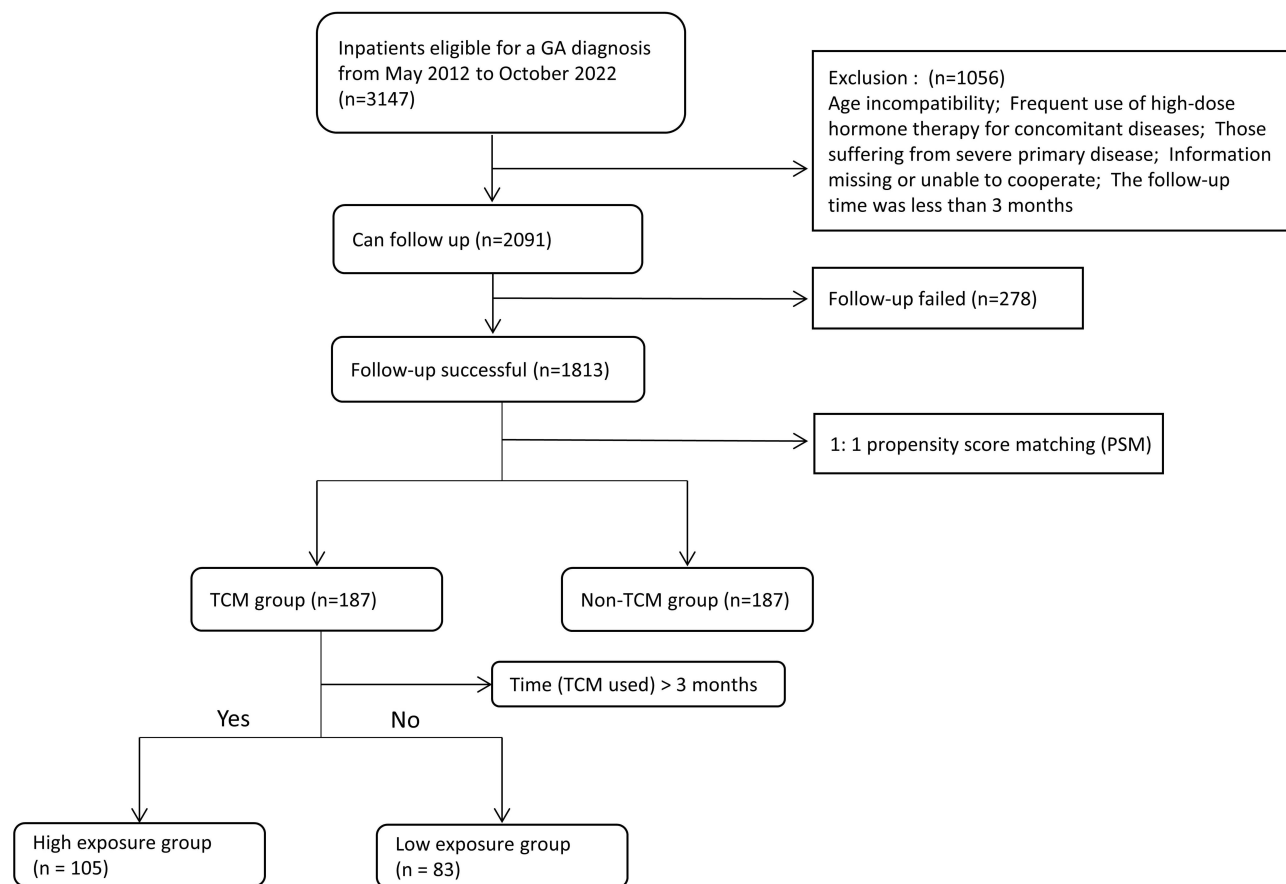


Figure 1 Flowchart of the study population.

Abbreviations: GA, gouty arthritis; TCM, traditional Chinese medicine.

The combined diseases of GA were hypertension, kidney disease, hyperlipidemia, and diabetes mellitus. The basic medicines of GA were mainly non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, glucocorticoids, and uric acid-lowering drugs. The endpoint events were defined as (1) readmission, (2) new tophus (tophus appears in body regions where tophus has not previously formed), (3) surgery (joint cavity irrigation, tophi excision, Joint repair or replacement, etc), (4) extra-articular lesions (gouty nephropathy, cardiovascular diseases, metabolic diseases, etc) and (5) all-cause death. Among them, (1) was the primary endpoint, and (2), (3), (4), (5) were the secondary endpoints.

Propensity Score Matching (PSM)

Since the number of GA cases who did not receive TCM decoction and CPM in our institution was small and the baseline status of GA patients might be an influential factor of endpoint events, we used propensity score matching (PSM) to eliminate baseline differences. The variables used for matching included gender, age, previous combined diseases (hypertension, kidney disease, hyperlipidemia, and diabetes mellitus), and basic medicines (NSAIDs, colchicine, glucocorticoids, and uric acid-lowering drugs). The grouping variables were TCM group and non-TCM group. The above covariates were used to generate scores for each patient using a multivariate logistic regression model with a 1:1 nearest-neighbor algorithm (caliper = 0.2). Each eligible patient was matched according to the score to obtain a matched cohort and perform baseline statistics.

Cox Proportional Risk Regression Analysis

Univariate and multivariate Cox regression models were constructed with the covariates including age, gender, hypertension, kidney disease, diabetes mellitus, hyperlipidemia, NSAIDs, colchicine, glucocorticoids, uric acid lowering drug, TCM treatment, duration of TCM treatment and drug combinations. The time effect of each covariate on the target variable “readmission” was analyzed to identify the independent influencing factors.

Kaplan-Meier Survival Curves

The cumulative risk of readmission events in patients in the TCM and non-TCM groups was compared using Kaplan-Meier survival curves. The TCM group was further divided into low and high exposure groups according to the duration of exposure to analyze the effect of the duration of TCM intervention on the risk of readmission events.

