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The Treatment with Xinfeng Capsule Can Reduce the Risk of Readmission for Patients with Rheumatoid arthritis:A Cohort Study of Approximately 10000 Individuals

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Objective: The present study aimed to investigate the potential association between the treatment with Xinfeng Capsule (XFC) and the risk of readmission among patients with rheumatoid arthritis (RA).

Methods: Through a retrospective approach, data were collected from all hospitalized patients diagnosed with RA at the First Affiliated Hospital of Anhui University of Chinese Medicine between 2013 and 2021. To mitigate selection bias and confounding factors, patients were stratified into an XFC group and a Non-XFC (Non-XFC) group based on their treatment status using propensity score matching with a 1:2 ratio. Variables such as age, gender, and baseline medications were adjusted. Subsequently, the Cox proportional hazards model was employed to calculate the hazard ratio (HR) for readmission among RA patients, while Kaplan-Meier curves were utilized to depict the incidence of readmission.

Results: A total of 9987 RA patients were included in this study. Following rigorous inclusion/exclusion criteria and propensity score matching, the XFC group comprised 2036 patients, while the Non-XFC group contained 4072 patients. The Cox proportional hazards model analysis revealed that XFC acted as a protective factor, significantly reducing the risk of readmission among RA patients. Further examination of Kaplan-Meier curves demonstrated that XFC use not only effectively lowered the frequency of readmissions but also exhibited a more pronounced effect in diminishing the risk of readmission with extended usage durations (beyond 12 months). Additionally, association rule analysis underscored the strong link between XFC and freedom from readmission, as well as the robust correlation between XFC usage and significant improvements in multiple laboratory indicators, including C3, C4, CRP, ESR, and others.

Conclusion: This study underscores a robust and long-term association between XFC usage and lower readmission rates among RA patients. As a protective factor against readmission risk in these patients, the clinical value of XFC merits further promotion and investigation.

Keywords: rheumatoid arthritis, readmission, cohort study, xinfeng capsule

Introduction

Rheumatoid arthritis (RA), a prevalent chronic autoimmune disorder, is characterized by widespread inflammatory responses, persistent synovitis progression, and gradual destruction of joint structures.[1,2] The disease manifests primarily through joint swelling, severe pain, and stiffness, ultimately leading to decreased joint function, heightened risk of disability, and various systemic complications affecting the heart, lungs, and hematological system, among others, as the condition progresses.[3–5] Furthermore, RA patients often grapple with mental health challenges such as anxiety and depression, further exacerbating the overall disease burden.[6,7] Given the complexity and chronicity of RA, its treatment necessitates comprehensive and sustained strategies. However, traditional Western medicines like non-steroidal anti-

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inflammatory drugs, anti-rheumatic drugs, and glucocorticoids, while capable of managing symptoms, often come with significant long-term side effects, impacting patients' quality of life and treatment adherence.[8–10] Emerging biologics and targeted small molecule drugs demonstrate remarkable efficacy but impose substantial financial burdens on patients and their families due to their high costs.[11,12] Consequently, there is an urgent need to explore safe, efficient, and cost-effective treatment options for RA.

Readmission rates serve as a crucial metric for evaluating the effectiveness of disease management, reflecting both the stability of disease control and the optimization of medical resource allocation, ultimately contributing to reduced patient economic burdens.[13–15] Unfortunately, current data indicate that readmission rates among RA patients remain high, particularly when disease activity is inadequately controlled or treatment adherence is poor.[16] The triggers for readmission are multifaceted, encompassing disease relapse, seasonal variations, surgical intervention needs, and exacerbations of comorbidities,[17–20] all of which intensify the physical and emotional toll on patients and strain the healthcare system. Therefore, researching effective therapies aimed at reducing readmission risks among RA patients and enhancing their quality of life has emerged as a pivotal focus of clinical medical research.

Xinfeng Capsule (XFC, prepared by Anhui Provincial Hospital of Traditional Chinese Medicine, Approval Number: Wan Yao Zhi Zi Z20050062, Patent Number: ZL201310011369.8), a formulation composed of Astragalus membranaceus, Coicis Semen, Centipede, and Tripterygium wilfordii Hook. F., has been clinically applied for over three decades with remarkable therapeutic effects.[21] In recent years, several studies have been conducted to investigate the application of XFC in the treatment of RA, yielding favorable outcomes. Clinical evidence indicates that XFC significantly alleviates symptoms such as joint pain, swelling, and morning stiffness in RA patients, effectively reduces disease activity, enhances patients' quality of life, and demonstrates good long-term safety profiles with no notable toxic or side effects.[21] Further studies have preliminarily unveiled that XFC may positively impact the pathological process of RA by modulating immune homeostasis, suppressing inflammatory responses, and improving hypercoagulable states in the blood,[22,23] thereby potentially reducing the risks of disease relapse and readmission.

Given this backdrop, the present study has designed a large-scale cohort study aimed at comprehensively evaluating the association between XFC treatment and the reduction of readmission risks among RA patients. A total of 9987 RA patients were enrolled in this retrospective cohort study, where patients' baseline characteristics, treatment protocols, and follow-up data were collected and analyzed. Through rigorous statistical analyses, the specific impact of XFC on the readmission rate among RA patients was explored, providing a more solid clinical basis for the application of XFC in RA treatment. A schematic diagram of the study protocol is presented in Figure 1.

Materials and Methods

Data Source and Study Population

Within the framework of a telephone-based follow-up cohort analysis, we conducted a retrospective review of clinical data pertaining to 9987 patients diagnosed with RA and admitted to the Rheumatology Department of the First Affiliated Hospital of Anhui University of Chinese Medicine between December 2011 and June 2021. This study adhered strictly to the principles outlined in the Declaration of Helsinki. The follow-up process ensured rigorous privacy protection for patients and posed no interference with their ongoing treatment plans. The Ethics Committee of the First Affiliated Hospital of Anhui University of Chinese Medicine has waived the requirement for informed consent (Approval No. 2022MCZQ01).

