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ORIGINAL RESEARCH

Role of Huangqin Qingre Chubi Capsule in the Reduction of the Risk of Re-Admission in Patients With Ankylosing Spondylitis: A Cohort Study

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Objective: This study evaluates whether Huangqin Qingre Chubi Capsule (HQC), a traditional Chinese medicine (TCM) compound, is associated with the risk of re-admission in patients with ankylosing spondylitis (AS).

Methods: In this study, we retrospectively collected the clinical data of 1,296 AS patients. Patients were allocated into HQC and non-HQC groups. Baseline data between the two groups were matched with propensity score matching (PSM). Influencing factors for the risk of re-admission in AS patients were analyzed with the Cox proportional hazards model. The effect of HQC intervention duration on the risk of re-admission was assessed with Kaplan-Meier survival curves. The random walk model and association rule analysis were utilized to determine the correlation between HQC and improvements in immunoinflammatory markers.

Results: The re-admission rate was significantly lower in the HQC group than in the non-HQC group ($P < 0.01$). The risk of re-admission was significantly lower in patients aged > 40 years ($P < 0.01$) than in patients aged < 40 years and also markedly lower in HQC users than in non-HQC users ($P < 0.01$), suggesting that age and the use of HQC were key factors influencing the risk of re-admission. Longer HQC intervention duration was associated with better improvements in ESR, CRP, and C4, and HQC was closely correlated with improvements in ESR, CRP, IgA, and C4.

Conclusion: HQC treatment can reduce the risk of re-admission in AS patients, which may be associated with improvements in ESR, CRP, IgA, and C4. The risk decreases with prolonged HQC treatment.

Keywords: Huangqin Qingre Chubi Capsule, ankylosing spondylitis, re-admission, cohort study, telephone follow-up

Introduction

Ankylosing spondylitis is a chronic inflammatory disease primarily involving the axial spine, with a prevalence rate of 0.1%−0.9%.[1] AS has a predilection to affect young males and is accompanied by various degrees of extra-articular manifestations represented by ocular, cardiovascular, and pulmonary involvement.[2–4] The exact etiology of AS remains unclear, although AS development has been reported to be closely related to genetics, immunity, and inflammation.[5–8]

Currently, ideal drugs are not available for the treatment of AS. Due to the persistent nature of AS, non-steroidal anti-inflammatory drugs (NSAIDs) and slow-acting antirheumatic drugs (DMARDs) have limited efficacy and even significant side effects.[9] Although TNF inhibitors are one of the widely used drugs for the treatment of AS, approximately 30% of AS patients present with side events or poor outcomes after treatment with TNF inhibitors, which severely restricts disease management.[10] Therefore, it is urgent to develop drugs for the treatment of AS and its secondary conditions.

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In recent years, clinical trials have confirmed that traditional Chinese medicine (TCM) has good efficacy in treating AS symptoms and improving its prognosis. Huangqin Qingre Chubi Capsules (HQC, Anhui Medicine Manufacture License: Z20200001, Patent Number: ZL201110095718.X) is an in-hospital TCM preparation of the First Affiliated Hospital of Anhui University of Chinese Medicine registered by the Food and Drug Administration of Anhui Province. HQC consists of five traditional Chinese herbs, namely Scutellaria baicalensis, Gardenia jasminoides, Coix seed, Peach kernel, and Clematis chinensis, and possesses strict quality control standards.[11,12] Preliminary studies have demonstrated HQC can effectively control the symptoms of acute arthritis attacks, reduce levels of erythrocyte sedimentation rate and C-reactive protein, and improve joint pain and extra-articular manifestations in AS treatment. However, it remains uncertain whether HQC can affect the risk of the endpoint event of AS, namely readmission. The application of meta-analysis, data mining, network pharmacology, and systems biology has dramatically boosted research on TCM-related therapies.[13–15] Accordingly, this retrospective cohort study explored and investigated the impact of HQC on the risk of readmission in AS patients and the correlation of this impact with inflammatory markers based on data mining, providing a reference for the long-term application of TCM in AS treatment.