Association Rule Analysis and Network Diagram

The association between drugs and GA clinical indexes was analyzed using the Apriori module in SPSS Modeler 18.0. The use of a single herbal medicine or CPM was recorded as T, otherwise as F; the improvement of test indexes was recorded as T, otherwise as F. In addition, the use of a single herbal medicine or CPM was set as the antecedent (LHS, X) and the test index as the consequent (RHS, Y). The minimum Support was set at 20%, the minimum Confidence was 80%, and the Lift was greater than 1.

Similarly, the association between drugs and endpoint events was analyzed. The use of a single herbal medicine or CPM was recorded as T, otherwise as F; the absence of endpoint events was recorded as T, otherwise as F. The remaining settings were as before.

The association rule formula¹⁸ is as follows.

$$\text{Support}(X \rightarrow Y) = \delta((X \cup Y))/N \quad (1)$$

$$\text{Confidence}(X \rightarrow Y) = \delta((X \cup Y))/(\delta(X)) \quad (2)$$

$$\text{Lift}(X \rightarrow Y) = \text{Confidence}((X \rightarrow Y))/(\delta(Y)) \quad (3)$$

Finally, the most representative associations were listed according to the results of Support, Confidence, and Lift, and the network diagram of the above associations was drawn.

Statistical Methods

Since some of the variables in this study contained missing values, the method of multiple imputations was used to fill the missing values to maximize the statistical power and reduce the bias. Continuous variables conforming to normal distribution were expressed as mean \pm standard deviation and compared using the *t*-test. Continuous variables that did not

conform to normal distribution were expressed as median (interquartile spacing) [M (P25, P75)] and compared using the Mann–Whitney *U*-test. Categorical variables were expressed as frequencies (percentages) and compared using the chi-square test or Fisher's test. A value of $P < 0.05$ was considered statistical significance.

Processing Tools

All data were imported into Excel 2019, SPSS Statistics 26.0, and SPSS Modeler 18.0 for analysis. The images were visualized using Cytoscape 3.9.1.

Results

Inclusion, Exclusion and Follow-Up Results

The data of 3147 patients with a primary diagnosis of GA discharged between May 2012 and October 2022 were retrieved from the medical case information management system. According to the inclusion and exclusion criteria, 184 patients with age incompatibility were excluded; 138 patients who required frequent high-dose hormone for combined diseases were excluded; 432 patients with severe primary diseases were excluded; 211 patients with incomplete information or unable to cooperate were excluded; 91 patients with less than 3 months of follow-up were excluded. A total of 2091 patients were finally included for follow-up, and 1813 cases were successfully followed up, with a failure rate of 13.2%.

Among the 1813 patients, there were 1737 (95.8%) male and 76 (4.2%) female, aged 18–85 years [mean (54.89 ± 15.14) years], and the duration of follow-up ranged from 3.0 months to 10.5 years [mean (50.58 ± 30.26) months]. There were 188 cases in the non-TCM group and 1625 cases in the TCM group.

Baseline Characteristics of GA Patients in the TCM and Non-TCM Groups Before and After PSM Matching

There were significant differences in the use of some basic drugs such as NSAIDs, colchicine, and uric acid-lowering drugs between the two groups before matching ($P < 0.05$). To avoid bias caused by the baseline, we used the 1:1 PSM to balance the bias between the two groups in terms of general conditions, combined diseases, and basic medicines. After matching, there were 187 cases in each of the two groups, with no statistically significant differences in age, gender, combined diseases, and basic medicines ($P > 0.05$). In terms of endpoint events, the incidence of recurrent and newly-onset tophus and all-cause death was significantly lower in the TCM group than that in the non-TCM group ($P < 0.05$). In addition, surgery and extra-articular lesions were not statistically different between the two groups ($P > 0.05$; [Table 1](#)).

Influential Factors of GA Readmission

We defined five endpoint events, of which “readmission” best represented the disease progression. Therefore, we used a Cox proportional risk model to analyze the risk factors for readmission in patients with GA. Univariate analysis showed that the risk of GA readmission was significantly lower in the TCM group compared with that in the non-TCM group [hazard ratio (HR) = 0.65, 95% confidence interval (95% CI) = 0.41–0.71, $P < 0.01$]. The risk of readmission was also significantly lower in patients taking NSAIDs (HR = 0.69, 95% CI = 0.37–0.91, $P = 0.04$) and uric acid-lowering drugs (HR = 0.57, 95% CI = 0.39–0.94, $P = 0.01$). In contrast, the risk of readmission was significantly higher in patients with combined hypertension (HR = 3.31, 95% CI = 2.23–3.97, $P = 0.03$) and kidney disease (HR = 2.23, 95% CI = 1.85–2.81, $P < 0.01$) ([Table 2](#)).

The results of multivariate analysis showed that combined kidney disease, NSAIDs, uric acid lowering drug, TCM treatment, duration of TCM treatment, and drug combinations were independent influencing factors for readmission. Among them, combined kidney disease (HR=2.04, 95% CI=1.66–2.79, $P < 0.01$) was a risk factor, while NSAIDs (HR=0.54, 95% CI=0.32–0.81, $P=0.01$), uric acid-lowering drugs (HR=0.64, 95% CI=0.34–1.57, $P=0.02$), and TCM treatment (HR=0.59, 95% CI=0.38–0.82, $P=0.02$) were protective factors. Notably, TCM treatment significantly reduced the risk of readmission by 41% in patients with GA.