Inclusion and Exclusion Criteria

Inclusion criteria: Fulfilling the 2010 RA classification criteria established by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR),[24] patients who agreed to participate in the study and consented to regular follow-up telephone interviews. Exclusion Criteria: Patients with incomplete clinical records, individuals suffering from severe comorbidities involving the circulatory, respiratory, or hematopoietic systems, pregnant or lactating women, patients with concurrent malignancies.

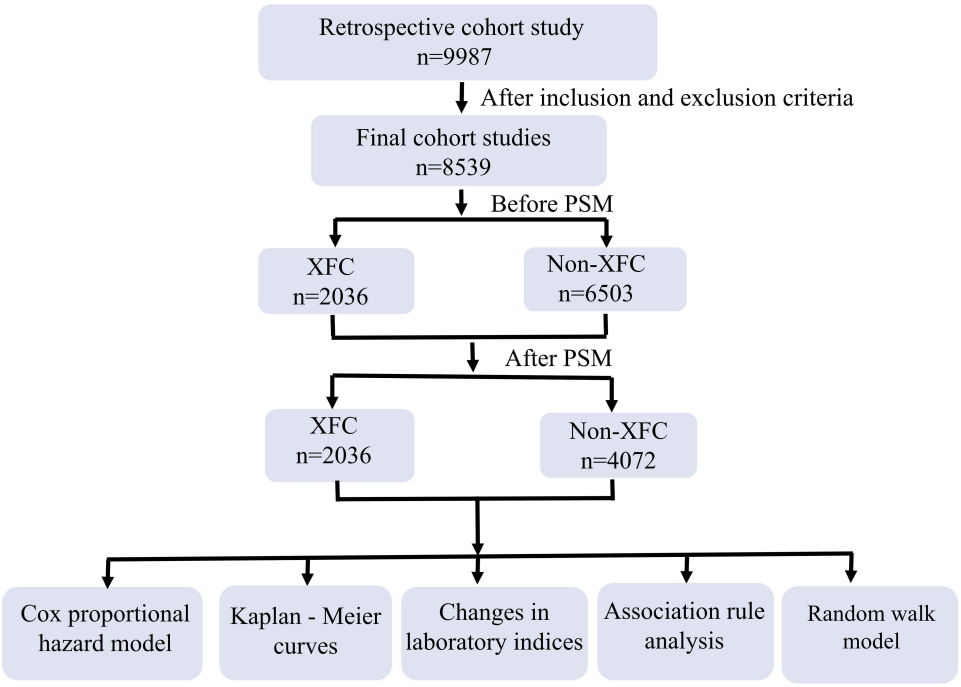


Figure 1 Research process of patient selection.

Content of Telephone Follow-Up

Utilizing the proprietary data processing system of the First Affiliated Hospital of Anhui University of Chinese Medicine (Patent No. 2017SR422234), we acquired baseline patient information such as name, age, gender, telephone number, and diagnostic details, which were subsequently verified through telephone follow-ups. The scope of follow-up encompassed the usage and duration of XFC, basic medications (including Disease-Modifying Anti-Rheumatic Drugs - DMARDs: methotrexate, leflunomide, and hydroxychloroquine; Non-Steroidal Anti-Inflammatory Drugs - NSAIDs: celecoxib, meloxicam, and lornoxicam; Glucocorticoids: methylprednisolone and prednisone acetate), traditional Chinese medicine usage and duration, as well as the occurrence of endpoint events. The primary endpoint events were defined as: RA exacerbations leading to readmission, extra articular lesions, surgical treatment, and death. All follow-up interviews were conducted by specialized rheumatologists, with each session administered by a single interviewer and simultaneously supervised and verified by two additional physicians.

Collection of Laboratory Indicators

From the enrolled patients, we collected a comprehensive set of laboratory parameters, including Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Rheumatoid Factor (RF), Immunoglobulin A (IgA), Immunoglobulin G (IgG), Immunoglobulin M (IgM), Complement Component 3 (C3), Complement Component 4 (C4), and Platelet Count (PLT).

Propensity Score Matching (PSM)

Propensity Score Matching (PSM) serves as an effective tool to mitigate confounding biases in observational study designs.[16] In this study, PSM was employed to balance baseline characteristics, including patient age, gender, and baseline treatment medications, between the XFC group and the Non-XFC group. The matching was conducted at a ratio of 1-XFC:2-Non-XFC, resulting in a cohort of 2036 patients in the XFC group and 4072 patients in the Non-XFC group. Additionally, within the XFC group, exposure was defined based on the duration of continuous oral XFC treatment, with ≤12 months categorized as low exposure and >12 months as high exposure.

Cox Proportional Hazards Model Analysis and Kaplan-Meier (K-M) Curves

The Cox proportional hazards model, a widely utilized statistical method in medical research, analyzes the impact of one or more covariates on patient survival time.[25] In this study, the readmission rate of matched RA patients served as the dependent variable, while age, gender, baseline medications, XFC use, and abnormal elevations in laboratory indicators were treated as covariates. The Cox model analysis was conducted, incorporating readmission times and follow-up durations. Univariate analysis was first performed to obtain preliminary results, followed by multivariate analysis to identify independent factors influencing readmission. Survival probabilities were illustrated using Kaplan-Meier (K-M) curves, with statistical significance assessed through the Log rank test.