Materials and Methods

Case Source

The Hospital Information System of the First Affiliated Hospital of Anhui University of Chinese Medicine was utilized to collect the clinical data of AS patients admitted to the Department of Rheumatology and Immunology of the Anhui Provincial Hospital of Traditional Chinese Medicine from September 2012 to September 2022. A total of 1,296 AS cases were selected, among which 1,155 cases (age: 37.19 ± 9.42 years) were finally included because of successful follow-up (10.87% loss to follow-up), including 855 males (74.02%) and 300 females (25.98%). There were 127 cases (10.99%) of primary hypertension, 46 cases (3.98%) of diabetes, 25 cases (2.16%) of hyperlipidemia, 855 cases (74.02%) taking NSAIDs, 417 cases (36.10%) taking disease-modifying antirheumatic drugs (DMARDs), and 107 cases (9.26%) taking glucocorticoids (GC).

Inclusion Criteria

Patients meeting all of the following criteria were included: Fulfilling the diagnostic criteria for AS as revised by the American College of Rheumatology (ACR) in 1984.[16] AS patients diagnosed and treated in the Department of Rheumatology and Immunology at the Anhui Provincial Hospital of Traditional Chinese Medicine from September 2012 to September 2022; patients aged ≥18 years; patients with complete medical records; patients providing informed consent.

Exclusion Criteria

Patients were excluded when meeting any of the following criteria: patients unable to communicate normally; patients unable to follow up regularly; patients with severe organ damage or severe malnutrition; pregnant or lactating women; patients with mental disorders or abnormal consciousness; patients with tumors or acute infections.

Data Collection

The following data were obtained: gender, age, underlying diseases (primary hypertension, diabetes mellitus, hyperlipidemia), history of standardized Western medicine drug use (NSAIDs, DMARDs, and GC), immunoinflammatory markers (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], immunoglobulin G [IgG], immunoglobulin M [IgM], immunoglobulin A [IgA], complement C3 [C3], and C4).

Data Processing

The retrieved data were standardized by doctors with the title of associate physician or above in an Excel 2016 table and then imported into a SQL Server database to establish an AS research library. To ensure the accuracy of all data, the above data were independently standardized by two people and checked for consistency.

Grouping and Interventions

Patients were classified into two groups: (1) the HQC group: patients received HQC (Dosage: three times daily, three tablets each time) treatment based on standardized Western medicine drugs; (2) the non-HQC group: patients received only treatment with standardized Western medicine drugs. In this study, we did not interfere with clinical treatment medication and selected only clinical data that met the requirements for analysis.

Propensity Score Matching (PSM)

PSM is a statistical method commonly used in medical research. It is aimed at controlling data bias and confounding variables through propensity score values to facilitate a more reasonable comparison between the experimental group and the control group. The calculation formula is as follows:

$$ATE = E(Y_1(x) - Y_0(x))$$

PSM was used to match baseline data, including gender, age, underlying diseases, history of standardized Western medicine drug use, and immunoinflammatory markers, between the HQC and non-HQC groups to eliminate the interference of gender, age, underlying diseases, and standardized Western medicine drugs on readmission results and balance the disease activity between the two groups. After PSM, there were 214 cases per group.

Cox Proportional Hazards Model Analysis

The COX proportional hazards model is a semi-parametric regression model proposed by the British statistician D.R. COX, which uses survival outcome and survival time as dependent variables, allowing for the simultaneous analysis of multiple factors affecting survival. It is the most commonly used multifactorial analysis method in survival analysis to date. The calculation formula is as follows:

$$h(t,x)/h(t,0) = \exp(w_1x_1 + w_2x_2 + \ldots)$$

With the readmission of AS patients as the dependent variable and age, gender, comorbidities, basic medication, and HQC use as independent variables, the Cox proportional hazards model analysis was performed by combining readmission and follow-up time. Univariate and multivariate analyses were conducted to screen influencing factors for readmission.

Random Walk Model

Data of AS patients were retrieved from the database with the SQL Server management system. The random walk model for immunoinflammatory indicators was generated with the ORACLE10g software to observe improvements in these indicators by HQC.

Association Rule Analysis

The Correlation Between HQC and the Observed Indicators Was Assessed With the Association

Rule analysis. HQC treatment was defined as "T", while non-HQC treatment was defined as "F". After HQC treatment, ESR, CRP, IgA, IgG, IgM, C3, and C4 were marked as "T" when decreased and as "F" when stabilized and increased. The Apriori module in IBM SPSS Modeler 18.0 software was used to analyze the association between HQC and immunoinflammatory indicators, with the specific formula as follows:[17]

$$Support(X \rightarrow Y) = \sigma(XUY)/N$$

$$Confidence(X \rightarrow Y) = \sigma(XUY)/\sigma(X)$$

$$Lift(X \rightarrow Y) = \text{Confidence}(X \rightarrow Y)/\sigma(Y)$$

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Cohort Study

Endpoint Event Definition

Readmission referred to two or more times of readmission of AS patients within a year due to worsening conditions.