Table I Baseline Characteristics of GA Patients Before and After PSM in the TCM Group and Non-TCM Group

Characteristic	Before PSM Matched				After PSM Matched			
	Total (n=1813)	Non-TCM Group (n=188)	TCM Group (n=1625)	P value	Total (n=374)	Non-TCM Group (n=187)	TCM Group (n=187)	P value
Age(years), n(%)								
≤60	1151(63.49)	116(61.70)	1035(63.69)	0.592	242(64.71)	115(61.50)	127(67.91)	0.194
>60	662(36.51)	72(38.30)	590(36.31)		132(35.29)	72(38.50)	60(32.09)	
Gender, n(%)								
Male	1737(95.81)	182(96.81)	1555(95.69)	0.470	364(97.33)	181(96.79)	183(97.86)	0.521
Female	76 (4.19)	6(3.19)	70(4.31)		10(2.67)	6(3.21)	4(2.14)	
Combined diseases, n(%)								
Hypertension	446(24.60)	53(28.19)	393(24.18)	0.227	94(25.13)	52(27.81)	42(22.46)	0.233
Kidney disease	873(48.15)	95(50.53)	778(47.88)	0.490	175(46.79)	94(50.27)	81(43.32)	0.178
Hyperlipidemia	910(50.19)	94(50.00)	816(50.22)	0.955	192(51.34)	94(50.27)	98(52.41)	0.679
Diabetes mellitus	268(14.78)	27(14.36)	241(14.83)	0.864	51(13.64)	27(14.44)	24(12.83)	0.651
Basic medicine, n(%)								
NSAIDs	866(47.77)	159(84.57)	707(43.51)	0.001	316(84.49)	158(84.49)	158(84.49)	1.000
Colchicine	1072(59.13)	165(87.77)	907(55.82)	0.001	332(88.77)	164(87.70)	168(89.84)	0.512
Glucocorticoid	373(20.57)	47(25.00)	326(20.06)	0.113	89(23.80)	46(24.60)	43(22.99)	0.716
Uric acid lowering drug	1169(64.48)	173(92.02)	996(61.29)	0.001	340(90.91)	172(91.98)	168(89.84)	0.472
Endpoint events, n (%)								
Readmission	1386(76.45)	161(85.64)	1225(75.38)	0.002	293(78.34)	160(85.56)	133(71.12)	0.001
New tophus	388(21.40)	60(31.91)	328(20.18)	0.001	102(27.27)	60(32.09)	42(22.46)	0.037
Surgery	32(1.77)	6(3.19)	26(1.60)	0.117	7(1.87)	6(3.21)	1(0.53)	0.056
Extra-articular lesion	446(24.60)	63(33.51)	383(23.57)	0.003	115(30.75)	63(33.69)	52(27.81)	0.218
All-cause death	64(3.53)	15(7.98)	49(3.01)	0.001	21(5.61)	15(8.02)	6(3.21)	0.043

Abbreviations: TCM, traditional Chinese medicine; PSM, propensity score matching; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2 The Cox Proportional Hazards Model for the Readmission of GA Patients

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age (year)						
≤ 60	–	–	–	–	–	–
>60	1.09	0.98–1.21	0.11	0.91	0.81–1.03	0.14
Gender						
Male	–	–	–	–	–	–
Female	0.78	0.60–1.01	0.06	1.01	0.91–1.25	0.13
Combined diseases						
Hypertension	3.13	2.23–3.97	0.03	1.44	1.09–2.45	0.17
Kidney disease	2.23	1.85–2.81	<0.01	2.04	1.66–2.79	<0.01
Hyperlipidemia	1.84	0.53–2.31	0.13	2.77	2.03–3.45	0.14
Diabetes mellitus	1.14	0.82–1.57	0.44	1.21	0.96–1.84	0.70
Basic medicine						
NSAIDs	0.69	0.37–0.91	0.04	0.54	0.32–0.81	0.01
Colchicine	0.77	0.43–0.99	0.68	0.82	0.55–1.28	0.83
Glucocorticoid	0.97	0.56–1.33	0.23	0.87	0.77–1.41	0.56
Uric acid lowering drug	0.57	0.39–0.94	0.01	0.64	0.34–1.57	0.02
TCM treatment						
Yes	0.65	0.41–0.71	<0.01	0.59	0.38–0.82	0.02
No	–	–	–	–	–	–
Duration of TCM treatment						
Low exposure (≤3 months)	–	–	–	–	–	–
High exposure (>3 months)	0.82	0.73–0.92	<0.01	0.80	0.78–0.84	<0.01
Drug combinations						
Only use TCM	–	–	–	–	–	–
Low exposure&uric acid lowering drug	0.69	0.59–0.81	<0.01	0.62	0.46–0.71	0.01
High exposure & uric acid lowering drug	0.63	0.50–0.77	0.03	0.55	0.47–0.67	<0.01
Low exposure&NSAIDs	0.71	0.61–0.84	<0.01	0.68	0.42–0.81	0.01
High exposure&NSAIDs	0.70	0.54–0.89	<0.01	0.66	0.44–0.79	<0.01

Abbreviations: HR, hazards ratio; 95% CI, 95% confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; TCM, traditional Chinese medicine.

Based on the above results, we further analyzed the impact of the duration of TCM treatment on readmission in GA. Similarly, we also examined the effects of TCM in combination with uric acid-lowering drugs or NSAIDs on readmission in GA. The results showed that compared to the low exposure group, the high exposure group (HR=0.80, 95% CI=0.78–0.84, $P < 0.01$) could reduce the readmission risk in GA by 20%. Moreover, drug combinations such as low exposure & uric acid-lowering drug, high exposure & uric acid-lowering drug, low exposure & NSAIDs, and high exposure & NSAIDs all demonstrated varying degrees of reduced readmission risk in GA compared to those using only TCM (all P values ≤ 0.01) (Table 2).

