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SMI-guided deep remission and TCM-assisted biologic De-intensification in rheumatoid arthritis: Yiqi-Jianpi-Tongluo combined with TNF-α inhibitors

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Abstract: **Background**: Achieving treatment targets in rheumatoid arthritis (RA) is feasible; however, safely tapering or discontinuing biologic agents remains challenging. Superb microvascular imaging (SMI) enables detection of subclinical synovitis, facilitating precise remission assessment. The Yiqi-Jianpi-Tongluo formula may help maintain disease stability, yet its role in combination with SMI-guided tapering is unclear. **Objective**: To evaluate whether SMI-guided deep remission effectively guides adalimumab (ADA) tapering and to assess the Yiqi-Jianpi-Tongluo formula in reducing recurrence risk during this process. **Method**: This retrospective study included 120 RA patients in clinical remission on stable ADA and methotrexate (January 2022–June 2024). Patients were stratified by baseline 28-joint SMI score (SMI=0 vs. SMI>0) and received either combined therapy (ADA reduced to 40mg/month + Yiqi-Jianpi-Tongluo formula) or Western therapy (ADA reduction alone). Methotrexate was continued. Primary endpoint was 12-month disease recurrence rate; secondary endpoints included ultrasound remission maintenance, traditional Chinese medicine (TCM) syndrome efficacy, inflammatory marker changes (CRP, IL-6, RF), and adverse events. Results: The combination group exhibited significantly lower 12-month recurrence rates (HR=0.368, 95% CI: 0.186–0.730, P=0.004), with consistent risk reduction across SMI strata. Baseline ultrasound remission was associated with significantly higher recurrence-free survival (HR=0.355, 95% CI: 0.179–0.702; P=0.004). The combination group also demonstrated superior ultrasound remission maintenance (90.32% vs. 69.23%, P=0.045) and TCM syndrome efficacy (80.33% vs. 54.24%, P=0.002), along with greater improvements in CRP, IL-6, and RF (all P<0.05). Adverse event rates were comparable (χ^2=0.128, P=0.721). **Conclusion**: SMI-guided deep remission effectively informs ADA tapering. Adding Yiqi-Jianpi-Tongluo formula significantly reduces recurrence risk, enhances remission maintenance, and improves symptoms without compromising safety, supporting an integrated strategy for RA remission management.

Keywords: Arthritis; Adalimumab; Chinese traditional; Drug tapering; Medicine; Rheumatoid; Treatment outcome; Ultrasonography

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease of unknown etiology, characterized primarily by persistent inflammation of multiple joints (Gravallese and Firestein, 2023). Its key pathological features include synovial hyperplasia in the joint cavity, thickening of the lining layer, pannus formation and infiltration of various inflammatory cells. These changes cause osteochondral destruction, ultimately resulting in joint deformity and functional impairment (Cush, 2022). In the early stages, the disease may cause symptoms such as joint pain and tenderness. As it progresses, joint swelling and prolonged morning stiffness may develop, significantly affecting patients' quality of life and work capacity (Wu *et al.*, 2022). Epidemiological studies indicate that the global prevalence of RA is approximately 0.5%-1.0%, with over 5 million patients in China (Venetsanopoulou *et al.*, 2022). Over the past two decades, with the widespread use of methotrexate (MTX) and the iterative development of targeted therapies such as tumor necrosis factor-α (TNF-α) inhibitors, interleukin-6 (IL-6) receptor antagonists and Janus kinase (JAK) inhibitors, RA treatment has entered the era of "treat-to-target" (T2T), leading to a significant improvement in clinical remission rates (Harigai and Sugihara, 2025; He *et al.*, 2025). However, the safe and effective tapering or discontinuation of biologic disease-modifying antirheumatic drugs (bDMARDs) after achieving clinical remission remains a critical challenge in clinical practice (Deng *et al.*, 2025). Long-term, full-dose use of bDMARDs not only imposes a substantial economic burden on patients but is also associated with an increased risk of adverse events such as infections, malignancies and cardiovascular complications (Schaefer *et al.*, 2025; Zhang *et al.*, 2025). Conversely, abrupt treatment tapering leads to disease recurrence in 30 60% of patients within 12 months, with earlier recurrence correlating with more severe joint structural damage and functional disability (Sakashita *et*

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al., 2022). Therefore, there is an urgent need to establish objective, sensitive and reproducible assessment systems to identify patients suitable for dose reduction and to implement effective interventions to minimize the risk of recurrence and infection.

Currently employed clinical remission criteria, including those based on the 28-joint disease activity score (DAS28) and the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Boolean definition, primarily rely on patients' subjective symptoms, physical examination and acute-phase reactant levels. These criteria are unable to identify "subclinical synovitis," a concealed yet persistent inflammatory state (Felson *et al.*, 2022; Simpson *et al.*, 2018). Studies have shown that even after achieving clinical remission, a proportion of arthritis patients exhibit residual synovitis detectable by magnetic resonance imaging (MRI) or musculoskeletal ultrasound (MSUS). This residual synovitis is one of the strongest predictors of future disease recurrence (Mazzoni *et al.*, 2023). In RA patients, ultrasound-detected synovitis is significantly associated with the risk of recurrence within one year and has already been incorporated into nomograms for predicting disease recurrence (Hu *et al.*, 2020). Superb microvascular imaging (SMI) is an emerging Doppler ultrasonography technology that suppresses clutter signals and enhances the display of low-velocity blood flow. It can clearly visualize neovascularization with a diameter of <1 mm within the synovium without the need for contrast agents, demonstrating significantly superior sensitivity compared to conventional power doppler ultrasound (PDUS) (Kurtulus Ozturk *et al.*, 2025). Quantitative SMI assessments revealed a significant correlation between synovial blood flow grading and RA disease activity (Ou *et al.*, 2024). MRI-detected synovitis and bone marrow edema are closely associated with patient-reported functional decline, suggesting that residual inflammation impacts long-term prognosis even during clinical remission (Nawata *et al.*, 2021). In the Japanese KURAMA cohort study (Matsuo *et al.*, 2020), an SMI score ≥1 in the wrist joint was identified as an independent predictor of RA recurrence (OR=3.08, *P*=0.001). However, data regarding SMI-guided bDMARDs tapering strategies in the Chinese population remain relatively scarce.

While determining the optimal timing for dose reduction, how to mitigate the risk of recurrence and infection following reduction is equally important. TNF-α inhibitors, such as adalimumab (ADA), are among the most widely used bDMARDs in China, with post-reduction disease recurrence rates remaining between 25% and 45% (Aletaha *et al.*, 2017). Although reducing the dosage can decrease the risk of infection, it is also accompanied by an increase in disease activity (Balay-Dustrude *et al.*, 2024). Therefore, identifying adjuvant therapies that can synergistically maintain remission, reduce infection and improve immune homeostasis has become a current research hotspot. Traditional Chinese medicine (TCM) has a long history of treating RA. From the perspective of traditional medicine, RA falls under the category of "Bi Zheng" in TCM. During the remission phase, it often manifests as a deficiency in the root and excess in the branch, with core pathogenesis being spleen Qi deficiency and collateral obstruction. The Yiqi-Jianpi-Tongluo formula, based on the Sijunzi decoction and Yupingfeng Powder, supplemented with blood-activating and collateral-dredging herbs such as *Spatholobus suberectus* and *Ligusticum chuanxiong*, has potential advantages in maintaining disease stability, preventing infections and regulating immunity. However, high-quality evidence on the Yiqi-Jianpi-Tongluo formula's role in dose reduction when combined with biological agents remains scarce. Therefore, there is an urgent need to establish objective, sensitive and reproducible assessment systems to identify patients suitable for dose reduction and to implement effective interventions to minimize the risk of recurrence and infection.

