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ORIGINAL RESEARCH

# Jin-Gu-Lian Capsule Did Not Significantly Improve Clinical Value in Rheumatoid Arthritis Therapy: A Real-World Study

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**Purpose:** To investigate the clinical value of adding Jin-gu-lian (JGL) capsules into rheumatoid arthritis (RA) treatment by examining its impact on disease activity and quality of life (QoL) through a real-world study (RWS).

**Patients and methods:** RWS was conducted to compare the inflammatory markers, including IgM-RF, ESR, and CRP, between RA patients treated with only Western medicine (reference group) and Western medicine plus JGL (study group) during one-year follow-up. The clinical data was acquired from the hospital information system (HIS). Telephone call-based follow-up on QoL (SF-36) and accompanying symptoms, including gastrointestinal complaints, attacks of pneumonia, herpes zoster, URTIs, UTIs, and LTBIs. Finally, the anti-rheumatic drugs given to both groups were also compared. RWS was further validated for its feasibility by performing studies with hydroxychloroquine (HCQ) treatment, which is a commonly used anti-rheumatic drug for RA with mild effect.

**Results:** The study group failed to show a significant effect on inflammatory markers, especially on the CRP levels, indicating no additional clinical value of supplementing with JGL. Similarly, at the endpoint, no significant differences between the two groups on QoL and related symptoms were observed. Our study suggests that the patients in the study group might need more anti-rheumatic drugs to fill the treatment insufficiency, and the application ratio of NSAIDs would be significantly higher than the reference group. By conducting this study on HCQ treatment, the positive aspects of controlling disease activity and reducing NSAIDs application were found, which demonstrates the utility of performing the RWS to evaluate the effect of JGL.

**Conclusion:** Adding JGL did not significantly improve the clinical efficacy of RA treatment by this RWS. Folk herbal prescriptions such as JGL are suggested to underwent strict clinical trials before application.

**Keywords:** real-world study, rheumatoid arthritis, traditional Chinese medicine, disease activity, hydroxychloroquine

## Introduction

Rheumatoid arthritis (RA) is one of the most common chronic autoimmune diseases affecting bone and cartilage by not only causing deformation but also accompanied with wide spread systemic complications such as anemia, interstitial lung disease, arteriosclerosis, etc.[1] Traditional Chinese medicine or herbal medicine has been reported to be one of the possible complementary methods in the management of RA.[2,3] However, most of the in vitro and animal experiments conducted were focused on basic research, and the clinical observations were not sufficiently conducted.

Different from the other reported compatibility of herbal medicines, single Chinese medicine or its active components that under exploring in RA treatment, the Jin-gu-lian (JGL) capsule is included in the Compilation of National Standard for Traditional Chinese Medicines (2002 edition)[4] and has been approved as the counter (OTC) medicine, covered by governmental health insurance for decades in China. Publications show its potential therapeutic mechanisms in RA

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through network pharmacology and animal experiment approaches.[4] A few clinical studies were reported,[5] but the use of JGL by classic folk prescriptions has not undergone a strict clinical trial.

Recently, we have performed a retrospective study to analyze the clinical effectiveness of JGL in RA patients through a real-world study (RWS). Patients' diseases activity indicated by rheumatoid factor (IgM-RF) levels, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) in their last year of treatment were collected, and quality of life (QoL) was assessed by following up based on 36-Item Short-Form Health Survey (SF-36). Besides, anti-rheumatic drugs applied and incidence of gastrointestinal (GI) symptoms and infections between the reference and the study groups were also compared. It was hypothesized that adding JGL to regular western medical treatment might benefit RA patients with better results in controlling disease activity or improving QoL.

# Methods

## Patient Selection

We selected patients based on the information recorded in the hospital information system (HIS). Patients who visited the rheumatology and immunology outpatient department of Zunyi Medical University from Aug. 2021 to Aug. 2022, diagnosed with RA based on ACR/EULAR 2010 classification criteria were recruited.[6] Patients with visits less than three times in the one-year study period were excluded. This retrospective trial was approved by the Ethics Committee of the Affiliated Hospital of Zunyi Medical University (KLL-2023-545). All procedures performed in the studies were in accordance with the ethical standards of the institutional and national research committee and followed the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Patients gave their informed consent to participate in this study protocol.