Exposure Intensity Definition

Oral administration of HQC for ≤ 12 months was defined as low exposure, and administration > 12 months as high exposure.

Follow-Up Method

Follow-up was conducted via telephone. Two trained doctors jointly performed telephone follow-up on eligible AS patients, with follow-up ending on December 10, 2023. Survival time was calculated in months.

Observation Indicators

The degree of improvements in the risk of readmission under different exposure intensities was observed. The flowchart of the cohort study is presented in Figure 1.

Statistical Methods

Statistical analysis was performed with SPSS 24.0 and GraphPad 8.0 software. Count data were listed as the number of cases or percentages and compared with the chi-square test. Continuous data were described as median (interquartile range [IQR]) and compared with the rank-sum test. Cox proportional hazards model and Kaplan-Meier survival curve analyses were conducted. $P < 0.05$ was considered statistically significant.

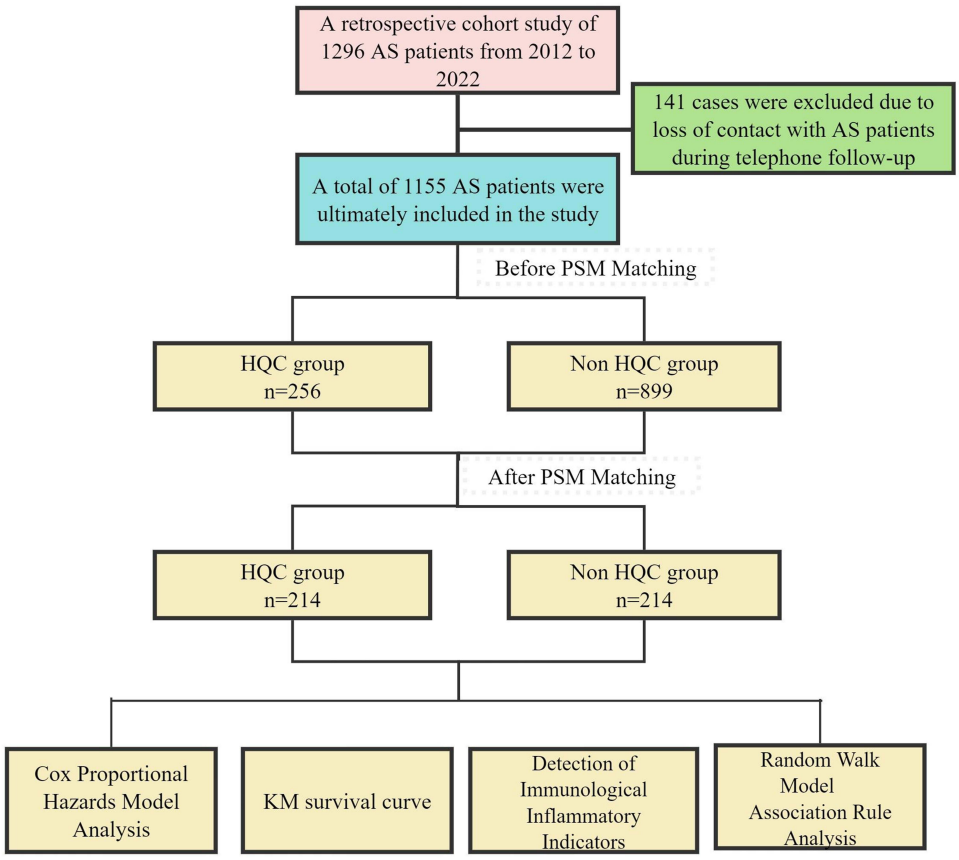

Figure 1 Flow Chart of Queue Research.

Results

Baseline Characteristics in the Two Groups

In this study, we followed up 1,296 AS patients hospitalized in Anhui Provincial Hospital of Traditional Chinese Medicine from September 2012 to September 2022 via telephone, among which 141 patients were lost to follow-up and 1,155 patients were successfully followed up. There were 256 patients in the HQC group and 899 patients in the non-HQC group, with significant differences in hypertension and DMARD use between the two groups ($P < 0.01$). The results are detailed in Table 1. After 1:1 PSM, 214 patients were finally included in each group. No statistically significant differences were found between the two groups in terms of age, gender, comorbidities, and baseline medications ($P > 0.05$). The results are detailed in Table 2.