Based on the aforementioned background and design, this study adopted a retrospective controlled design. It enrolled RA patients who achieved clinical remission and were planned for ADA dose reduction. Patients were stratified according to baseline SMI scores. The study then compared the efficacy and safety differences between treatment regimens that combined or did not combine the Yiqi-Jianpi-Tongluo formula within these different risk strata. This research primarily focused on observing the impact of the combined regimen on the 12-month disease recurrence rate, maintenance of ultrasound remission (UR), improvement in TCM syndrome scores and key inflammatory markers. It aimed to contribute evidence towards achieving individualized, precise and safe long-term disease management.

MATERIALS AND METHODS

Research content

Based on the aforementioned background, this study adopted a retrospective controlled design. It enrolled RA patients who achieved clinical remission and were planned for ADA dose reduction. Patients were stratified according to baseline SMI scores. The study then compared the efficacy and safety differences between treatment regimens that combined or did not combine the Yiqi-Jianpi-Tongluo formula within these different risk strata. This research primarily focused on observing the impact of the combined regimen on the 12-month disease recurrence rate, maintenance of ultrasound remission (UR), improvement in TCM syndrome scores and key inflammatory markers. It aimed to contribute evidence towards achieving individualized, precise and safe long-term disease management.

Study subjects

This retrospective clinical study initially considered 148 RA patients in clinical remission who visited our hospital between January 2022 and June 2024; after applying inclusion and exclusion criteria, 120 were enrolled. All patients received a baseline regimen of ADA 40 mg every two weeks + MTX 10 mg once weekly for over 12 weeks and underwent 28-joint SMI scoring. Based on the SMI scores, patients were divided into two groups: the non-UR (NUR) group (SMI>0) and the UR group (SMI=0). Patients in each of these groups were further subdivided into a Chinese and Western medicine combination group (ADA reduction + Yiqi-Jianpi-Tongluo formula) and a Western medicine group (ADA reduction only).

All patients had their ADA dosage reduced from 40 mg every two weeks to 40 mg once monthly, while maintaining the same oral MTX regimen. The follow-up period was 12 months. The primary endpoint was disease recurrence within 12 months after dose reduction. Secondary endpoints included the maintenance rate of UR, efficacy based on TCM syndrome evaluation and inflammatory markers such as C-reactive protein (CRP), IL-6 and rheumatoid factor (RF). Safety indicators comprised adverse events recorded throughout treatment. The detailed study flowchart is shown in fig. 1.

Inclusion criteria

(1) Meet the clinical diagnostic criteria for RA (Western medicine) and the TCM syndrome pattern of spleen qi deficiency.
(2) Currently on a stable treatment regimen consisting of weekly oral MTX (10 mg) and bi-weekly subcutaneous ADA (40 mg), maintained for over 12 weeks.
(3) DAS28<2.6.
(4) Aged between 18 and 70 years.

Exclusion criteria

(1) Concomitant use of other DMARDs (besides MTX), corticosteroids, or non-steroidal anti-inflammatory drugs.
(2) Inability to cooperate, or joint pain/swelling caused by trauma or any other diseases.
(3) Diagnosis of other autoimmune diseases.
(4) Severe psychiatric disorders.
(5) Severe cardiovascular, neurological, pulmonary, renal, or hepatic dysfunction, or malignancy.
(6) Known active bacterial, viral, fungal, or mycobacterial infections.
(7) Lost to follow-up or non-adherence to the prescribed medication regimen.
(8) Pregnancy or lactation.

Sample size calculation

This retrospective cohort study calculated the sample size based on the primary endpoint: the disease recurrence rate within 12 months after ADA dose reduction. Referring to previous literature (Emery *et al.*, 2020), the expected recurrence rate in the Western medicine group was approximately 40%, while the Chinese and Western medicine combination group was hypothesized to reduce the recurrence rate to 20%. With a set power (1-β) of 0.8 and a significance level (α) of 0.05 (two-sided test), sample size estimation for comparing two proportions was performed using G*Power software. The calculation indicated a required sample size of approximately 55 patients per group. Consequently, a total of 120 patients were enrolled, with approximately 60 assigned to each group, ensuring adequate statistical power for subgroup analyses.

Grouping

A total of 120 patients from our hospital were enrolled. All patients had been receiving a stable regimen of ADA injection 40 mg subcutaneously every two weeks combined with MTX 10 mg orally once weekly for over 12 weeks and had a DAS28 score of<2.6. At baseline, SMI values were assessed and pre-study treatment information, medical history and demographic data were collected. SMI scoring of 28 joints (bilateral metacarpophalangeal joints, proximal interphalangeal joints, shoulders, elbows, wrists and knees) was also performed.

Patients were stratified according to their UR status (SMI=0 vs. SMI>0) and were then grouped by treatment modality, receiving either Western medicine therapy alone or a combination of Chinese and Western medicine therapy. This resulted in four groups with the following final sizes (as also shown in Fig. 1): ① UR-Western medicine group (n=26); ② UR-Chinese and Western medicine combination group (n=31); ③ NUR-Western medicine group (n=33); ④ NUR-Chinese and Western medicine combination group (n=30).

All patients had their ADA injection dosage reduced from 40 mg every two weeks to 40 mg once monthly. The treatment for the Western medicine group consisted of: ADA injection 40 mg subcutaneously once monthly combined with MTX 10 mg orally once weekly. The Chinese and Western medicine combination group received the Western medicine regimen plus the self-formulated Yiqi-Jianpi-Tongluo formula. Prescription composition: *Astragalus membranaceus (Huangqi)* 15 g, *Pseudostellaria heterophylla (Taizishen)* 10 g, *dry-fried Atractylodes macrocephala (Chao Baizhu)* 10 g, *Poria cocos (Fuling)* 10 g, *Saposhnikovia divaricata (Fangfeng)* 6 g, *honey-fried Glycyrrhiza uralensis (Zhigancao)* 5 g, *Spatholobus suberectus (Jixueteng)* 12 g, *Ligusticum chuanxiong (Chuanxiong)* 10 g. The formula was administered using our hospital's prepared granule formulation. Dosage: one sachet each time, twice daily, dissolved in warm water.

Follow-up period

The observation endpoint was set at 12 months. DAS28 was assessed at months 3, 6 and 9 and recurrence events during the follow-up period were recorded for each group.