Association Rule Analysis

Patients using XFC were defined as T, while those not using XFC were defined as F. Improvements in ESR, CRP, IgA, IgG, IgM, C3, C4, RF, and PLT after XFC treatment were designated as T, and lack of improvement as F. Readmission was coded as F, and no readmission as T. This framework facilitated the discovery of correlations between XFC use, observed indicators, and readmission. The specific calculation formulas for association rule analysis followed previous research.[26]

Random Walk Model

The random walk model, grounded in individual patient treatment outcomes, visualizes the cumulative therapeutic effects as random walk paths when a sufficient sample size is achieved. This model was utilized with Oracle Developer Suite 10g to evaluate the international biomedical immune-inflammatory index and observe improvements in laboratory indicator compatibility with medications.[27]

Statistical Analysis

Data normality was assessed using the Shapiro–Wilk test. Continuous variables with normal distributions were expressed as mean ± standard deviation, while non-normally distributed variables were presented as medians [interquartile range (IQR)]. Categorical variables were reported as numbers (percentages). Statistical significance was determined using the Mann–Whitney *U*-test, Student's *t*-test, Wilcoxon signed-rank test, or chi-square test, as appropriate. A P-value < 0.05 was considered statistically significant.

Results

Demographic Characteristics of RA Patients in the XFC and Non-XFC Groups

A total of 8539 RA patients were included in this study, with 2036 patients in the XFC group and 6503 patients in the Non-XFC group. Significant differences ($P < 0.05$) were observed between the two groups in terms of age, gender, usage of baseline medications (TCM, DMARDs, NSAIDs, Glucocorticoids), and endpoint events (readmission and death). Notably, the readmission rate among RA patients in the XFC group was significantly lower compared to the Non-XFC group ($P < 0.05$). To mitigate baseline biases, a 1:2 PSM approach was applied to balance age, gender, and basic medicine usage between the groups. Following PSM, 6108 RA patients were included, with 2036 patients in the XFC group and 4072 in the Non-XFC group. Analysis revealed no significant differences ($P > 0.05$) in age and basic medicine usage between the two groups post-matching, yet an imbalance persisted in gender distribution. This disparity could be attributed to limitations inherent in the propensity score method, specific constraints of the matching algorithm, and characteristics of the data itself. In terms of endpoint events, the incidence of readmission in the XFC group was significantly lower than in the Non-XFC group ($P < 0.05$; Table 1).

Factors Influencing Readmission Among RA Patients

The Cox proportional hazards model was employed to identify risk factors for readmission among RA patients (Table 2). Univariate analysis indicated that the readmission rate in the XFC group was significantly lower than that in the Non-XFC group (Hazard Ratio (HR) = 0.60, 95% CI = 0.55, 0.65, $P < 0.001$). Similarly, patients receiving Traditional Chinese Medicine

Table 1 Baseline Characteristics of RA Patients Before and After PSM

Characteristics	Before PSM matched				After PSM matched			P value
	level	XFC (N=2036)	Non-XFC (N=6503)	P value	level	XFC (N=2036)	Non-XFC (N=4072)	
Age (years), n (%)	Median (IQR)	62.0 (53.0 to 69.5)	55.0 (48.0 to 66.0)	<0.001	Median (IQR)	62.0 (53.0 to 69.5)	60.0 (53.0 to 69.0)	0.081
	>60	1058 (52%)	2469 (38%)	<0.001	>60	1058 (52%)	2015 (49.5%)	0.072
	18–60	978 (48%)	4034 (62%)		18–60	978 (48%)	2057 (50.5%)	
Gender	Female	1556 (76.4%)	5470 (84.1%)	<0.001	Female	1556 (76.4%)	3277 (80.5%)	<0.001
	Male	480 (23.6%)	1033 (15.9%)		Male	480 (23.6%)	795 (19.5%)	
Basic medicine, n (%)								
TCM	Yes	1451 (71.3%)	4825 (74.2%)	0.010	Yes	1451 (71.3%)	2972 (73%)	0.166
	No	585 (28.7%)	1678 (25.8%)		No	585 (28.7%)	1100 (27%)	
DMARDs	Yes	1491 (73.2%)	4361 (67.1%)	<0.001	Yes	1491 (73.2%)	2971 (73%)	0.846
	No	545 (26.8%)	2142 (32.9%)		No	545 (26.8%)	1101 (27%)	
NSAIDs	Yes	1490 (73.2%)	3850 (59.2%)	<0.001	Yes	1490 (73.2%)	2908 (71.4%)	0.155
	No	546 (26.8%)	2653 (40.8%)		No	546 (26.8%)	1164 (28.6%)	
Glucocorticoids	Yes	1259 (61.8%)	3970 (61%)	0.541	Yes	1259 (61.8%)	2545 (62.5%)	0.634
	No	777 (38.2%)	2533 (39%)		No	777 (38.2%)	1527 (37.5%)	
End point events, n (%)								
Readmission	Yes	806 (39.6%)	2786 (42.8%)	0.010	Yes	806 (39.6%)	1627 (40%)	0.803
	No	1230 (60.4%)	3717 (57.2%)		No	1230 (60.4%)	2445 (60%)	
Extra articular lesions	Yes	394 (19.4%)	1301 (20%)	0.539	Yes	394 (19.4%)	787 (19.3%)	1.000
	No	1642 (80.6%)	5202 (80%)		No	1642 (80.6%)	3285 (80.7%)	
Surgical treatment	Yes	48 (2.4%)	154 (2.4%)	1.000	Yes	48 (2.4%)	82 (2%)	0.433
	No	1988 (97.6%)	6349 (97.6%)		No	1988 (97.6%)	3990 (98%)	
Death	Yes	74 (3.6%)	162 (2.5%)	0.008	Yes	74 (3.6%)	119 (2.9%)	0.155
	No	1962 (96.4%)	6341 (97.5%)		No	1962 (96.4%)	3953 (97.1%)	

Table 2 Univariate and Multivariate Analysis of Factors Influencing Readmission in RA Patients