Table 1 Demographic Characteristics of Patients in HQC and Non-HQC Groups

	Number of Cases 1155	**HQC Group 256**		**Non HQC Group 899**		***P* Value**
	N	**n**	**%**	**n**	**%**	
Age						
Mean±SD		37.19±9.42		37.27±9.36		0.70
Gender						0.37
Males	855	191	74.6	664	73.9	
Females	300	65	25.4	235	26.1	
Hypertension	127	37	14.5	90	10.0	<0.01**
Diabetes	46	11	4.3	35	3.9	0.22
Hyperlipidemia	25	6	2.3	19	2.1	0.77
NSAIDs	855	205	80.1	650	72.3	0.03
DMARDs	417	126	49.2	291	32.4	<0.01**
GC	107	25	9.8	82	9.1	0.26

Notes: Compared with the HQC group,** P<0.01.
Abbreviations: NSAIDs, Nonsteroidal Anti-Inflammatory Drugs; DMARDs, Disease-modifying Antirheumatic Drugs; GC, glucocorticoids.

Table 2 Demographic Characteristics of Patients in HQC and Non-HQC Groups After Propensity Score Matching

	Number of Cases 428	**HQC Group 214**		**Non HQC Group 214**		***P* Value**
	N	**n**	**%**	**n**	**%**	
Age						
Mean±SD		36.95±10.42		36.93±10.49		0.72
Gender						0.77
Males	318	160	74.8	158	73.9	
Females	110	54	25.2	56	26.1	
Hypertension	50	26	12.1	24	11.2	0.62
Diabetes	22	11	5.14	11	5.14	1.00
Hyperlipidemia	11	6	2.8	5	2.3	0.92
NSAIDs	308	156	72.9	152	71.1	0.61
DMARDs	198	101	47.2	97	45.3	0.46
GC	44	22	10.3	22	10.3	1.00

Abbreviations: NSAIDs, Nonsteroidal Anti-Inflammatory Drugs; DMARDs, Disease-modifying Antirheumatic Drugs; GC, glucocorticoids.

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Factors Influencing Re-Admission of AS Patients

The Cox proportional hazards model was used to identify risk factors for readmission of AS patients. The results are detailed in Table 3. Univariate analysis results demonstrated that the readmission rate of AS patients aged over 40 years was significantly lower than that of patients aged under 40 years (hazard ratio [HR] = 0.56, 95% confidence interval [95% CI] = 0.41−0.67, P < 0.01). The readmission rate was markedly lower in the HQC group than in the non-HQC group (HR = 0.82, 95% CI = 0.71−0.95, P< 0.01). Furthermore, the multivariate analysis was performed to screen independent factors affecting the readmission of AS patients. The results manifested that the readmission rate was dramatically lower in AS patients over 40 years old than in patients under 40 years old (HR = 0.64, 95% CI = 0.51−0.77, P< 0.01). The HQC group exhibited substantially lower readmission rates than the non-HQC group (HR = 0.77, 95% CI = 0.65−0.89, P< 0.01). Overall, the re-admission rate of AS patients decreases after the age of 40 years, and HQC use is a protective factor that reduces the readmission rate of AS patients.

Kaplan-Meier Survival Curve Analysis of Risk of Re-Admission for AS Patients Treated With HQC

Kaplan-Meier survival curve analysis results revealed a markedly lower risk of readmission in the HQC group than in the non-HQC group (P= 0.017). The results are detailed in Figure 2A. HQC users were categorized into low exposure (TCM intervention duration ≤ 12 months) and high exposure (intervention duration > 12 months) groups. Compared with the low exposure group, the high exposure group had a significantly lower readmission rate (P = 0.029). The results are detailed in Figure 2B.

Effect of HQC on Immunoinflammatory Indicators in AS Patients

After HQC treatment, the levels of ESR, CRP, IgA, IgG, C3, and C4 were reduced (P < 0.01), with no statistically significant changes in IgM levels (P > 0.05). The results are detailed in Table 4.