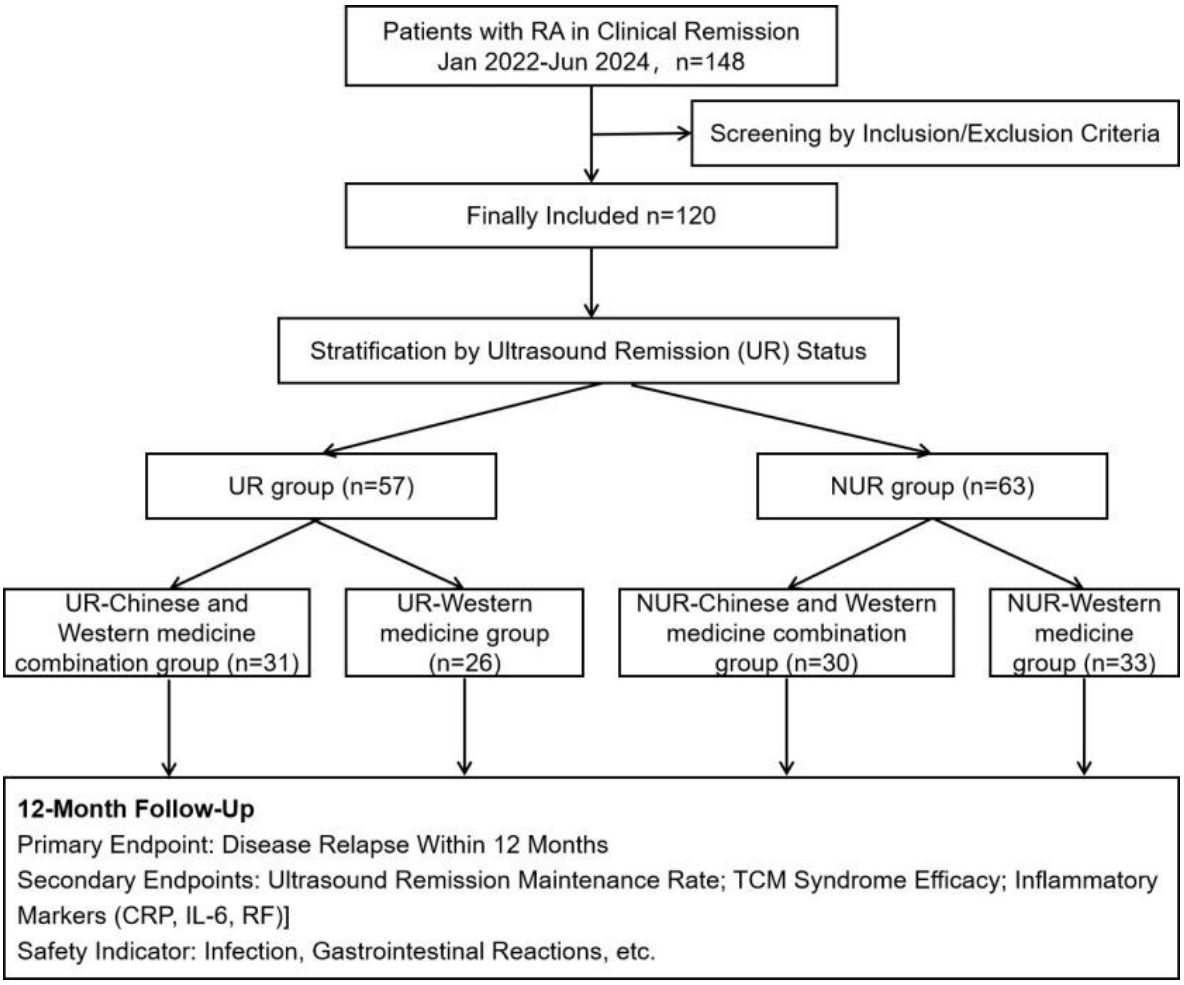

Fig. 1: Study flow.

Disease recurrence was defined as either two consecutive DAS28-ESR values ≥2.6 at least 4 weeks apart, or a single DAS28-ESR ≥2.6 accompanied by clinical evidence of flare. The date of the first qualifying DAS28 measurement was recorded as the recurrence date. Both scheduled and unscheduled visits were captured.

Ultrasonographic evaluation

High-frequency color Doppler ultrasonography was performed using Philips EPIQ5 and EPIQ7 ultrasound systems equipped with a high-frequency probe (center frequency: 18 MHz). Bilateral metacarpophalangeal joints, proximal interphalangeal joints, shoulders, elbows, wrists and knees were examined. Two-dimensional grayscale (GS) synovial thickness and SMI blood flow signals were collected. Longitudinal and transverse scans were performed for each joint to assess synovial hypertrophy. The site with the most severe synovial proliferation in bilateral joints was selected and the probe was fixed for SMI assessment. Color SMI mode was activated and gain and depth were adjusted to achieve the clearest image. Microvascular blood flow signals within the hyperplastic synovium were observed. When significant blood flow signals were detected, images were stored and included in the analysis. All ultrasound evaluations were jointly interpreted by two experienced radiologists to reach a consensus imaging diagnosis. Both radiologists were blinded to the patients' treatment groups (combination vs. Western medicine) and to the timepoint of the scan (baseline or follow-up) during image assessment. Inter-rater reliability for GS and SMI scoring was assessed using Cohen's kappa (κ) for categorical agreement. For GS scoring, κ=0.85. For SMI scoring, κ=0.88, indicating excellent agreement.

Semi-quantitative scoring of GS and SMI for each joint was performed according to the 2017 EULAR consensus on musculoskeletal ultrasound scoring (Terslev *et al.*, 2017).

(1) GS semi-quantitative scoring criteria: Score 0: No synovial hypertrophy; Score 1: Synovial hypertrophy present but not exceeding the line connecting the bone tops; Score 2: Synovial hypertrophy exceeding the bone top line with a concave upper surface; Score 3: Synovial hypertrophy exceeding the bone top line with a convex upper surface

(2) SMI semi-quantitative scoring criteria: Score 0: No blood flow signal within the hypertrophic synovium; Score 1: Detection of 3 single-point flow signals / 2 single-point + 1 confluent flow / 2 confluent flow signals; Score 2: Blood flow signals more than grade 1 but covering <50% of the hypertrophic synovial area; Score 3: Extensive blood flow signals within the hypertrophic synovium, covering ≥50% of the synovial area.
(3) Calculation of the 28-joint SMI Score: For each of the 28 assessed joints (bilateral metacarpophalangeal joints, proximal interphalangeal joints, shoulders, elbows, wrists and knees), a semi-quantitative SMI score (0-3) was assigned based on the criteria described above. The 28-joint SMI sum score was calculated by adding the individual joint scores, yielding a theoretical range of 0 to 84. For the primary stratification in this study, ultrasound remission (UR) was defined as a 28-joint SMI sum score of 0, indicating the complete absence of detectable synovial blood flow in all examined joints. The non-ultrasound remission (NUR) group comprised patients with a sum score >0, indicating the presence of subclinical synovitis in at least one joint.

Adherence monitoring

Adherence to the herbal sachets was monitored through a combination of methods: Sachet counts: Patients were instructed to return all unused sachets at each follow-up visit (3, 6, 9 and 12 months). Patient diaries: Participants recorded daily intake of the herbal formula. Adherence was defined as consumption of ≥90% of prescribed sachets. No placebo was used in the Western medicine group due to the retrospective nature of the study.