Characteristics	Univariate					Multivariate				
	N	Event N	HR	95% CI	p-value	N	Event N	HR	95% CI	p-value
Age	6108	2669	1.01	1.01, 1.01	<0.001	6108	2669	1	1.00, 1.01	0.55
Age>60										
No	3042	1295	—	—		3042	1295	—	—	
Yes	3066	1374	1.28	1.19, 1.38	<0.001	3066	1374	1.24	1.08, 1.43	0.003
Gender										
Male	1275	494	—	—		1275	494	—	—	
Female	4833	2175	1.16	1.06, 1.28	0.002	4833	2175	1.1	1.00, 1.22	0.056
XFC										
No	4072	1863	—	—		4072	1863	—	—	
Yes	2036	806	0.6	0.55, 0.65	<0.001	2036	806	0.61	0.56, 0.66	<0.001
TCM										
No	1659	680	—	—		1659	680	—	—	
Yes	4449	1989	0.83	0.76, 0.90	<0.001	4449	1989	0.81	0.74, 0.89	<0.001
DMARDs										
No	1658	637	—	—		1658	637	—	—	
Yes	4450	2032	1.17	1.07, 1.28	<0.001	4450	2032	1.12	1.02, 1.24	0.022

(*Continued*)

Table 2 (Continued).

Characteristics	Univariate					Multivariate				
	N	Event N	HR	95% CI	*p*-value	N	Event N	HR	95% CI	*p*-value
NSAIDs										
No	1696	789	—	—		1696	789	—	—	
Yes	4412	1880	0.94	0.87, 1.03	0.18	4412	1880	1.04	0.95, 1.14	0.41
Glucocorticoids										
No	2279	883	—	—		2279	883	—	—	
Yes	3829	1786	1.28	1.18, 1.39	<0.001	3829	1786	1.16	1.06, 1.27	0.001
Extra articular lesions										
No	4856	1838	—	—		4856	1838	—	—	
Yes	1252	831	1.95	1.80, 2.12	<0.001	1252	831	1.87	1.72, 2.03	<0.001
Surgical treatment										
No	5956	2578	—	—		5956	2578	—	—	
Yes	152	91	1.41	1.14, 1.73	0.001	152	91	1.11	0.90, 1.37	0.32
Death										
No	5903	2634	—	—		5903	2634	—	—	
Yes	205	35	1.11	0.80, 1.55	0.53	205	35	1.02	0.72, 1.44	0.93
IgA↑										
No	5450	2385	—	—		5450	2385	—	—	
Yes	658	284	0.95	0.84, 1.07	0.4	658	284	0.97	0.85, 1.10	0.61
IgG↑										
No	5234	2299	—	—		5234	2299	—	—	
Yes	874	370	0.96	0.86, 1.07	0.43	874	370	0.96	0.85, 1.08	0.51
IgM↑										
No	5925	2593	—	—		5925	2593	—	—	
Yes	183	76	0.91	0.72, 1.14	0.4	183	76	0.93	0.74, 1.17	0.52
C3↑										
No	1097	460	—	—		1097	460	—	—	
Yes	5011	2209	1.19	1.08, 1.32	<0.001	5011	2209	0.94	0.73, 1.21	0.63
C4↑										
No	1108	457	—	—		1108	457	—	—	
Yes	5000	2212	1.21	1.10, 1.34	<0.001	5000	2212	1.17	0.91, 1.49	0.23
CRP↑										
No	2505	1076	—	—		2505	1076	—	—	
Yes	3603	1593	1.06	0.99, 1.15	0.11	3603	1593	0.99	0.90, 1.09	0.78
ESR↑										
No	2951	1275	—	—		2951	1275	—	—	
Yes	3157	1394	1.07	0.99, 1.16	0.072	3157	1394	1.02	0.93, 1.12	0.67
RF↑										
No	1367	493	—	—		1367	493	—	—	
Yes	4741	2176	1.3	1.18, 1.44	<0.001	4741	2176	1.18	1.06, 1.31	0.002
PLT↑										
No	977	427	—	—		977	427	—	—	
Yes	5131	2242	0.93	0.84, 1.03	0.19	5131	2242	1.04	0.94, 1.16	0.46

(TCM) treatment also exhibited a lower risk of readmission (HR = 0.83, 95% CI = 0.76, 0.90, P < 0.001). Conversely, patients older than 60 years of age demonstrated a significantly elevated risk of readmission (HR = 1.28, 95% CI = 1.19, 1.38, P < 0.001). Additionally, female gender, treatment with DMARDs and Glucocorticoids, the presence of extra-articular lesions, and surgical treatment were all associated with an increased risk of readmission among RA patients. Furthermore, abnormal elevations in C3, C4, and RF levels also contributed to a higher risk of readmission (P < 0.01; Figure 2A). Multivariate

A

Characteristics	Total	Events	HR (95% CI)
Age	6108	2669	1.01 (1.01 to 1.01)
Age.60			
No	3042	1295	-
Yes	3066	1374	1.28 (1.19 to 1.38)
Gender			
Male	1275	494	-
Female	4833	2175	1.16 (1.06 to 1.28)
XFC			
No	4072	1863	-
Yes	2036	806	0.60 (0.55 to 0.65)
TCM			
No	1659	680	-
Yes	4449	1989	0.83 (0.76 to 0.90)
DMARDs			
No	1658	637	-
Yes	4450	2032	1.17 (1.07 to 1.28)
NSAIDs			
No	1696	789	-
Yes	4412	1880	0.94 (0.87 to 1.03)
Glucocorticoids			
No	2279	883	-
Yes	3829	1786	1.28 (1.18 to 1.39)
Extra.articular.lesions			
No	4856	1838	-
Yes	1252	831	1.95 (1.80 to 2.12)
Surgical.treatment			
No	5956	2578	-
Yes	152	91	1.41 (1.14 to 1.73)
Death			
No	5903	2634	-
Yes	205	35	1.11 (0.80 to 1.55)
IgA↑			
No	5450	2385	-
Yes	658	284	0.95 (0.84 to 1.07)
IgG↑			
No	5234	2299	-
Yes	874	370	0.96 (0.86 to 1.07)
IgM↑			
No	5925	2593	-
Yes	183	76	0.91 (0.72 to 1.14)
C3↑			
No	1097	460	-
Yes	5011	2209	1.19 (1.08 to 1.32)
C4↑			
No	1108	457	-
Yes	5000	2212	1.21 (1.10 to 1.34)
CRP↑			
No	2505	1076	-
Yes	3603	1593	1.06 (0.99 to 1.15)
ESR↑			
No	2951	1275	-
Yes	3157	1394	1.07 (0.99 to 1.16)
RF↑			
No	1367	493	-
Yes	4741	2176	1.30 (1.18 to 1.44)
PLT↑			
No	977	427	-
Yes	5131	2242	0.93 (0.84 to 1.03)