Relationship Between HQC Intervention Duration and Improvements in Immuno-Inflammatory Indicators

According to the random walk model, longer HQC intervention duration was associated with better improvements in ESR, CRP, and C4. The results are detailed in Figure 3.

Table 3 Factors Influencing Re-Admission of AS Patients

		Univariate Analysis			Multivariate Analysis		
	Number of Re-Admission	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-Value**
Age							
≤ 40	130						
>40	50	0.56	0.41–0.67	<0.01**	0.64	0.51–0.77	<0.01**
Gender							
Males	135						
Females	45	0.77	0.52–0.87	0.276	0.90	0.79–0.96	0.28
HQC	68	0.82	0.71–0.95	<0.01**	0.77	0.65–0.89	<0.01**
Hypertension	19	1.55	1.40–1.71	0.321	1.57	1.41–1.70	0.22
Diabetes	10	1.27	1.19–1.37	0.457	1.16	1.05–1.29	0.50
Hyperlipidemia	2	1.16	1.01–1.27	0.670	1.15	1.02–1.29	0.55

Notes: Compared with the patients aged ≤40 years, ** P<0.01. Compared with the Non HQC group, ** P<0.01. Multivariate analysis model including Age, Gender, Hypertension, Diabetes and Hyperlipidemia.
Abbreviations: HR, Hazard Ratio, CI, Confidence Interval.

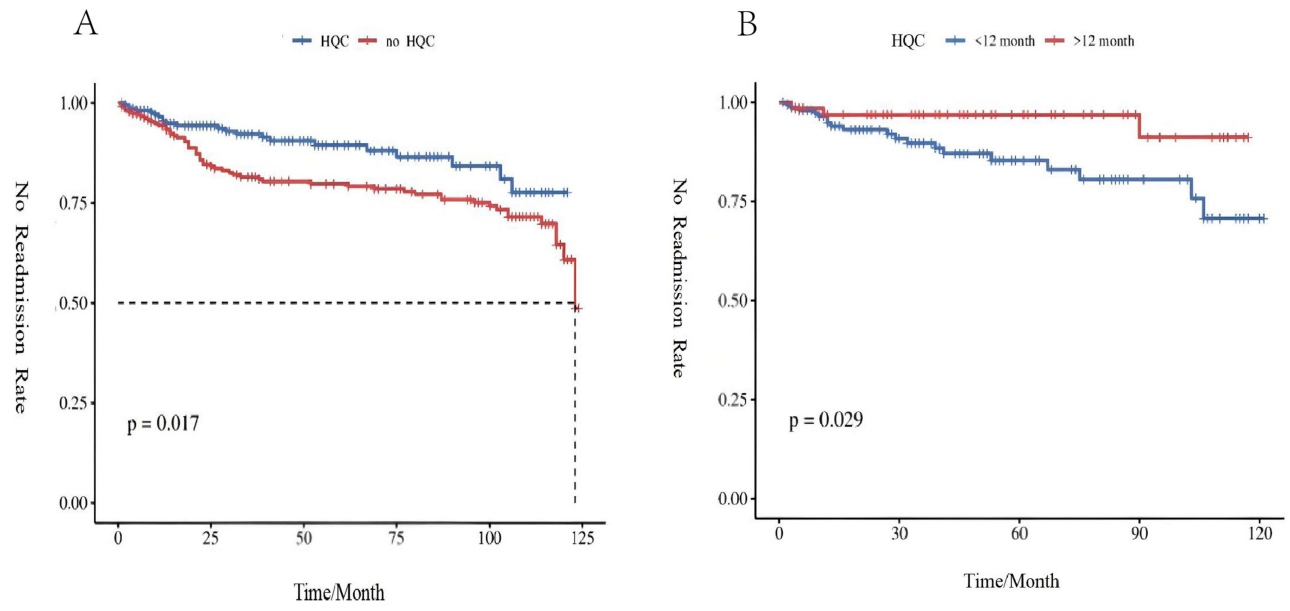

Figure 2 Kaplan-Meier Survival Curve Analysis Results of Risk of Re-Admission for AS Patients Treated with HQC. (**A**) Kaplan-Meier curves for the HQC group and the non-HQC group. (**B**) Kaplan-Meier curve for HQC intervention time.

Association Rule Analysis Between HQC and Immunoinflammatory Indicators

Association rule analysis results displayed that HQC had a high degree of association with ESR, CRP, IgA, and C4 (support > 50%, confidence > 60%, lift > 1). The results are detailed in Table 5.