Laboratory assessment

Fasting venous blood samples were collected from all participants for the measurement of complete blood count, CRP, RF, IL-6, erythrocyte sedimentation rate (ESR) and hepatic and renal function parameters. Instruments: AU680 fully automatic biochemical analyzer (Beckman Coulter, USA), ESR fully automated dynamic ESR analyzer (Shanghai Xunda Medical Instrument Co., Ltd., China).

Clinical evaluation

(1) DAS28 calculation: DAS28-ESR was computed from: TJC: tender joint count (0-28), SJC: swollen joint count (0-28), ESR: (mm/h), GH: global health (0-100 mm VAS). Formula: DAS28-ESR=$0.56 \times \sqrt{TJC} + 0.28 \times \sqrt{SJC} + 0.70 \times \ln(ESR) + 0.014 \times GH$ (Terslev, Naredo, Aegerter, Wakefield, Backhaus, Balint, Bruyn, Iagnocco, Jousse-Joulin, Schmidt, Szkudlarek, Conaghan, Filippucci and D'Agostino, 2017). Interpretation: <2.6: remission, 2.6-3.2: low activity, 3.2-5.1: moderate activity, >5.1: high activity.

(2) TCM syndrome score (Zheng *et al.*, 2002): A 10-item TCM syndrome scale—derived from the Guiding Principles for Clinical Research of New Chinese Medicines in the Treatment of Bi-Syndrome—was used: joint pain, swelling, tenderness, limited flexion/extension, morning stiffness, local heat, fatigue, spontaneous sweating, loose stools and reduced appetite. Each item is graded 0-3 (or 0-1); higher scores indicate greater severity.

Therapeutic efficacy was calculated as: [(pre-treatment score - post-treatment score) / pre-treatment score] × 100%. Categories: Clinical control: ≥95% reduction, Marked response: ≥70% to <95% reduction, Partial response: ≥30% to <70% reduction, No response: <30% reduction. Total effective rate=[(clinical control + marked response + partial response) / total patients] × 100%.

Statistical methods

All analyses were run in SPSS 25.0. Categorical data are shown as n (%); continuous data as mean±SD (normal) or median [IQR] (non-normal). Within-group changes were evaluated with the paired t-test (normal) or Wilcoxon signed-rank test (non-normal); between-group differences with the χ^2 test (categorical), independent t-test (normal continuous) or Mann-Whitney U test (non-normal continuous). Recurrence were analysed with survival methods. Significance was set at two-tailed $P<0.05$.

RESULTS

Comparison of baseline characteristics in RA patients

Table 1 and the newly added table 2 summarizes the baseline characteristics of the 120 retrospectively enrolled RA patients in clinical remission. The data demonstrate no significant intergroup differences in demographics, lifestyle factors, disease duration, prior biologic exposure, baseline disease activity components (TJC, SJC, ESR, GH), seropositivity status (RF, anti-CCP), radiographic damage scores, prior steroid use, or MTX co-prescription with folic acid (all $P > 0.05$), confirming balanced baseline characteristics and comparability between the two treatment groups.

Comparison of disease recurrence within 12 months of dose reduction

Tables 2-5 and Figs. 2-5 show that, during the 12-month follow-up, the integrated Chinese-Western regimen containing the Yiqi-Jianpi-Tongluo formula significantly lowered the risk of recurrence compared with Western therapy alone. Kaplan-Meier analysis demonstrated a markedly lower overall recurrence hazard in the Chinese and Western medicine combination group (HR=0.368, 95 % CI 0.186-0.730; log-rank P=0.004).

The M (Q_1, Q_3) of the 28-joint SMI sum score at baseline was 1 (0, 3), with a range from 0 to 8. 57 patients (47.50%) had a sum score of 0 (UR group) and 63 patients (52.50%) had a sum score >0 (NUR group). Among the NUR patients, the distribution of sum scores was as follows: 1 (n=22), 2 (n=18), 3-5 (n=17) and >5 (n=6).

Stratified analyses confirmed this benefit in both the UR (SMI=0) group (HR=0.219, 95% CI 0.059-0.818; *P*=0.031) and the NUR (SMI>0) group (HR=0.463, 95 % CI 0.208-1.030; *P*=0.048), with prolonged recurrence-free survival in each. Moreover, patients who were in UR at baseline had a significantly higher recurrence-free survival rate than those who were not (HR=0.355, 95% CI 0.179-0.702; *P*=0.004).

These findings indicate that deep remission defined by SMI is a reliable predictor of recurrence risk after dose reduction and that adjunctive treatment with the Yiqi-Jianpi-Tongluo formula provides additional protection during ADA tapering.

Maintenance of UR

The Yiqi-Jianpi-Tongluo formula-supplemented regimen conferred a clear advantage in sustaining UR (SMI=0). As shown in table 6, at the 12-month visit the proportion of patients who remained in UR was 90.32 % (28/31) in the integrated Chinese-Western group versus 69.23 % (18/26) in the Western-only group; the difference was statistically significant (χ^2=4.039, *P*=0.045). Thus, adding the Yiqi-Jianpi-Tongluo formula to ADA tapering therapy more effectively preserves deep articular UR in RA patients.

Efficacy in TCM-syndrome improvement

Based on TCM-syndrome scores, the addition of the Yiqi-Jianpi-Tongluo formula produced a marked clinical benefit. Table 7 shows that the total effective rate for TCM-syndrome improvement was 80.33% (49/61) in the integrated Chinese-Western group, significantly higher than the 54.24% (32/59) observed in the Western-only group (χ^2=9.306, *P*=0.002). These data indicate that supplementing ADA tapering with the Yiqi-Jianpi-Tongluo formula more effectively ameliorates TCM-defined symptoms in RA patients.

Changes in inflammatory markers

After 12 months of treatment, the integrated Chinese-Western group demonstrated a superior anti-inflammatory effect. As shown in table 8, baseline CRP, IL-6 and RF levels were comparable between the two groups (all *P*>0.05). All three indices fell significantly from baseline in both arms (all *P*<0.001); however, the integrated-therapy group achieved markedly lower values for CRP (t=5.135, *P*<0.001), IL-6 (t=6.755, *P*<0.001) and RF (t=2.651, *P*=0.009) than the Western-only group. These findings indicate that adjunctive use of the Yiqi-Jianpi-Tongluo formula more effectively suppresses systemic inflammation and improves serological markers in RA patients undergoing ADA tapering.

Safety analysis

Both regimens were well tolerated. Table 9 shows that the overall incidence of adverse events did not differ between the integrated Chinese-Western group and the Western-only group (χ^2=0.128, *P*=0.721). Reported adverse events were mild to moderate and included injection-site reactions (4.92% vs 5.08%), upper respiratory tract infections (3.28% vs 1.69%) and nausea (1.64% vs 1.69%); all resolved with symptomatic management. No serious adverse events related to the study medication were recorded. Thus, adding the Yiqi-Jianpi-Tongluo formula to ADA tapering did not impose any additional safety risk.