Kaplan–Meier Survival Curve Analysis of the Time Effect of TCM on GA Readmission

Kaplan–Meier survival curves were used to compare the readmission risk between the TCM group and the non-TCM group. And we further explore the effect of TCM duration on the readmission risk. In the TCM group, GA patients treated with TCM decoction or CPM for ≤ 3 months were defined as the low exposure group, and those with > 3 months of TCM decoction or CPM as the high exposure group. The curves demonstrated that GA patients usually experienced readmission within a relatively short period of time after an episode, and approximately 50% of patients experienced readmission within three years. The risk of readmission was significantly lower in the TCM group than that in the non-TCM group (log-rank $P < 0.01$; (Figure 2a)). Also, the risk of readmission was significantly lower in the high exposure group than that in the low exposure group (log-rank $P < 0.01$; (Figure 2b)). There was also a significant difference in the readmission rate between the high and low exposure groups ($P < 0.01$; Table 3).

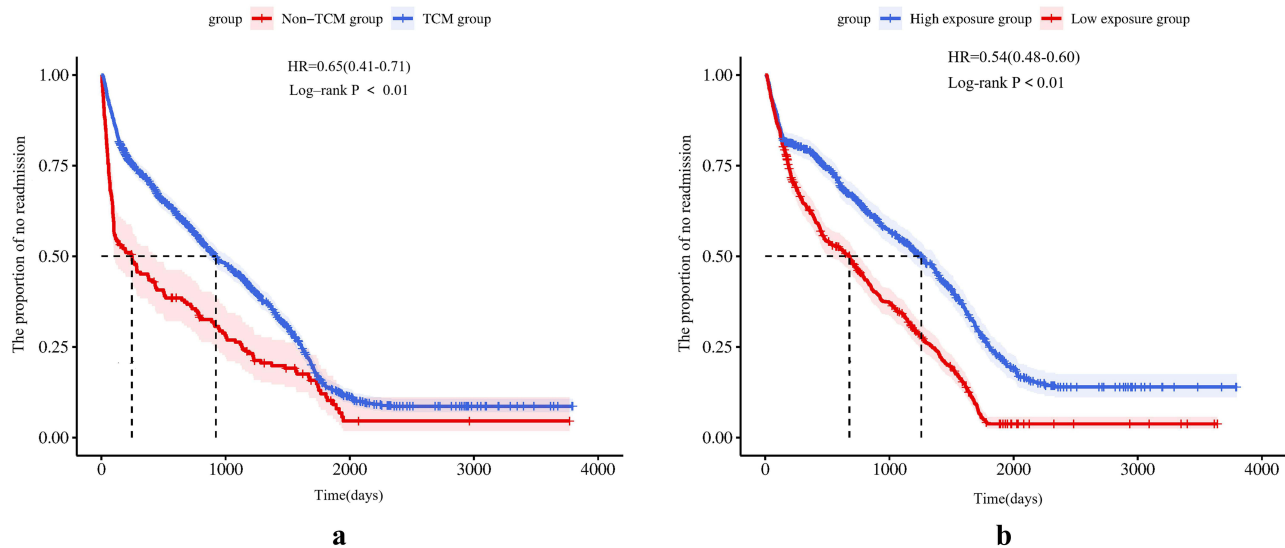


Figure 2 The K-M survival curve of readmission in GA patients. (a) The K-M survival curve was used to analyze the effect of TCM on the risk of readmission. (b) The K-M survival curve was utilized to assess the effect of TCM intervention duration on the risk of readmission.

Abbreviations: TCM, traditional Chinese medicine; HR, hazard ratio.

Effect of TCM Intervention Duration on the Test Indexes of GA Patients

ESR, PLT, NLR, C3, C4, CRP, UA, and TC levels were reduced in the low exposure group after treatment compared to those before treatment ($P < 0.01$). Similarly, ESR, PLT, NLR, C3, C4, CRP, UA, Cr, TG, and TC levels were reduced in the high exposure group after treatment compared to those before treatment ($P < 0.01$). Moreover, the changes of the above indexes before and after treatment in the low and high exposure groups were compared, and the results showed that the decrease in TG and TC levels was more pronounced in the high exposure group than that in the low exposure group ($P < 0.01$; Table 4).

Use Frequency of Herbal Medicines and CPMs in GA Patients

We analyzed the drug prescriptions of 1625 GA patients in the TCM group before PSM matching and calculated the use frequency of drugs. The top 20 herbal medicines used frequently could be divided into five major categories, namely, diuretic and dehumidifying medicine, heat-clearing and detoxifying medicine, blood-activating and stasis-removing medicine, spleen-strengthening and qi-invigorating medicine, and wind-dispelling and dehumidification medicine, as shown in Table 5. Similarly, the top 2 CPMs in the use frequency were HQC and XFC (Table 6).

Association Rule Analysis of TCM Treatment and Test Indexes in GA Patients

Association rule analysis was performed with herbal medicines and CPMs as the antecedent and test indexes improvement as the postcedent. Specifically, the use of herbal medicines and CPMs was defined as T and the non-use as F. The decrease of ESR, PLT, NLR, WBC, C3, C4, hs-CRP, UA, Cr, BUN, TG, and TC was recorded as T and the non-decrease was defined as F. The results showed that the use of Yiyiren, Cheqiancao, Tufuling, Huangbai, Chuanniuxi, and HQC

Table 3 The Incidence of Readmission in the Low Exposure Group and High Exposure Group

	Low Exposure (n=727)	High Exposure (n=898)	P value
Readmission	644(88.58%)	581(64.70%)	<0.01
No readmission	83(11.42%)	317(35.30%)	