Discussion

In recent years, TCM has been increasingly chosen by AS patients because of its exact efficacy.[18,19] The inclusion of TCM in the clinical treatment of AS has been a consensus among domestic experts.[20]

After adjustment for possible confounding factors, this study unveiled that HQC effectively reduced the levels of immunoinflammatory markers such as ESR, CRP, IgA, and IgG in AS patients. Inflammation in AS can be driven by the recruitment of inflammatory cells and the subsequent release of inflammatory cytokines.[21] The expression of immunoinflammatory markers is elevated during the active phase of AS. Therefore, HQC decreases the risk of readmission in AS patients possibly due to the synergistic anti-inflammatory and immunomodulatory effects of multiple components and targets of HQC. HQC is a TCM preparation with strict quality control standards, consisting of five traditional Chinese herbs: Scutellaria baicalensis, Gardenia jasminoides, Coix seed, Peach kernel, and Clematis chinensis. Pharmacological studies have clarified the active components of HQC and established high-performance liquid chromatography fingerprint

Table 4 Effect of HQC on Immunoinflammatory Indicators in AS Patients

Indicators	Pre-Treatment Indicators	Post-Treatment Indicators	Z Value	*P* value
ESR (mm/h)	41.00 (25.00,59.00)	23 (14,41)	−11.235	<0.01**
CRP (mg/L)	43.73 (26.7,69.96)	8.63(3.05,21.10)	−12.831	<0.01**
IgA (g/L)	2.7(2.06,3.61)	2.55(1.94,3.4)	−4.781	<0.01**
IgG (g/L)	13.59(10.28,15.9)	12.7(10.28,15.50)	−4.083	<0.01**
IgM (g/L)	1.12(0.87,1.44)	1.12(0.86,1.43)	−0.423	0.672
C3 (g/L)	124.4(1.46,142.4)	111(1.35,132.4)	−7.862	<0.01**
C4 (g/L)	26.1(0.38,34.6)	22.5(0.34,29.50)	−9.086	<0.01**

Notes: Compared with the HQC group before treatment, * * P<0.01.

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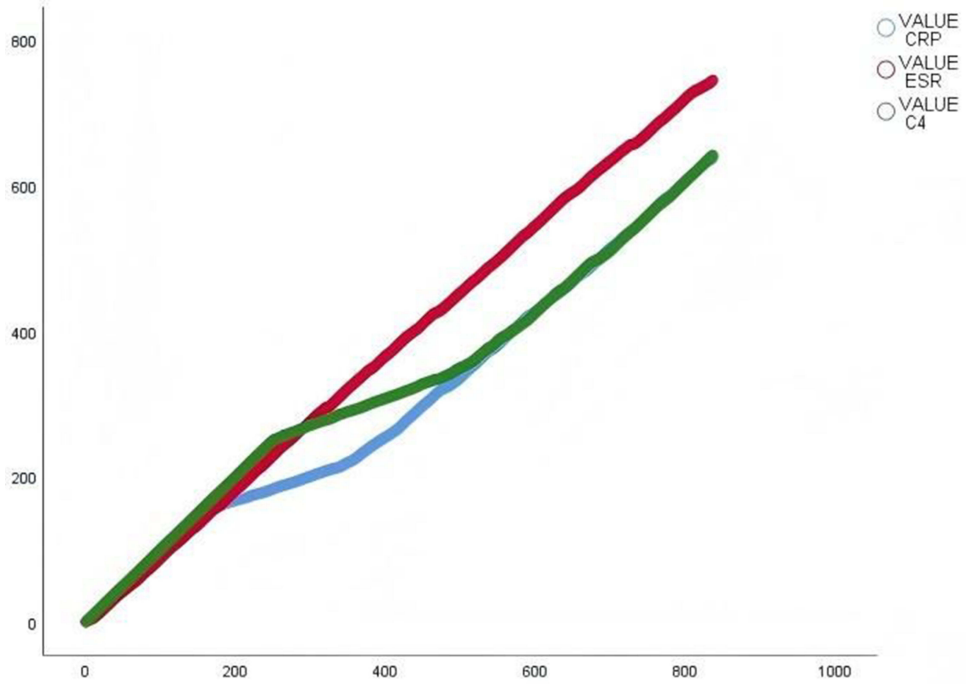