DISCUSSION

The goal of RA therapy is to curb inflammation, so mitigating pain, progressive structural damage and dysfunction caused by inflammation. However, the reliability of accurately assessing synovial inflammation and treatment response in RA has remained a challenge in rheumatology research (Soloman *et al.*, 2024). A study (Wang *et al.*, 2025) reported that even among RA patients receiving biologic agents who achieved clinical remission, some still exhibited radiographic progression, suggesting that subclinical inflammation may persist and lead to bone erosion. The EULAR has endorsed MSUS as a tool for assessing RA activity, tracking therapeutic responses and forecasting disease trajectory (Batalov *et al.*, 2025). MSUS can assess structural changes such as synovial hyperplasia, joint effusion and bone erosion via Grayscale Ultrasound (GSUS) and detect synovial blood flow signals via PDUS, reflecting the degree of inflammatory activity (Molina Collada *et al.*, 2021).

Studies have shown that MSUS scores positively correlate with disease activity scores like DAS28 and can effectively distinguish between patients in remission and those with active disease (Chen and Chen, 2023). However, MSUS has limitations in detecting microvessels and low-velocity blood flow within the synovium, which may lead to an underestimation of inflammatory activity. Furthermore, the image quality and diagnostic accuracy of MSUS are highly dependent on the operator's experience and technical skill, introducing significant subjectivity and issues with reproducibility.

SMI is a relatively new technology applied for microvascular assessment in recent years. Compared to color Doppler ultrasound, it can more clearly display low-velocity flow in fine vessels, addressing the limitations of traditional ultrasound blood flow imaging modalities (Diao *et al.*, 2022). A study (Kurtulus Ozturk *et al.*, 2025) demonstrated that SMI is significantly superior to clinical examination and PDUS in visualizing synovial blood flow in RA patients, providing greater utility and capability in detecting synovial vascularity and monitoring disease activity. However, studies utilizing SMI to assess joint synovial blood flow in RA patients who have achieved clinical remission after treatment—a state characterized by significantly reduced synovial hyperplasia—remain relatively scarce. This study retrospectively analyzed 120 RA patients who had achieved clinical remission. It systematically evaluated the value of SMI-defined "deep

remission" in guiding ADA dose reduction within a Chinese population and investigated the modulating effects of the Yiqi-Jianpi-Tongluo formula on disease recurrence, infection risk and immune-inflammatory markers during the tapering process. The results indicated that the UR status defined by SMI significantly predicted the risk of recurrence after dose reduction. Furthermore, the combination therapy with Yiqi-Jianpi-Tongluo formula not only further reduced the recurrence rate but also demonstrated synergistic advantages in maintaining UR, improving TCM syndrome scores and suppressing systemic inflammation.

The primary finding of this study is that SMI-defined "deep remission" holds significant clinical value in predicting disease recurrence following biologic dose reduction. Although clinical scores such as DAS28 are widely used for assessing disease activity, their capacity to identify subclinical synovitis is limited. As a high-sensitivity Doppler ultrasonography technique, SMI enables the non-invasive and dynamic assessment of microvascular generation within the synovium, thereby reflecting the true state of local inflammation more accurately (Yabunaka *et al.*, 2021). The results of this study demonstrated that patients with a baseline SMI score of 0 had a significantly lower recurrence rate within 12 months compared to those with an SMI score>0 (15.79% vs. 38.10%), along with a longer recurrence-free survival (HR=0.355, *P*=0.004). This finding is consistent with the study (Molina Collada *et al.*, 2021), who also reported that ultrasound-defined remission status was independently associated with a lower risk of recurrence in RA patients assessed using PDUS. However, the superior capability of SMI in detecting low-velocity blood flow renders it more sensitive in identifying early or mild synovitis. This study further validates the predictive efficacy of SMI in a Chinese RA population, providing localized evidence to support its broader application in clinical practice. It should be noted that the retrospective nature of this study may introduce inherent selection bias and unmeasured confounding factors, which we have aimed to mitigate through stringent inclusion criteria and baseline balance testing. Nonetheless, these findings require prospective validation in randomized controlled trials.

Leveraging the established prognostic significance of SMI, we further investigated the adjunctive role of the Yiqi-Jianpi-Tongluo formula decoction during ADA tapering. In the overall cohort—and consistently across SMI-defined strata—add-on therapy with Yiqi-Jianpi-Tongluo formula significantly reduced the risk of recurrence (HR=0.368, *P*=0.004). Among patients who were in UR at baseline, the recurrence rate fell from 26.92 % in the Western-only group to 6.45 % in the combination group (HR=0.219, *P*=0.031). Beyond recurrence prevention, Yiqi-Jianpi-Tongluo formula conferred a clear advantage in sustaining deep remission: by study end 90.32 % of patients receiving the herbal formula retained an SMI score of 0, versus 69.23% of controls (P=0.045). CRP, IL-6 and RF also decreased to a significantly greater extent with add-on therapy, suggesting that the formula may act directly on joint pathology by suppressing synovial neo-angiogenesis and inflammatory-cell infiltration—effects compatible with the multi-target, multi-pathway modulation characteristic of Chinese herbal medicines. In TCM, the quiescent phase of RA is viewed as "root-deficiency with branch-excess": spleen-Qi deficiency forms the root, while collateral obstruction represents the branch. YJTL addresses both aspects: *Astragali Radix*, *Pseudostellariae Radix* and *Atractylodis Macrocephalae Rhizoma* replenish Qi and strengthen the spleen to consolidate the root, whereas *Spatholobi Caulis* and *Chuanxiong Rhizoma* invigorate blood and unblock collaterals to expel pathogenic factors. The combined action achieves supporting the righteous and dispelling evil, unblocking collaterals and stopping pain. Modern pharmacology offers supportive evidence. *Astragalus polysaccharides* enhance T/B/NK cell function, boost cellular immunity and down-regulate TNF-α and IL-6 (Qin *et al.*, 2025; Xu *et al.*, 2024); *Pseudostellaria polysaccharides* rebalance Th1/Th2 responses and increase NK activity (Li *et al.*, 2023); The water-soluble galactoglucomannan from Poria attenuates RA via modulation of JAK2/STAT3 and NF-κB signalling (Lei *et al.*, 2025); *Saposhnikovia divaricata* exerts anti-inflammatory effects through the AGE-RAGE, PI3K-Akt, TNF, MAPK and Toll-like pathways (Jing *et al.*, 2025); *Spatholobus* dilates peripheral vessels, improves micro-circulation and directly inhibits inflammatory cytokines (Pan *et al.*, 2023); *Ligustrazine*, an alkaloid from *Chuanxiong*, suppresses IL-6 and TNF-α in both macrophages and endothelial cells (Ye *et al.*, 2021). These mechanisms may complement TNF-α blockade, helping to preserve immune homeostasis during dose reduction.