Table 4 Effect of TCM Intervention Duration on Test Indexes in GA Patients

Indexes	Low Exposure Group (n=727)		High Exposure Group (n=898)	
	Before Treatment	After Treatment	Before Treatment	After Treatment
ESR (mm/h)	24.00(10.00,48.00)	15.00(7.00,28.00)*	23.00(10.00,44.00)	14.00(7.00,27.00)
PLT (10 ⁹ /L)	212.00(164.00, 261.00)	202.00(158.00, 259.00)*	211.00(167.75, 260.25)	197.00(149.75, 254.00)#
NLR	3.53(2.30,5.70)	2.81(1.90,4.23)*	3.47(2.23,5.41)	2.80(1.83,4.21)#
WBC (10 ⁹ /L)	7.80(6.16,9.98)	7.91(6.26,10.31)	7.74(6.04,10.19)	7.92(6.26,10.31)
C3 (g/L)	113.00(1.57, 140.20)	106.40(1.42, 130.10)*	108.70(1.45, 139.55)	102.20(1.36, 127.83)#
C4 (g/L)	27.70(0.47,36.60)	25.00(0.41,34.00)*	26.05(0.41,35.73)	24.40(0.37,32.60)#
hs-CRP (mg/L)	17.30(3.02,52.11)	1.91(0.77,6.84)*	14.91(3.09,48.34)	2.22(0.82,8.03)#
UA (μmol/L)	476.00(398.00, 558.00)	427.00(360.00, 503.00)*	487.50(414.00, 576.00)	427.00(363.00, 507.00)#
Cr (μmol/L)	83.40(70.30, 105.60)	82.80(71.30, 100.50)	82.90(71.50, 101.83)	82.25(70.38,98.25)#
BUN (mmol/L)	5.63(4.49,7.36)	5.81(4.57,7.76)	5.55(4.52,7.24)	5.64(4.33,7.35)
TG (mmol/L)	1.49(1.01,2.22)	1.58(0.96,2.24)	1.46(1.01,2.16)	1.42(0.81,2.31)# ^Δ
TC (mmol/L)	4.57(3.97,5.25)	4.41(3.72,5.11)*	4.71(3.96,5.46)	4.35(3.63,5.15)# ^Δ

Notes: Compared with the low exposure group before treatment, *P < 0.01. Compared with the high exposure before treatment, #P < 0.01. Compared with the low exposure group difference (after treatment - before treatment), ^ΔP < 0.01.

Abbreviations: ESR, erythrocyte sedimentation rate; PLT, platelet; NLR, neutrophil-lymphocyte ratio; WBC, white blood cell; C3, complement component 3; C4, complement component 4; hs-CRP, high-sensitive C-reactive protein; UA, uric acid; Cr, creatinine; BUN, blood urea nitrogen; TG, triglyceride; TC, total cholesterol.

Table 5 The Use Frequency of Chinese Herbal Medicines

Category	Herb	Generic Name	Number(%)	Medicinal Part	Meridian Tropism
Diuretic and dehumidifying medicine	Yiyiren	<i>Coix Seed</i>	1452(89.35%)	Mature kernel	Spleen, stomach, lung
	Cheqiancao	<i>Plantago depressa Willd</i>	1332(81.97%)	Whole grass	Liver, kidney, bladder
	Zexie	<i>Alisma orientalis</i>	1003(61.72%)	Tuber	Kidney, bladder
	ChuiPENCAO	<i>Sedum sarmentosum Bunge</i>	713(43.88%)	Whole grass	Liver, gallbladder, small intestine
	Fuling	<i>Indian Buead</i>	646(39.75%)	Sclerotium	Heart, lung, spleen, kidney
Heat-clearing and detoxifying medicine	Bixie	<i>Dioscorea hypoglauca Palibin</i>	869(53.48%)	Root	Kidney, stomach
	Huangbai	<i>Phellodendron chinense Schneid</i>	1239(76.25%)	Bark	Kidney, bladder
	Pugongying	<i>Taraxacum mongolicum Hand. Mazz.</i>	855(52.62%)	Whole grass	Liver, stomach
	Shancigu	<i>Cremastra appendiculata (D.Don) Makino</i>	732(45.05%)	Pseudobulb	Liver, spleen
Blood-activating and stasis-removing medicine	Tufuling	<i>Smilax glabra Roxb.</i>	1246(76.68%)	Tuber	Liver, stomach
	Chuanniuxi	<i>Cyathula officinalis Kuan</i>	1004(61.78%)	Root	Liver, kidney
	Yujin	<i>Curcuma wenyujin Y.H.Chen et C.Ling</i>	763(46.95%)	Root tuber	Liver, heart, lung
	Zelan	<i>Lycopus lucidus Turcz.</i>	726(44.68%)	Overground part	Liver, spleen
	Taoren	<i>Prunus persica (L.) Batsch</i>	818(50.34%)	Mature seed	Heart, liver, large intestine
Danshen	<i>Salvia miltiorrhiza Bge.</i>	790(48.62%)	Root	Heart, Liver,	
	Honghua	<i>Carthamus tinctorius L.</i>	1035(63.69%)	Flower	Heart, liver

(Continued)

Table 5 (Continued).

Category	Herb	Generic Name	Number(%)	Medicinal Part	Meridian Tropism
Spleen-strengthening and Qi-invigorating medicine	Gancao	<i>Glycyrrhiza uralensis</i> Fisch.	766(47.14%)	Root	Heart, lung, spleen, stomach
	Shanyao	<i>Dioscorea opposita</i> Thunb.	778(47.88%)	Root	Lung, spleen, kidney
	Chenpi	<i>Citrus reticulata</i> Blanco	691(42.52%)	Mature pericarp	Lung, spleen
Wind-dispelling and dehumidification medicine	Weilingxian	<i>Clematis chinensis</i> Osbeck	840(51.69%)	Root	Bladder

Table 6 The Use Frequency of Chinese Patent Medicines

Name	Number(%)	Effect
Huangqin Qingre Chubi capsule (HQC)	813(50.03%)	Clearing heat and dampness, dispelling wind and relieving pain
Xinfeng capsule (XFC)	525(32.31%)	Replenish qi and spleen, remove dampness and dredge collaterals

was strongly associated with the improvement of NLR, hs-CRP, TG, ESR, C3, and C4 (Table 7). The diagram of the association network for all terms also demonstrated similar results (Figure 3).