Figure 3 The relationship between HQC intervention duration and improvements in CRP, ESR, and C4.

profiles for 12 batches of HQC.[11,12] Several modern pharmacological studies reported that natural components such as baicalin and baicalein have therapeutic effects on autoimmune diseases.[22] HQC can effectively suppress the levels of inflammatory cytokines IL-1β,IL-6, and IL-8 in AA rats.[23] Additionally, prior studies elucidated that geniposide from *Gardenia jasminoides* inhibited the increase in arthritis index, improved secondary foot swelling, and diminished the degree of inflammatory cell infiltration in rats with adjuvant arthritis.[24,25] Peach kernel, as a ministerial drug, shows significant advantages in treating AS patients with blood stasis syndrome since it can promote blood circulation and relieve stasis.[26] The main active component of *Clematis chinensis*, total saponins, can inhibit the excessive proliferation of fibroblast-like synoviocytes in AS, which may be achieved by regulating the lncRNA OIP5-AS1/miR-410-3p/Wnt7b axis.[27] Our previous studies revealed that HQC treatment significantly reduced the levels of inflammatory markers (ESR and CRP), Bath AS Disease Activity Index scores, Bath AS Metrology Index scores, Bath AS Functional Index scores, and visual analogue scale scores.[28] Altogether, HQC can significantly improve immuno-inflammation in AS. However, the detailed mechanism awaits further research.

Cohort studies rank second only to randomized controlled trials in evidence-based medicine and have strong argumentative strength, which can better reveal the objective causal relationship between two events. In the present study, the Cox proportional hazards regression analysis disclosed that HQC use was a protective factor against the readmission of AS patients. The Kaplan-Meier survival curve analysis showed that the readmission rate in the HQC group was markedly lower than that in the non-HQC group and that longer HQC intervention duration was associated

Table 5 Association Rule of HQC and Immunoinflammatory Indicators

Pre-Item	Post-Item	Support (%)	Confidence (%)	Lift
HQC	ESR	98.5	83.1	1.19
HQC	CRP	99.4	92.3	1.10
HQC	IgA	53.6	63.9	1.04
HQC	C4	54.2	64.8	1.06

with a lower risk of readmission. The random walk model exhibited that prolonged HQC intervention duration was correlated with better improvements in ESR, CRP, and C4. The association rule analysis displayed that HQC was strongly correlated with improvements in ESR, CRP, IgA, and C4. All these results illustrated that HQC could reduce the risk of readmission in AS patients and that exposure intensity was substantially correlated with the risk of the endpoint event, readmission, in AS patients. The risk of readmission in AS patients decreased as exposure intensity was elevated, indicating that long-term HQC treatment exerts a positive effect on reducing the risk of readmission in AS patients.

Because the design of cohort studies inherently possesses certain biases and confounding factors, this study has some limitations. First, male patients accounted for more than 74% of participants. Accordingly, the results may not be entirely applicable to female AS patients. Second, patients were selected from a single center, possibly introducing some medication bias, and the sample size was relatively small, which is an important issue to be addressed in future research.

In the absence of timely diagnosis and effective treatment, AS can persist and lead to spinal deformities and stiffness, severely affecting the quality of life of patients. The current use of NSAIDs and SAARDs has certain limitations or causes significant side reactions, which calls for improving measures for evidence-based interventions of AS. The use of TCM in the treatment of AS is worth further exploration because of its advantages of multi-pathways, multi-methods, and multi-targets.

Conclusion

In summary, HQC is a protective factor against the readmission of AS patients, which significantly reduces the risk of readmission. Additionally, prolonged HQC use lowers the risk of readmission in AS patients. Although it is difficult to attribute these results solely to the use of HQC, this new finding may offer new insights for healthcare professionals in clinical practice and simultaneously provide references for more comprehensive and in-depth research in the future.

Data Sharing Statement

The datasets used in this study can be obtained from the author upon request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Anhui Provincial Hospital of Traditional Chinese Medicine (Approval Number: 2023AH-52; Approval Date: July 27, 2023). We fully protected the privacy of patients and did not interfere with their treatment choices.

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Author Contributions

All authors have made substantial contributions to the work reported, whether that is in conception, research design, execution, data acquisition, analysis and interpretation, or in all of these areas. They have participated in drafting, revising or critically reviewing the article; given final approval of the version to be published; agreed to its submission to the journal; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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