Regarding potential herb-drug interactions, constituents of the YJTL formula have been studied for their immunomodulatory and metabolic effects. For instance, *Astragalus membranaceus* and *Glycyrrhiza uralensis* are known to modulate cytochrome P450 enzymes and P-glycoprotein, which could theoretically influence the metabolism of concurrent drugs (Jia *et al.*, 2025; Wang *et al.*, 2025). However, in the context of this study, no clinically significant pharmacokinetic interactions with MTX or ADA were observed. The immunomodulatory properties of herbs such as *Astragalus* and *Pseudostellaria heterophylla* may synergistically support immune regulation without antagonizing the effects of MTX or ADA. To ensure safety, all patients underwent regular monitoring of liver function, renal function and complete blood counts at baseline and every 3 months during the 12-month follow-up. No persistent abnormal liver or renal function tests attributable to the herbal formula were recorded. These findings suggest that the YJTL formula, at the dosage used, did not introduce additional hepatorenal toxicity or clinically relevant interactions with MTX/ADA in this cohort.

Table 1: Comparison of baseline data of patients

Variables	Chinese and Western medicine combination group (n=61)	Western medicine group (n=59)	Statistic	*P*
Gender, n (%)			χ^2=0.300	0.584
Male	29 (47.54%)	31 (52.54%)		
Female	32 (52.46%)	28 (47.46%)		
Age (years), Mean±SD	45.56±7.21	44.32±6.16	t=1.008	0.316
BMI (kg/m²), Mean±SD	23.45±2.18	22.79±2.35	t=1.599	0.113
Region, n (%)			χ^2=0.515	0.473
Urban area	35 (57.38%)	30 (50.85%)		
Rural area	26 (42.62%)	29 (49.15%)		
Marriage, n (%)			-	0.892
Married	47 (77.05%)	46 (77.97%)		
Unmarried	3 (4.92%)	4 (6.78%)		
Divorced/Widowed	11 (18.03%)	9 (15.25%)		
Disease duration (years), M (Q_1, Q_3)	6 (4, 7)	6 (5, 7)	Z=-0.872	0.383
Underlying diseases, n (%)				
Hypertension	6 (9.84%)	8 (13.56%)	χ^2=0.403	0.525
Hyperlipidemia	7 (11.48%)	9 (15.25%)	χ^2=0.371	0.543
Diabetes mellitus	9 (14.75%)	5 (8.47%)	χ^2=1.148	0.284
History of smoking, n (%)	20 (32.79%)	21 (35.59%)	χ^2=0.105	0.746
History of alcohol consumption, n (%)	19 (31.15%)	22 (37.29%)	χ^2=0.503	0.478
Prior Biologic DMARD Exposure, n (%)	0 (0%)	0 (0%)	-	-
Baseline DAS28-ESR components				
TJC (0-28), Mean±SD	1 (0, 1)	1 (0, 1)	Z=-0.515	0.607
SJC (0-28), Mean±SD	0 (0, 1)	0 (0, 1)	Z=-0.587	0.557
ESR (mm/h), Mean±SD	12.25±4.54	13.08±5.10	t=-0.953	0.343
GH (VAS 0-100 mm), Mean±SD	14.52±6.33	15.81±7.21	t=-1.042	0.300
Seropositivity, n (%)				
RF positive	52 (85.25)	50 (84.75)	χ^2=0.006	0.939
anti-CCP positive	48 (78.69)	46 (77.97)	χ^2=0.009	0.923
Van der Heijde-Sharp Score, M (Q_1, Q_3)	5 (3, 8)	6 (2, 8)	Z=-0.388	0.698
Prior steroid use (within 3 months), n (%)	0 (0%)	0 (0%)	-	-
MTX with folic acid co-prescription, n (%)	61 (100%)	59 (100%)	-	-

Note: BMI, body mass index; DAS28-ESR, disease activity score in 28 joints using erythrocyte sedimentation rate; TJC, tender joint count; SJC, swollen joint count; ESR, erythrocyte sedimentation rate; GH, global health; VAS, visual analog scale; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide; MTX, methotrexate.

Table 2: Comparison of recurrence-free survival rate between the NUR group and UR group

Group	NUR group (n=63)	UR group (n=57)
Recurrence, n (%)	24 (38.10%)	9 (15.79%)
No recurrence, n (%)	39 (61.90%)	48 (84.21%)
Mean (95% CI)	9.429 (8.554 to 10.303)	11.316 (10.854 to 11.778)
HR (95%CI)	2.819 (1.424 to 5.578)	0.355 (0.179 to 0.702)
Log-rank χ^2	8.509	
P	0.004	

Table 3: Comparison of recurrence-free survival rate between the Chinese and Western medicine combination group and Western medicine group

Group	Chinese and Western medicine combination group (n=61)	Western medicine group (n=59)
Recurrence, n (%)	10 (16.39%)	23 (38.98%)
No recurrence, n (%)	51 (83.61%)	36 (61.02%)
Mean (95% CI)	11.164 (10.651 to 11.676)	9.458 (8.557 to 10.358)
HR (95%CI)	0.368 (0.186 to 0.730)	2.716 (1.369 to 5.386)
Log-rank χ^2	8.353	
P	0.004	

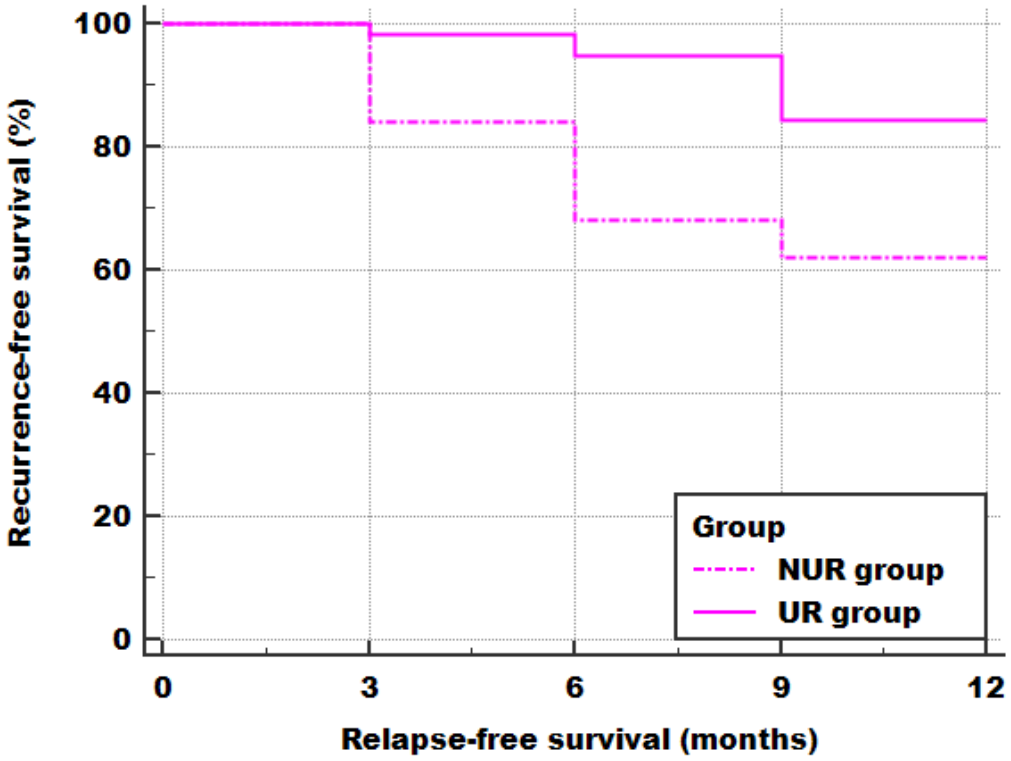

Fig. 2: Comparison of Recurrence-free survival rate between the NUR group and UR group