Association Rule Analysis of TCM Treatment and Endpoint Events in GA Patients

Association rule analysis was performed with herbal medicines and CPMs as the antecedent and the absence of endpoint events as the postecedent. Specifically, the use of herbal medicines and CPMs was defined as T and the non-use as F. The absence of endpoint events was defined as T, otherwise as F. The results showed that the use of Danshen, Chenpi, HQC, and Taoren was more associated with no readmission (Figure 4a); the use of Fuling and HQC was associated with no new tophus (Figure 4b); Shancigu and Tufuling were associated with no extra-articular lesions (Figure 4c; Table 8). Surgery and all-cause death had very few cases in this study and were not significantly associated with any of the antecedents.

Table 7 The Association Between the Use of TCM and the Improvement of Test Indexes

Number	The Aforesaid	The Consequent	Support (%)	Confidence (%)	Lift
1	Yiyiren	NLR↓	76.68	89.81	1.02
2	Cheqiancao	NLR↓	61.69	90.36	1.05
3	HQC	NLR↓	40.03	82.01	1.52
4	HQC and tufuling	NLR↓	24.55	83.38	1.11
5	Yiyiren	hs-CRP↓	50.03	87.05	1.36
6	Huangbai and HQC	hs-CRP↓	21.35	90.78	1.88
7	Cheqiancao and HQC	hs-CRP↓	40.37	87.56	1.37
8	Chuanniuxi	TG↓	46.95	81.53	1.26
9	Huangbai	TG↓	51.79	85.32	1.18
10	Chuanniuxi and yiyiren	TG↓	35.02	83.51	1.19
11	Tufuling	ESR↓	35.12	81.99	1.29
12	Cheqiancao	ESR↓	43.76	86.36	1.78
13	Yiyiren and cheqiancao	ESR↓	22.98	83.44	1.11
14	HQC	ESR↓	36.82	80.18	1.06
15	Yujin	C3↓	23.09	80.76	1.12
16	Honghua	C4↓	21.77	81.45	1.10

Abbreviations: NLR, neutrophil-lymphocyte ratio; HQC, Huangqin Qingre Chubi capsule; hs-CRP, high-sensitive C-reactive protein; TG, triglyceride; ESR, erythrocyte sedimentation rate; C3, complement component 3; C4, complement component 4.

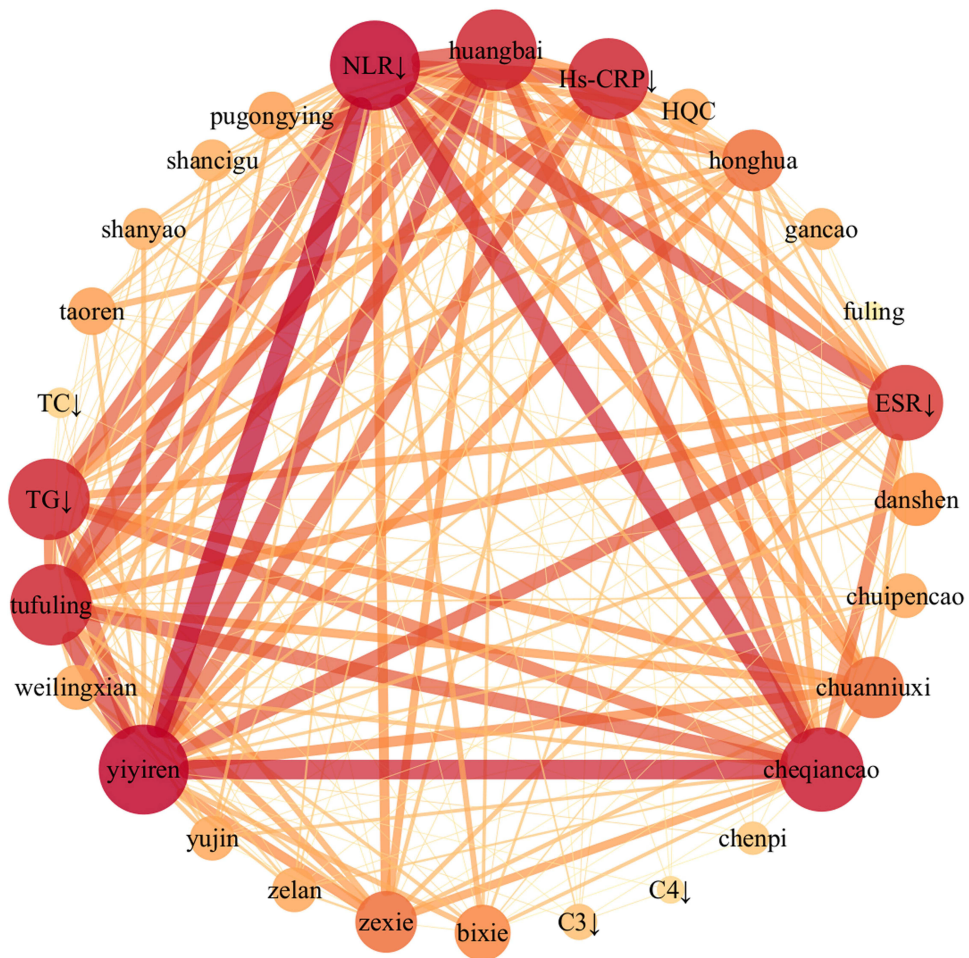


Figure 3 The network diagram of associations between TCM and test indexes.
Notes: Circles represent terms, and larger circles and darker colors represent terms that occur more often. The line represents the association between two items, and the thicker line and darker color represent the stronger association between the two items.
Abbreviations: NLR, neutrophil-lymphocyte ratio; hs-CRP, high-sensitive C-reactive protein; HQC, Huangqin Qingre Chubi capsule; ESR, erythrocyte sedimentation rate; C3, complement component 3; C4, complement component 4; TG, triglyceride; TC, total cholesterol.