B

Characteristics	Total	Events	HR (95% CI)
Age	6108	2669	1.00 (1.00 to 1.01)
Age.60			
No	3042	1295	-
Yes	3066	1374	1.24 (1.08 to 1.43)
Gender			
Male	1275	494	-
Female	4833	2175	1.10 (1.00 to 1.22)
XFC			
No	4072	1863	-
Yes	2036	806	0.61 (0.56 to 0.66)
TCM			
No	1659	680	-
Yes	4449	1989	0.81 (0.74 to 0.89)
DMARDs			
No	1658	637	-
Yes	4450	2032	1.12 (1.02 to 1.24)
NSAIDs			
No	1696	789	-
Yes	4412	1880	1.04 (0.95 to 1.14)
Glucocorticoids			
No	2279	883	-
Yes	3829	1786	1.16 (1.06 to 1.27)
Extra.articular.lesions			
No	4856	1838	-
Yes	1252	831	1.87 (1.72 to 2.03)
Surgical.treatment			
No	5956	2578	-
Yes	152	91	1.11 (0.90 to 1.37)
Death			
No	5903	2634	-
Yes	205	35	1.02 (0.72 to 1.44)
IgA↑			
No	5450	2385	-
Yes	658	284	0.97 (0.85 to 1.10)
IgG↑			
No	5234	2299	-
Yes	874	370	0.96 (0.85 to 1.08)
IgM↑			
No	5925	2593	-
Yes	183	76	0.93 (0.74 to 1.17)
C3↑			
No	1097	460	-
Yes	5011	2209	0.94 (0.73 to 1.21)
C4↑			
No	1108	457	-
Yes	5000	2212	1.17 (0.91 to 1.49)
CRP↑			
No	2505	1076	-
Yes	3603	1593	0.99 (0.90 to 1.09)
ESR↑			
No	2951	1275	-
Yes	3157	1394	1.02 (0.93 to 1.12)
RF↑			
No	1367	493	-
Yes	4741	2176	1.18 (1.06 to 1.31)
PLT↑			
No	977	427	-
Yes	5131	2242	1.04 (0.94 to 1.16)

Figure 2 Forest plot of COX proportional hazards model. (**A**) Single factor analysis forest map; (**B**) Multi factor analysis forest plot (conducted multiple factor analysis on all variables).

analysis, incorporating all variables, was conducted to screen for independent factors influencing readmission among RA patients. The results revealed that compared to patients in the Non-XFC group, those in the XFC group had a 39% reduced risk of readmission (HR = 0.61, 95% CI = 0.56, 0.66, P < 0.001). Patients in the TCM group also experienced a 19% decrease in readmission risk. Conversely, being over 60 years old increased the risk of readmission by 24%, while the use of DMARDs and Glucocorticoids elevated the risk by 12% and 16%, respectively. The presence of extra-articular lesions significantly raised the risk by 87%, and abnormal elevations in RF levels contributed to an 18% increase in readmission risk (P < 0.01 or P < 0.05). These findings suggest that XFC and TCM are protective factors against readmission among RA patients, while age, NSAIDs, Glucocorticoids, extra-articular lesions, and abnormal RF levels are risk factors (Figure 2B).

K-M Survival Curve Analysis of the Impact of XFC on Readmission Among RA Patients

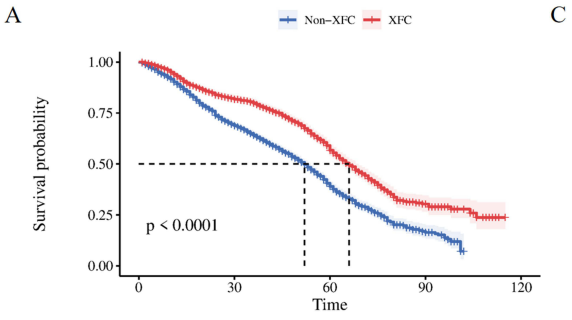
The Kaplan-Meier (K-M) survival curve was utilized to compare the risk of readmission between the XFC group and the Non-XFC group, with a further exploration into the influence of XFC intervention duration on this risk. Notably, the XFC group exhibited a significantly lower risk of readmission compared to the Non-XFC group (log-rank $P < 0.0001$; Figure 3A). Within the XFC group, patients were stratified based on the duration of XFC intervention, with ≤12 months defined as low exposure and >12 months defined as high exposure. The high exposure subgroup demonstrated a markedly lower readmission rate compared to the low exposure subgroup ($P = 0.00038$; Figure 3B). Additionally, the high exposure subgroup had a significantly lower risk of readmission compared to the low exposure subgroup (log-rank $P < 0.01$; Figure 3C).

Effect of XFC on Immune and Inflammatory Indicators in RA Patients

Compared to pre-treatment levels, the Non-XFC group exhibited a significant decrease in IgA, IgG, C3, C4, CRP, ESR, RF, and PLT levels after treatment ($P < 0.01$). In the XFC group, a similar reduction was observed in these immune and inflammatory indicators post-treatment, with statistically significant differences noted for IgA, IgG, C3, C4, CRP, ESR, RF, and PLT levels ($P < 0.05$ or $P < 0.01$). Notably, the XFC group demonstrated a superior efficacy in reducing C3, C4, CRP, and RF levels compared to the Non-XFC group ($P < 0.05$ or $P < 0.01$; Table 3).