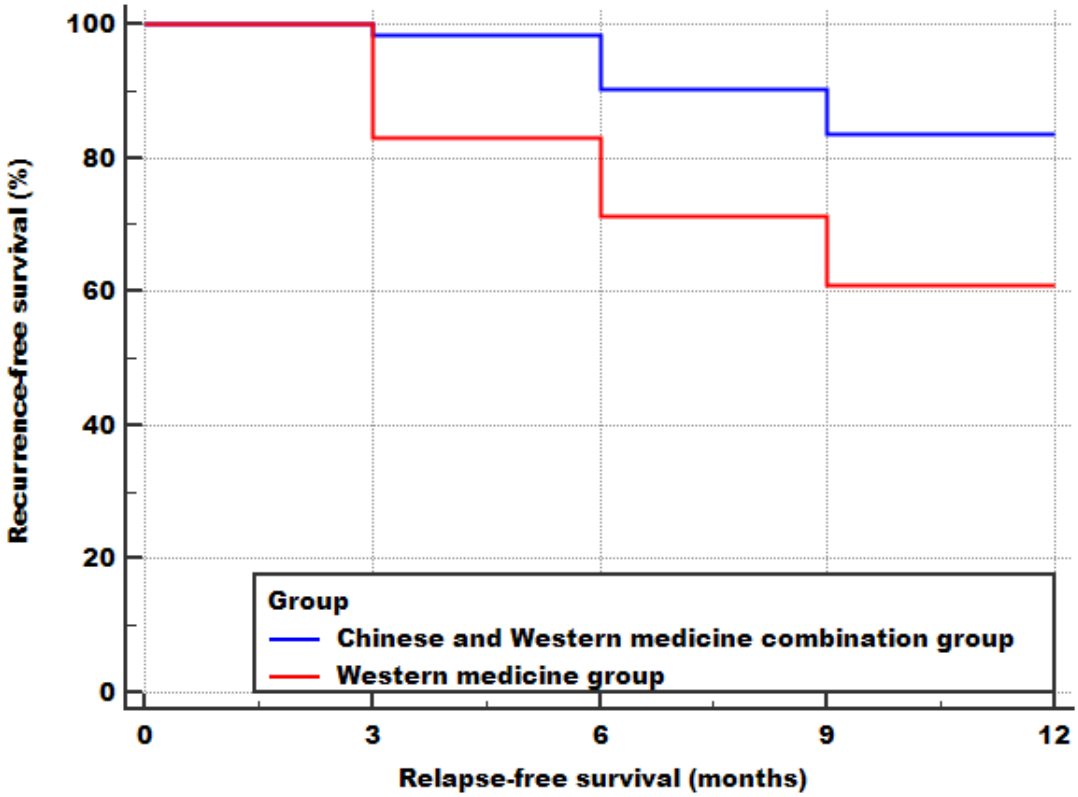

Fig. 3: Comparison of recurrence-free survival rate between the Chinese and Western medicine combination group and Western medicine group

Table 4: Comparison of recurrence-free survival rate between the UR-Chinese and Western medicine combination group and UR-Western medicine group

Group	UR-Chinese and Western medicine combination group (n=31)	UR-Western medicine group (n=26)
Recurrence, n(%)	2 (6.45%)	7 (26.92%)
No recurrence, n(%)	29 (93.55%)	19 (73.08%)
Mean (95% CI)	11.806 (11.547 to 12.066)	10.731 (9.816 to 11.645)
HR (95%CI)	0.219 (0.059 to 0.818)	4.568 (1.222 to 17.068)
Log-rank χ^2	4.647	
P	0.031	

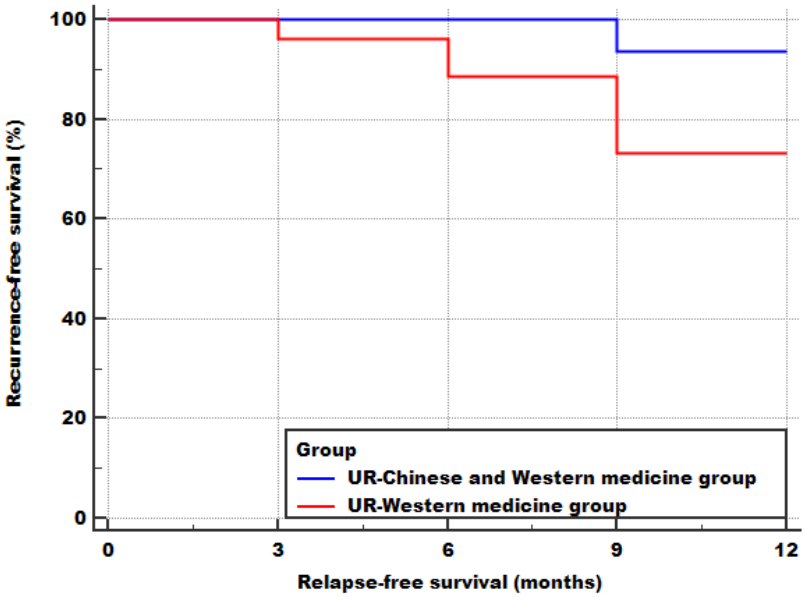

Fig. 4: Comparison of recurrence-free survival rate between the UR-Chinese and Western medicine combination group and UR-Western medicine group

Table 5: Comparison of recurrence-free survival rate between the NUR-Chinese and Western medicine combination group and NUR-Western medicine group

Group	NUR-Chinese and Western medicine combination group (n=30)	NUR-Western medicine group (n=33)
Recurrence, n(%)	8 (26.67%)	16 (48.48%)
No recurrence, n(%)	22 (73.33%)	17 (51.52%)
Mean (95% CI)	10.500 (9.550 to 11.450)	8.455 (7.110 to 9.799)
HR (95%CI)	0.463 (0.208 to 1.030	2.162 (0.971 to 4.815
Log-rank χ^2	3.913	
P	0.048	

Table 6: Comparison of maintenance rate of UR

Group	UR-Chinese and Western medicine combination group (n=31)	UR-Western medicine group (n=26)
SMI=0, n (%)	28 (90.32%)	18 (69.23%)
SMI>0, n (%)	3 (9.68%)	8 (30.77%)
χ^2	4.039	
P	0.045	