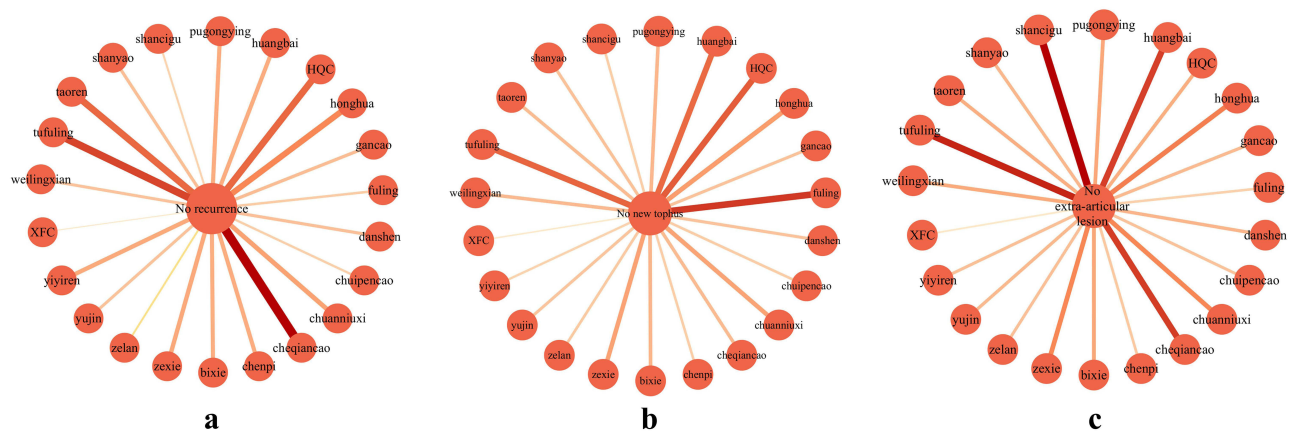


Figure 4 The network diagram of association rule analysis between TCM and endpoint events in GA patients. (a) The network diagram of associations between TCM and no readmission. (b) The network diagram of associations between TCM and no new tophus. (c) The network diagram of associations between TCM and no extra-articular lesions.
Abbreviations: HQC, Huangqin Qingre Chubi capsule; XFC, Xinfeng capsule.

Table 8 The Association Between the Use of TCM and the Absence of Endpoint Events

Number	The Aforesaid	The Consequent	Support (%)	Confidence (%)	Lift
1	Cheqiancao	No readmission	48.62	87.89	1.18
2	Tufuling	No readmission	42.52	84.22	1.13
3	HQC	No readmission	50.03	83.27	1.12
4	Taoren	No readmission	50.34	82.88	1.11
5	Fuling	No new tophus	39.75	81.11	1.01
6	HQC	No new tophus	50.03	80.81	1.01
7	Shancigu	No extra-articular lesion	45.05	88.66	1.12
8	Tufuling	No extra-articular lesion	76.68	87.72	1.11

Abbreviation: HQC, Huangqin Qingre Chubi capsule.

Discussion

GA is a common inflammatory joint disease with a high readmission rate.^{2,19} In our study, the readmission rate of GA patients reached 76.45% (1386/1813), and some patients had at least three readmissions within one year. In ancient China, GA was once called the disease of wealth and empire, indicating that the etiology of GA was more related to lifestyle. As productivity grows, people are prone to high-protein and high-fat diets in their daily life, eventually leading to a high intake of purines.²⁰ As a result, the prevalence of GA increases constantly, especially in economically developed areas.^{21,22}

The existing therapeutic drugs such as NSAIDs, colchicine, and glucocorticoids provide rapid pain relief in GA patients but also cause significant side effects.^{23–25} Uric acid-lowering drugs such as febuxostat and allopurinol can inhibit uric acid production, but long-term use tends to overwhelm the liver and kidney.^{26,27} GA patients may experience liver and kidney function reduction after years of recurrent attacks and medications.

To our knowledge, the present study is the first retrospective cohort study to evaluate the effect of TCM on GA patients. TCM holds great promise for complex chronic diseases with the advantages of multi-target, multi-component, and less adverse effects. Modern pharmacological studies have also found that some ingredients in these TCM decoctions can ameliorate GA symptoms, reduce inflammatory responses, and promote uric acid excretion. Accordingly, this study recruited 2091 GA patients with a follow-up period of up to 10 years, aiming to find evidence-based medical evidence for TCM in the treatment of GA.

This study had a rigorous follow-up plan design, which recorded the disease and medication status of each GA patient in detail and objectively. For the subsequent data analysis, PSM was used to eliminate bias, with age, gender, previous relevant diseases, and basic medicines used as matching variables. After matching, we found that the TCM group had an approximately 14% reduction in readmission rate, an approximately 10% reduction in new tophus, and an approximately 5% reduction in all-cause mortality compared to the non-TCM group.