## Experimental Groups

In total, 1032 RA patients, who gave oral consent to participate in this investigation, were selected, including 483 cases receiving only Western medicine (reference group), and 549 cases receiving JGL and Western medicine (study group). Furthermore, hydroxychloroquine (HCQ), a mild conventionally synthesized disease-modifying anti-rheumatic drugs (csDMARDs) for RA treatment,[7] was chosen to repeat the study as a methodological justification to validate whether this RWS protocol was applicable or not.

## Collection of Disease Activity Parameters

Laboratory test results (IgM-RF levels, ESR, and CRP) recorded in HIS were used to evaluate disease activity.[8] Successive patient data were recorded with baseline, within three months (m), 3–6 m, 6–9 m, and 9–12 m. If a patient visited more than once during one of these defined periods, a lower value would be put into our data for analysis.

## Telephone Call Based Following Up on QoL

QoL of all RA patients recruited was assessed using the 36-Item Short-Form Health Survey (SF-36).[9] SF-36 survey was followed up by telephone calls to inquire about the current health conditions of patients. Besides, the attacks of pneumonia, herpes zoster, upper respiratory tract infections (URTIs), urinary tract infections (UTIs), and gastrointestinal (GI) symptoms in their last year of treatment were also inquired (Supplementary Data S1). Oral consent to participate in the interview was provided by the investigated patients. All the patients underwent chest high-resolution computed tomography (HRCT), and the complications of pulmonary tuberculosis (latent or active) were recorded from HIS.

## Drugs Used for Treatment

It is difficult to accurately figure out the drugs received, courses, and dosages of each drug given to patients. This is mainly because patients cannot recall clearly, while HIS does not include patients' information about visiting other hospitals. So the investigators recorded all the anti-rheumatic drugs prescribed in one whole year for every patient, including glucocorticoids (GCs), nonsteroidal anti-inflammatory drugs (NSAIDs), conventionally synthesized disease-modifying antirheumatic drugs (csDMARDs), JAK inhibitors (JAKi), TNF inhibitors (TNFi) and Jin-gu-lian Capsules (JGL).

## Statistical Analysis

Statistical analysis was performed using the GraphPad Prism 9 software. The measurement data of the normal distribution were expressed as mean ± SD, and an independent sample *t*-test was used to compare the two groups. Measurement data of non-normal distribution were expressed as mean (Q2, Q4) in tables and mean with 95% CI in figures, and the Mann–Whitney *U*-test was used to compare two groups. The missing data were deleted because they constituted a small proportion. The counting data were analyzed by using a chi-square (or Fisher's exact) test based on the sample numbers. Significance was set at $p < 0.05$.

# Results

## Demographic Features and Baseline Disease Activity Levels

The gender distribution and disease course in the reference and study groups had no significant differences. However, the patients in the study group were 2.08 years older than the reference group ($p < 0.001$). The titer of IgM-RF in the study group was higher than the reference group ($p < 0.05$), the ESR and CRP levels were without any significant differences (Table 1). Besides as a diagnostic marker, RF titer is also associated with disease activity in RA.[10] The baseline differences of RF titer may potentially implicate effectiveness assessment of JGL. Thus, stratification analysis of the two groups was conducted, and it turned out patients with RF titer above 300 IU/mL in the Study group were significantly higher than that of Reference group (Supplementary Table 1 and Supplementary Figure 1 in Supplementary Data S2). Cases with RF titer between 300 and 900 IU/mL (n=7) and above 900 IU/mL (n=21) were randomly chosen for rejection. The adjusted cases in the two groups showed no additional statistical differences in RF titer (Supplementary Figure 2 in Supplementary Data S2). The following research on effectiveness indicated by RF titer were addressed by adjusted cases.

## Subjective Feedbacks from the Patients

Based on the questionnaires (Supplementary Data S1), the question "Are you following the doctor's advice?" could be considered as patients' compliance with the treatment. Surprisingly, compliance in the reference group was better than the study group ($p < 0.05$, Figure 1A). However, for the data set with adjusted RF levels, the patients showed no significant differences on compliance between the two groups (Figure 1B). The subjective feedback from the patients on overall satisfaction level to treatment and recovery level was similar between the two groups (Figure 1C and D).