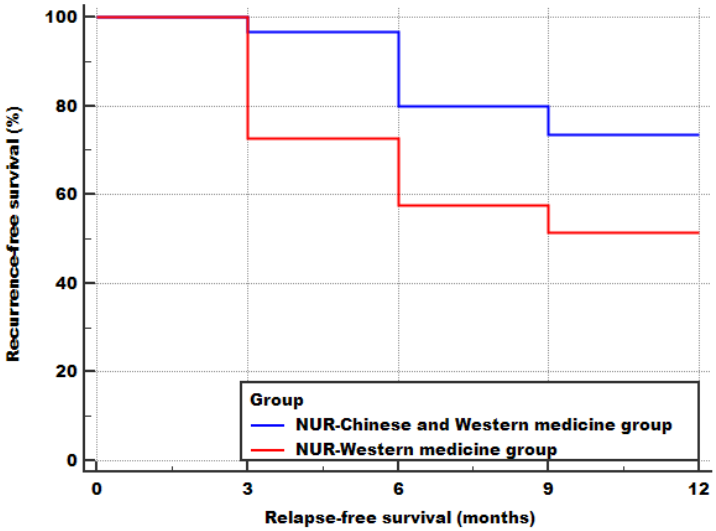

Table 5: Comparison of therapeutic effects on TCM syndromes

Group	Chinese and Western medicine combination group (n=61)		Western medicine group (n=59)
Ineffective rate, n (%)	12 (19.67%)		27 (45.76%)
Total effective rate, n (%)	49 (80.33%)		32 (54.24%)
χ^2		9.306	
P		0.002	

Table 8: Comparison of inflammatory indicators

CRP (mg/L)	Chinese and Western medicine combination group (n=61)	Western medicine group (n=59)	Between-group t	Between-group *P*
Pre-treatment	4.42±1.20	4.39±1.23	0.091	0.928
Post-12 months	2.54±0.77	3.36±0.98	5.135	<0.001
Within-group t	9.870	5.563		
Within-group *P*	<0.001	<0.001		
IL-6 (pg/mL)	Chinese and Western medicine combination group (n=61)	Western medicine group (n=59)	Between-group t	Between-group *P*
Pre-treatment	42.28±8.46	40.19±7.22	1.460	0.147
Post-12 months	21.22±5.65	28.47±6.12	6.755	<0.001
Within-group t	16.719	10.367		
Within-group *P*	<0.001	<0.001		
RF (IU/mL)	Chinese and Western medicine combination group (n=61)	Western medicine group (n=59)	Between-group t	Between-group *P*
Pre-treatment	112.44±30.64	117.66±28.68	0.963	0.338
Post-12 months	79.69±19.43	90.44±24.76	2.651	0.009
Within-group t	7.512	5.661		
Within-group *P*	<0.001	<0.001		

Table 9: Safety comparison

Adverse reactions	Chinese and Western medicine combination group (n=61)		Western medicine group (n=59)
Injection site reaction	3 (4.92%)		3 (5.08%)
Upper respiratory tract infection	2 (3.28%)		1 (1.69%)
Headache	0 (0.00%)		1 (1.69%)
Abdominal pain	0 (0.00%)		1 (1.69%)
Nausea	1 (1.64%)		1 (1.69%)
χ^2		0.128	
P		0.721	

Safety profiles did not differ between groups: all adverse events were mild or moderate and no serious reactions occurred. Notably, combined therapy did not raise infection risk; respiratory tract infections were numerically less frequent (1.69% vs 3.28%). This observation may be associated with the immunomodulatory effects of the Yiqi-Jianpi-Tongluo formula. Furthermore, the incidence of gastrointestinal reactions was also lower in the Chinese medicine group, suggesting potential benefits of the Yiqi-Jianpi-Tongluo formula in improving spleen and stomach function. These results further support the safety and feasibility of this combination regimen in clinical practice.

The findings of this study provide localized evidence for the clinical management of RA in China. Furthermore, it innovatively integrates SMI with TCM, proposing a tapering strategy of "SMI-guided reduction combined with the Yiqi-Jianpi-Tongluo formula." This approach surpasses the limitations of conventional strategies, such as fixed-dose tapering or tapering based solely on clinical indicators, by offering greater precision. Additionally, the relatively low cost of the Chinese herbal formula can significantly reduce the overall treatment burden for patients, making it particularly suitable for RA patients in China with limited financial resources and potentially improving long-term treatment adherence.

Study limitations

This study was a retrospective controlled trial. Although stringent inclusion/exclusion criteria and tests for baseline characteristic balance were applied to minimize bias, selection bias cannot be entirely ruled out. Future prospective randomized controlled trials (RCTs) are necessary to further validate the reliability of these conclusions. Regarding sample size, while the total sample of 120 patients met statistical power requirements, the subgroup sizes were relatively small, which may affect the stability of the findings. Moreover, the follow-up period was limited to 12 months, preventing assessment of long-term efficacy and safety. Additionally, this study focused primarily on clinical outcomes and did not delve into the mechanism of action of the Chinese herbal formula or conduct analysis of its active components, which limits its utility for subsequent drug development. Future research should involve multicenter, large-sample prospective RCTs that enroll RA patients in remission from multiple hospitals across China, extend the follow-up duration and specifically evaluate long-term recurrence rates, joint structural protection and safety to generate high-level evidence for guideline development. Furthermore, *in-vitro* and *in-vivo* studies utilizing network pharmacology approaches should be conducted to investigate the effects of the Yiqi-Jianpi-Tongluo formula and its active components on inflammatory cytokine release, immune cell function and relevant signaling pathways. This study did not employ a placebo control in the Western medicine group, which may introduce expectation or placebo effects, particularly in patient-reported outcomes such as TCM syndrome scores. However, the primary endpoint (ultrasound remission) and objective inflammatory markers are less susceptible to such bias. Adherence was monitored via sachet returns and patient diaries, though self-reporting may still overestimate compliance. Future prospective randomized controlled trials should incorporate placebo-controlled designs and more objective adherence measures to minimize these potential biases.

CONCLUSION

In summary, this study conducted in a Chinese RA population confirms that SMI-defined deep remission can serve as an effective basis for guiding ADA tapering. The combination of the Yiqi-Jianpi-Tongluo formula with ADA dose reduction significantly reduced the risk of disease recurrence, improved the maintenance rate of UR, ameliorated TCM syndrome scores and inflammatory markers, without increasing safety risks, thereby providing an important adjunctive strategy for biologic tapering.

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None.

Authors' contributions

Yu Li, Yaqin Zhu: Conceived and designed the research and analyzed data. Drafted and revised the manuscript critically for important intellectual content; Xubin Qi, Rui Shen, Haizhong Zhang: Contributed to the acquisition, analysis and interpretation of data. Provided substantial intellectual input during the drafting and revision of the manuscript; Yu Li: Participated in the conception and design of the study. Played a key role in data interpretation and manuscript preparation. All authors have read and approved the final version of the manuscript.

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Data availability statement

The data supporting the findings of this study can be obtained from the corresponding author upon request.

Ethical approval

All data collection and retrospective analysis procedures complied with "ethical review measures for biomedical research involving humans" and the principles of the Declaration of Helsinki (Wen *et al.*, 2025). The study protocol was approved by the Institutional Ethics Committee of Haining People's Hospital (approval number: 2022-81). Given the retrospective nature of the study, which involved only anonymized medical record review without direct patient contact or intervention, the requirement for individual informed consent for this study was waived by the Ethics Committee. All identifiable

personal information in this study was de-identified to ensure data confidentiality.

Conflict of interest

The authors affirm that they do not have any financial conflict of interest.

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