Readmission is the most common endpoint event for rheumatic diseases, which can reflect the progress of GA patients to some extent. Further cox proportional risk regression analysis identified TCM treatment, NSAIDs, uric acid-lowering drugs, and drug combinations were independent protective factor for readmission. With the prolonged duration of TCM treatment, the protective performance of the high exposure group increased by 20% compared to the low exposure group. When TCM is combined with uric acid lowering drug or NSAIDs, it exhibits a superior effect compared to the sole use of TCM. We therefore concluded that TCM has a positive effect on delaying GA readmission, especially when it is used in combination with uric acid lowering drug or NSAIDs, in consistence with the findings found in previous studies.²⁸

The duration of TCM treatment also affects the risk of disease readmission. The results of the K-M survival curve showed that the high exposure group had a lower risk of readmission than the low exposure group. Then the test indexes of the low exposure group and high exposure group before and after treatment were compared. We found that TCM reduced some indexes of inflammation, immunity, lipid metabolism, and renal function in GA patients, and that the high exposure group had an advantage over the low exposure group in reducing lipid metabolism. These results suggest that long-term use of TCM decoction and CPM contributed to delaying the progression of GA, improving the related indexes, and causing little or no renal damage.

We counted the top 20 herbal medicines and top 2 CPMs used in this study, correlated the use of these drugs with the improvement of test indexes and the absence of endpoint events, and plotted the association network using the Apriori algorithm. Apriori algorithm, a novel association analysis method based on big data, is an important component of data mining and can be used to determine combined patterns and correlations of target events and treatments.^{29,30} Our association rule analysis revealed that Tufuling, Chenqiancao, Yiyiren, Huangbai, Danshen, Chenpi, and HQC were the core drugs for improving test indexes and delaying endpoint events in GA patients. Modern pharmacological studies have shown that the total flavonoids of *C. glabra* in Tufuling can inhibit xanthine oxidase activity and upregulate the expression of uric acid-related transporter protein and its mRNA in renal tissues, thereby reducing uric acid significantly.³¹ The extract of Yiyiren can treat rheumatoid arthritis by inhibiting pro-inflammatory factors and reducing oxidative stress.³² The HQC developed by our team has shown favorable efficacy in the acute exacerbation of many rheumatic diseases. Our *in vitro* study found that HQC suppressed inflammatory responses of T cells in the serum of GA patients by downregulating miR-23a-3p and upregulating PTEN.³³ Animal studies found that HQC ameliorated inflammatory responses in RA through the FZD8-Wnt/ β -catenin signaling axis.³⁴ In brief, clarifying the core drugs in GA treatment is conducive to guiding the clinical medication or developing new CPMs.

CPM as a new form of TCM combines modern pharmaceutical technology and traditional Chinese medicine theory, but in essence, it still belongs to the category of TCM.³⁵ Therefore, this study allocated GA patients receiving HQC treatment to the TCM group for analysis. HQC (patent number ZL201110095718.X) is a characteristic CPM developed by our team, consisting of Huangqin, Zhizi, Yiyiren, Taoren and Weilingxian. We found a strong association between the use of HQC and the reduction of NLR in GA patients, with a support of 50.03%, a confidence of 82.01%, and a lift of 1.52. NLR is a composite inflammatory index that has received more attention in recent years in rheumatic diseases,³⁶ immune diseases,³⁷ inflammation,³⁸ and tumors.³⁹ NLR is defined as the ratio of the absolute number of neutrophils to the absolute number of lymphocytes in blood routine, which dynamically reflects the relative relationship between neutrophils and lymphocytes, thus suggesting inflammatory changes in patients.⁴⁰ Some researchers⁴¹ found that NLR was higher in GA patients compared to healthy adults and that NLR was positively correlated with ESR and CRP, suggesting the ability of NLR to assess the disease activity of GA. In this study, we found that HQC effectively reduced NLR in GA patients, indicating that HQC may contribute to repressing immune inflammatory reactions in GA. Further animal and cellular experiments are warranted to validate the pharmacological effects and therapeutic mechanisms of HQC in GA.

The strengths of this study are: first, it is the first retrospective, large-sample, and long-term cohort study on TCM for GA; second, the protocol of this cohort study is derived from our team's previous studies and further improved, making the protocol more mature and reliable; third, this study also emphasizes the analysis of CPM while analyzing TCM decoction, and the patients who used CPM or TCM decoction were included in the TCM group.

This study also has several limitations. Firstly, all patients included were from one medical institution, which may lead to selection bias. Secondly, merely 76 female patients were included. Due to the small sample size, the data should be interpreted with caution in female GA patients. Finally, we failed to record as many baseline characteristics of the patients as possible before hospitalization. Although we used PSM to control for these biases, the variables we used for matching did not include all baseline characteristics. In the future, we need to conduct large sample randomized controlled trials to further clarify the efficacy of TCM on GA. Animal experiments and cell experiments are also necessary, and we need to explore the molecular mechanisms of TCM in the treatment of GA.

Conclusions

To sum up, TCM can improve test indexes and delay endpoint events in GA patients. This study provides a reference for the comprehensive treatment of GA in the clinic. Further, we need to explore the pharmacological effects and molecular mechanisms of TCM on GA or conduct a large sample of randomized controlled trials to determine whether the findings revealed in this study are generalizable.

Data Sharing Statement

The data used in this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent Statement

The present study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui University of Chinese Medicine (2023AH-52). Verbal consent was obtained from all study participants after they were fully informed of the purpose of the study, the Ethics Committee of the First Affiliated Hospital of Anhui University of Chinese Medicine approved the verbal informed consent process. All the procedures were conducted according to all applicable institutional and governmental regulations concerning the ethical use of human volunteers in compliance with the Declaration of Helsinki.

Consent for Publication

This paper is our original work. We certify that this manuscript has not been published in part or whole elsewhere in any language, and it has not been submitted to any other journal for reviews.

We certify that all authors named deserve authorship, and that all authors have agreed to be so listed and have read and approved the manuscript and its submission to International Journal of General Medicine.

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Disclosure

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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