## IgM-RF Levels

The IgM-RF levels, which were proposed as a disease activity index in the reference and study groups (with cases adjusted for baseline consistency), were significantly decreased during the one-year treatment, but during follow-up, no significant differences were observed (Figure 2A). A total of 86 (reference) and 134 (study) cases were used to analyze the RF levels in the follow-up period (Figure 2B). At the baseline, RF levels in the study group were higher than those in the reference group. However, there was no evidence to show better or worse performance of the study group compared to the reference group (Figure 2C).

**Table 1** Baseline Features of the Reference and Study Groups

| Comparison items | Reference group (n) | Study group (n) | Statistic | P value |
|---|---|---|---|---|
| Gender (male: female) | 86: 397 | 119: 430 | NA | 0.137 |
| **Age (y/o)** | **52.10 ± 11.91** (483) | **54.18 ± 10.35** (549) | **t = 0.301** | **0.001** |
| Disease course (years) | 7.92 (2, 10) (483) | 6.35 (2, 10) (549) | U = 128,708 | 0.223 |
| **IgM-RF (IU/mL)** | **334.1 (52, 377)** (323) | **456 (60, 500)** (397) | **U = 58,182** | **0.016** |
| ESR (mm/h) | 49.50 ± 33.68 (379) | 50.18 ± 31.68 (451) | t = 0.296 | 0.383 |
| CRP (mg/L) | 24.26 ± 38.91 (223) | 24.94 ± 38.08 (434) | t = 0.248 | 0.402 |

**Notes**: The rows with bold characters were with statistical significance.
**Abbreviations**: NA, not applicable; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein.

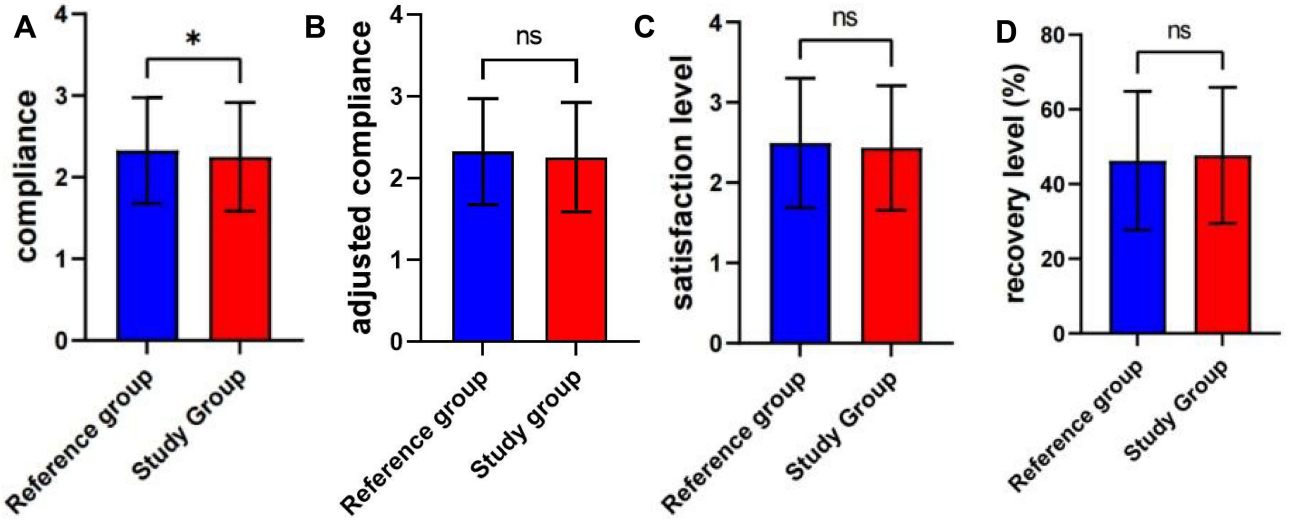


**Figure 1** Subjective feedback from the patients. (**A** and **B**) Patients' compliance in the reference group (n = 483) was higher than the study group (n = 549), but the difference gone with adjusted cases in the study group (n=521). (**C** and **D**) The satisfaction level and the recovery level were similar between the two groups.
**Note**: *P < 0.05;
**Abbreviation**: ns, no significance.