Association Rule Analysis of XFC Treatment with Laboratory Indicators and Readmission in RA Patients

An association rule analysis was conducted, with XFC treatment as the antecedent and improved laboratory indicators as the consequent. The results revealed that the support and confidence levels between XFC and improvements in CRP, RF, PLT, ESR, C3, and C4 indicators were all greater than 30%. To investigate the correlation between XFC and readmission among RA patients, readmission was defined as F, and no readmission was defined as T. The association rule analysis



C

Readmission, n (%)	XFC group			*P* value
	Overall (n=2036)	Low exposure (n=864)	High exposure (n=1172)	
Yes	806 (40%)	379 (44%)	427 (36%)	<0.01
No	1230 (60%)	485 (56%)	745 (64%)	

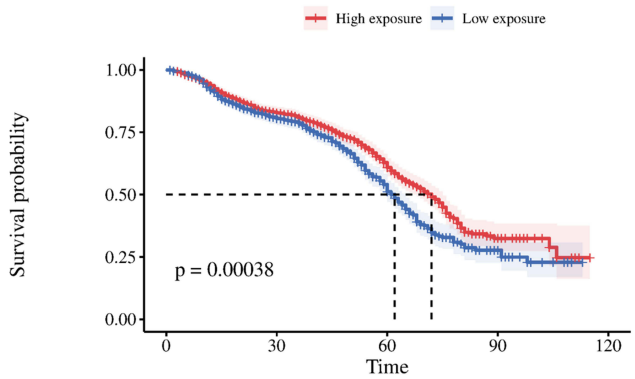


Figure 3 K-M survival curve of RA patients readmitted. (**A**) Using K-M survival curve to analyze the impact of XFC on readmission risk; (**B**) Using K-M survival curve to evaluate the impact of XFC intervention time on readmission risk; (**C**) The incidence of readmission in the low exposure group and high exposure group.

Table 3 Effect of XFC on Immune and Inflammatory Markers in RA Patients

Indicators	Non-XFC (n =4072)		XFC (n=2036)	
	Pre-Treatment	Post-Treatment	Pre-Treatment	Post-Treatment
IgA (g/L)	2.480[1.870,3.240]	2.390[1.810,3.110]##	2.500[1.870,3.380]	2.430[1.810,3.260]*
IgG (g/L)	12.500[10.000,15.220]	12.040[9.700,14.510]##	12.900[10.300,15.950]	12.400[10.010,15.220]**
IgM(g/L)	1.180[0.860,1.600]	1.190[0.870,1.600]	1.170[0.870,1.580]	1.190[0.870,1.600]
C3 (g/L)	107.900[84.800,126.100]	103.300[81.400,119.300]##	104.900[1.660,125.600]	100.200[1.500,118.700]**ΔΔ
C4 (g/L)	23.300[15.100,29.600]	21.100[13.200,27.300]##	21.700[0.510,28.900]	19.800[0.430,26.900] **ΔΔ
CRP (mg/L)	15.130[2.990,40.400]	2.410[0.560,10.230]##	18.050[3.820,44.490]	2.090[0.500,8.510]**Δ
ESR (mm/h)	39.000[21.000,64.000]	26.000[14.000,44.000]##	43.000[23.000,69.000]	27.000[16.000,45.000]**
RF (U/mL)	79.500[18.800,216.400]	69.000[17.000,191.900]##	64.900[14.600,194.000]	58.200[14.100,176.600]* ΔΔ
PLT(×10^9/L)	4.030[3.730,4.340]	3.960[3.660,4.280]##	4.040[3.750,4.360]	3.970[3.660,4.290]**

Note: Compared with the Non-XFC group before treatment, # P<0.05, # # P<0.01. Compared with the XFC group before treatment, * P<0.05, * * P<0.01. The differences between the Non-XFC group were compared (before treatment - after treatment), Δ P < 0.05, ΔΔP<0.01.

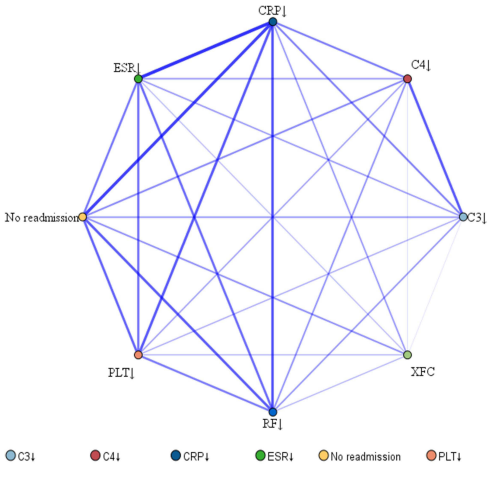
outcomes indicated a strong association between XFC treatment and no readmission, with a support level exceeding 60%, a confidence level greater than 30%, and a lift greater than 1 (Figure 4).

Random Walk Evaluation Model for Laboratory Indicators

The random walk step lengths for C3, C4, CRP, ESR, IgA, and IgG were respectively calculated as 11364, 10,023, 13,939, 12,996, 11362, and 11366. The corresponding random positive growth rates for these indicators were 0.135, 0.163, 0.261, 0.438, 0.100, and 0.111. The comprehensive evaluation record counts amounted to 5342, 4792, 7871, 7015, 5340, and 5344 entries, respectively. The clinical significance of these data lies in the fact that each time the comprehensive evaluation indices for C3, C4, CRP, ESR, IgA, and IgG increase, patients would need to undertake an estimated number of steps equivalent to 7.44, 6.12, 3.83, 2.28, 10.00, and 8.98, respectively (Figure 5).