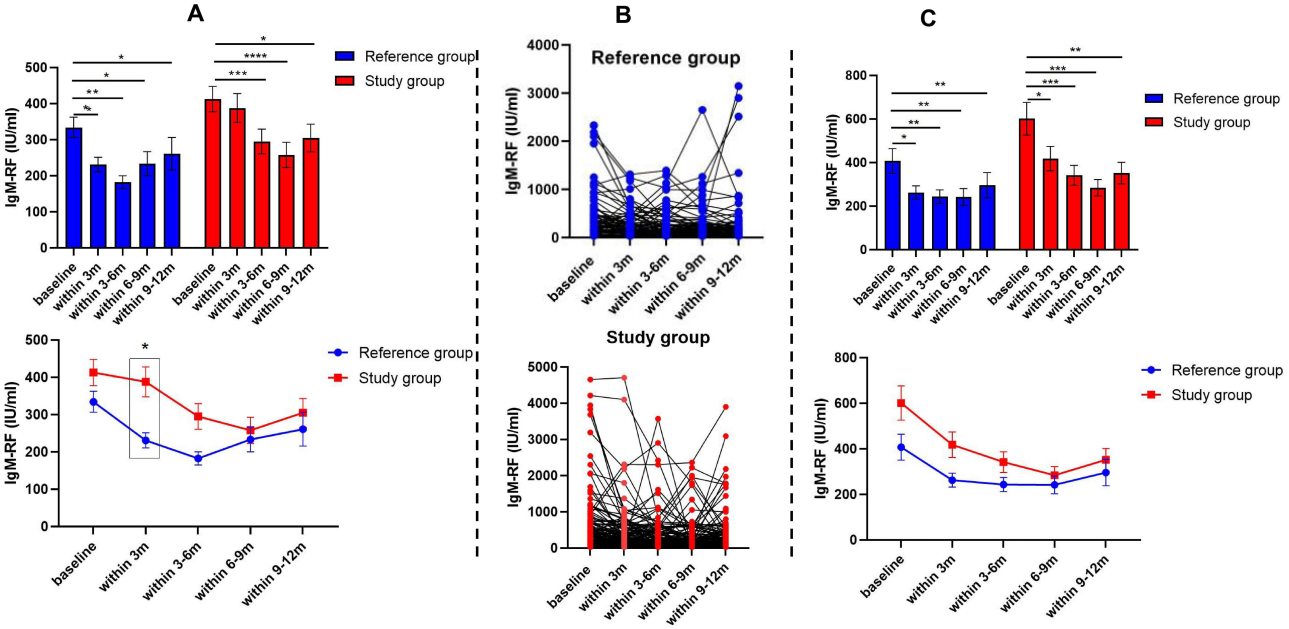


**Figure 2** The IgM-RF levels of the reference and the study groups (with cases adjusted for baseline consistency) in the one-year follow-up. (**A**) Data of all patients showed a significant decrease of IgM-RF levels in each group; (**B** and **C**) Patients with RF results of all five consecutive time nodes in each group (n = 86 in the reference group, and n = 134 in the study group).
**Notes**: *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001.
**Abbreviation**: IgM-RF, Rheumatoid factor.

## ESR Levels

ESR is most commonly applied as inflammatory level index and is also used in evaluating the effectiveness of treatment for RA.[11] Similar to the IgM-RF levels in the reference and the study groups, ESR levels were significantly decreased during one-year treatment in both the groups. However, the reference group showed lower levels of ESR from 3 to 12 m (Figure 3A). A total of 113 (reference) and 153 (study) cases with ESR results of all five consecutive time nodes were used (Figure 3B), but no significant differences between the groups at the five time nodes were found during the one-year follow-up (Figure 3C).