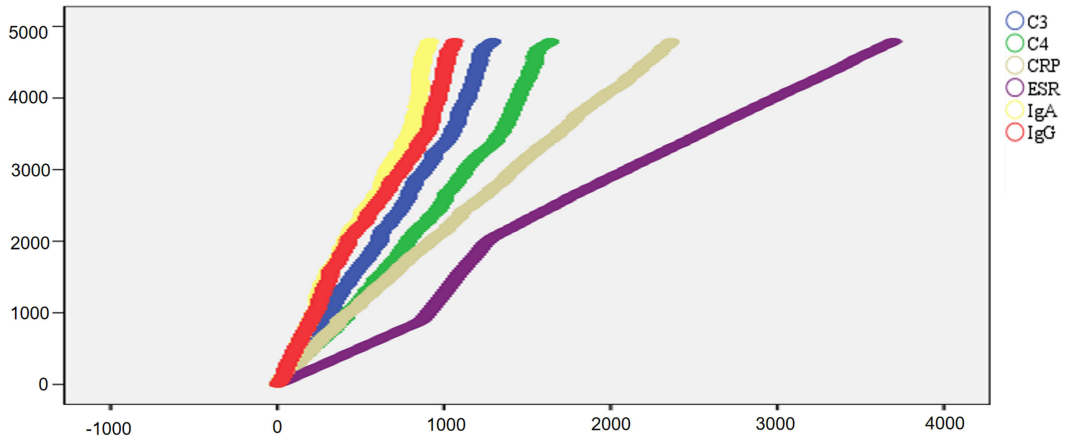
Discussion

RA, a chronic, inflammatory, and progressive autoimmune disorder, is characterized by its multisystem involvement, high incidence, and substantial risk of disability, leading to a protracted course of illness that significantly impairs patients' quality of life.[28,29] In light of these challenges, the present study innovatively integrates cohort research with clinical big data mining techniques to explore the dynamics of clinical laboratory indicators in RA patients and delve into



The aforesaid	The consequent	Support (%)	Confidence (%)	Lift
XFC	No readmission	60.167	33.469	1.004
XFC	CRP↓	53.929	35.185	1.056
XFC	RF↓	47.626	32.107	0.963
XFC	PLT↓	44.597	34.985	1.050
XFC	ESR↓	41.110	35.165	1.055
XFC	C4↓	34.807	30.809	0.924
XFC	C3↓	32.155	30.295	0.909

Figure 4 Association Rule Analysis of XFC Treatment with Laboratory Indicators and Readmission in RA Patients. Note: The thickness of the lines is proportional to the strength of the correlation between the indicators.



Index	Maximum value of random fluctuation	Random walk steps	Positive growth rate of walking	Improvement factor	Power value of random fluctuation	Comprehensive evaluation record	ratio
C3 (g/L)	1528	11364	0.135	0.286	0.469±0.106	5342	7.440
C4 (g/L)	1637	10023	0.163	0.342	0.528±0.094	4792	6.120
CRP (mg/L)	3635	13939	0.261	0.462	0.559±0.109	7871	3.830
ESR (mm/h)	5697	12996	0.438	0.812	0.620±0.155	7015	2.280
IgA (g/L)	1136	11362	0.100	0.213	0.484±0.095	5340	10.000
IgG (g/L)	1266	11366	0.111	0.237	0.472±0.106	5344	8.980

Figure 5 Random Walk Evaluation Model for Laboratory Indicators in RA Patients Treated with XFC. Note: The length of the horizontal lines increases with the number of steps, while the height of the vertical lines rises with the enhancement of intervention effectiveness.

the protective and risk factors influencing readmission risk, particularly validating the potential correlation between the use of the TCM preparation XFC and patients' readmission rates.

XFC, an efficacious TCM compound for treating RA, has demonstrated remarkable therapeutic effects in clinical practice.[21] This formulation centers on Astragalus membranaceus and Coicis Semen as the principal herbs, complemented by Centipede and Tripterygium wilfordii Hook. f. as the assistant herbs, collectively exerting a harmonizing effect on strengthening spleen, resolving dampness, promoting blood circulation, and alleviating pain. Modern pharmacological studies reveal that astragaloside IV in Astragalus membranaceus inhibits the proliferation of fibroblast-like synoviocytes (FLSs) in RA rats by modulating the lncRNA LOC100912373/miR-17-5p/PDK1 axis,[30] while total flavonoids from Astragalus membranaceus mitigate joint damage in arthritic rats via the OPG/RANKL/NF-κB pathway.[31] Coicis Semen suppresses the activation of NF-κB, MAPK pathways, and NLRP3 inflammasomes, thereby reducing inflammatory responses.[32] The primary active components of Tripterygium wilfordii Hook. f., such as triptolide, inhibit IL-6-induced proliferation and inflammation in RA-FLSs through the JAK2/STAT3 signaling pathway while modulating the hsa-circ -0003353/ microRNA-31-5p/CDK1 axis to suppress fibroblast-like cell activity.[33,34] Celastrol, another active ingredient, inhibits macrophage inflammatory polarization via NF-κB and Notch1 pathways, decreasing the secretion of proinflammatory cytokines and thereby hindering RA progression.[35] The bioactive polypeptide from Centipede alleviates inflammatory responses by inhibiting the NF-κB signaling pathway and ameliorates bone destruction in arthritic mice.[36,37] Previous studies have confirmed XFC's potent anti-inflammatory and immunomodulatory effects, significantly reducing various clinical laboratory indicators in RA patients, including ESR, hs-CRP, RF, and CCP, by inhibiting NF-κB pathway activation, decreasing serum proinflammatory factors, alleviating immune-inflammatory responses, and ultimately improving RA symptoms.[38] Animal and cellular experiments further substantiate XFC's ability to mitigate arthritic symptoms and suppress inflammatory reactions in immune cells.[39–41]

In recent years, the role of TCM in the treatment of RA has garnered significant interest and attention from clinicians and researchers alike.[42] Studies have indicated that long-term (over 2 years) TCM intervention significantly reduces the

risk of fractures among RA patients by more than 50%.[43] Furthermore, long-term TCM treatment not only positively delays the onset of extra-articular manifestations in RA patients but also helps reduce their likelihood of occurrence.[44] Additional research has found that TCM compound treatment acts as a protective factor, associated with a decreased risk of rehospitalization for RA patients. Importantly, TCM compound treatment also improves self-perception of patients (SPP), enhancing the quality of life and satisfaction of RA patients.[16] Previous explorations have also unveiled a close association between XFC and improvements in immune-inflammatory markers, optimization of red blood cell parameters, and reduced readmissions among RA patients.[45] To gain a deeper understanding of these relationships, this study established a cohort comprising 8539 RA patients through telephone follow-ups and thoroughly analyzed their baseline demographics, medication histories, readmission risks, and other relevant factors. Univariate analysis revealed that female, DMARDs treatment, Glucocorticoids treatment, extra-articular lesions, and surgical treatment were all factors that increased the risk of readmission among RA patients. Moreover, abnormally elevated levels of C3, C4, and RF were also significantly associated with an increased readmission risk. Notably, XFC and TCM therapy emerged as effective means of mitigating this risk. To further identify independent factors influencing readmission in RA patients, we employed multivariate analysis, comprehensively considering all relevant variables. The results demonstrated that being aged over 60, using NSAIDs, undergoing Glucocorticoids treatment, having extra-articular lesions, and exhibiting abnormally high RF levels were all independently associated with an increased risk of readmission. Conversely, XFC and TCM therapy were once again confirmed to have a significant protective effect against readmission. Subsequent Kaplan-Meier survival curve analysis reinforced these findings, indicating that not only did XFC usage reduce the risk of readmission among RA patients, but the longer the duration of treatment (exceeding 12 months), the more pronounced this effect became. This discovery underscores the efficacy of XFC in controlling RA progression and minimizing disease recurrence. We speculate that the remarkable therapeutic outcomes of XFC may stem from the synergistic effects of its multiple active components, which work through multi-pathway, multi-target mechanisms to exert key functions such as anti-inflammation, antioxidant stress, and immune modulation,[22,23] thereby achieving comprehensive treatment for RA.

Subsequently, we delved deeper into the clinical data of 2036 RA patients who received XFC treatment. The results revealed a decline in the patients' IgA, IgG, C3, C4, CRP, ESR, RF, and levels PLT following oral administration of XFC. Notably, the XFC group demonstrated a superior performance in reducing C3, C4, CRP, and RF levels compared to the non-XFC group. Association rule mining, a technique primarily used to uncover correlations between variables, enhances the comprehensibility and interpretability of data and hidden patterns within it.[46] Our further analysis employing association rules unveiled a significant correlation between XFC and improvements in CRP, RF, PLT, ESR, C3, and C4 levels, as well as a close link to reduced readmissions. Additionally, the application of random walk models illuminated the long-term associations between XFC and these improvements, underscoring its significance in developing an effective comprehensive evaluation system for TCM in clinical practice.[47] By assessing the relationship between walking steps and biomarker improvements, this study further confirmed the long-term correlation between XFC and enhancements in C3, C4, CRP, ESR, IgA, and IgG.

While rigorous efforts were made to ensure the scientific rigor of this study in terms of sample size, study design, and statistical analysis, several limitations persist. Firstly, key data after treatment, such as medication use, treatment duration, and endpoint events, were obtained and verified through telephone follow-ups. However, due to patients' subjectivity and limitations in memory, there may be risks of response bias and recall bias, which could potentially affect the accuracy of the study results. Secondly, when assessing the efficacy of XFC, the study did not exclude the potential interference of western medicines and other traditional Chinese medicines, nor did it evaluate the combined efficacy of western medicines, other traditional Chinese medicines, and XFC. This may lead to an inaccurate and incomplete assessment of XFC's efficacy. Furthermore, this study was conducted in a single institution, so the results may only be applicable to a small subset of the population. To verify the broad applicability of XFC, further multicenter and prospective studies are needed. Additionally, as an observational study, we could not completely eliminate the influence of confounding factors on the results. Although we adopted propensity score matching to adjust for confounders, some unknown or difficult-to-quantify factors may still have interfered with the findings, resulting in gender imbalance between the matched groups. Secondly, the study's findings are primarily based on Chinese patient data, and their

applicability to patients of other ethnicities or regions remains to be validated. Addressing these limitations, future research can be improved and expanded in several directions: Firstly, enlarging the sample size and geographical scope to enhance the study's generalizability and reliability. Secondly, delving deeper into the specific mechanisms of XFC and optimizing treatment protocols for personalized medicine. Lastly, strengthening international collaboration and exchanges to facilitate the dissemination and application of traditional Chinese medicine globally.

Conclusion

Drawing upon a large-scale cohort study and rigorous data mining techniques, this research underscores XFC as a remarkable protective factor that not only mitigates the risk of readmission and prolongs survival among RA patients but also markedly ameliorates their clinical immune-inflammatory biomarkers. This discovery not only offers fresh insights and avenues for clinical management of RA but also provides robust evidence for the application of traditional Chinese medicine in the management of autoimmune diseases. Looking ahead, we will embark on a more comprehensive exploration of the specific mechanisms of XFC and the optimization of treatment protocols, aiming to achieve superior therapeutic outcomes and reduced healthcare costs.

Data Sharing Statement

The datasets in the present study can be obtained from the author corresponding on request.

Ethics Approval and Consent to Participate

The Ethics Committee of the First Affiliated Hospital of Anhui University of Chinese Medicine has waived the requirement for informed consent (Approval No. 2022MCZQ01).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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