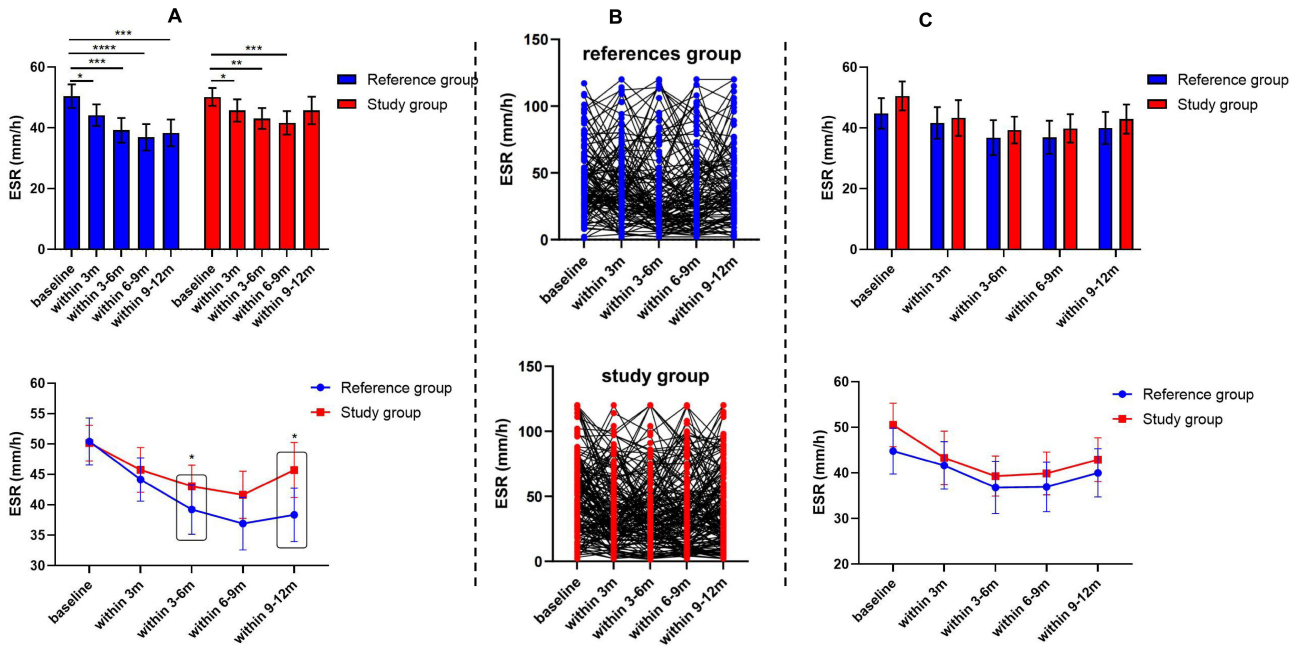


**Figure 3** The ESR levels of the reference and the study groups in the one-year follow-up. (**A**) Both the reference and the study groups showed a significant decrease in ESR levels within one year following up, and at time points of 3–6 m and 9–12 m, the ESR levels in the reference group were lower than the study groups; (**B** and **C**) For the patients with ESR results of all five consecutive time nodes in each group showed no significant differences (n = 113 in the reference group, and n = 153 in the study group).
**Notes**: *P < 0.05; **P < 0.01; ***p < 0.001; ****P < 0.0001.
**Abbreviation**: ESR, Erythrocyte sedimentation rate.

## CRP Levels

As an acute-phase plasma protein and a component of the acute-phase response, CRP is routinely assessed as a marker of systemic inflammation in RA.[12,13] Similar to the ESR levels in the reference and the study groups, CRP levels were all significantly decreased during the one-year treatment, and the reference group showed lower levels of ESR in 3–6m (Figure 4A). A total of 93 (reference) and 143 (study) cases with CRP results of all five consecutive time nodes were used (Figure 4B). Although the reference group had lower CRP levels within one-year follow-up, it is challenging to conclude which group was better controlled than the other because of differences in the baseline CRP levels (Figure 4C).

## Comparison of QoL

SF-36 is one of global measures of health-related QoL.[14] Patients in the study group showed better outcomes in body pain, mental health, vitality, and social functioning, while comparing the QoL with SF-36. The overall scores between the reference and study groups were without any significant differences (Table 2).

## Incidence of GI Symptoms, Infections

The complications of GI symptoms and attacks of pneumonia, herpes zoster, URTIs, UTIs, and LTBIs were without any significant differences between the reference and the study groups (Table 3).

## Application of Anti-Rheumatic Drugs

The available anti-rheumatic medicines for RA patients in this institution were GCs, NSAIDs, csDMARDs, JAKi, and TNFi. The most often used csDMARDs for RA patients include methotrexate (MTX), leflunomide (LEF), hydroxychloroquine (HCQ), salazosulfapyridine (SASP), iguratimod (IGU), and glucosidorum tripterygll totorum (GTW). The application of types of anti-rheumatic drugs in the reference group was 3.44 (2, 4) per patient in the last year, which was significantly less than the study group value: 3.77 (3, 5) (excluding JGL) (Figure 5A). The most frequently used drug was MTX, followed by LEF and NSAIDs. The application of NSAIDs, LEF, and JAKi were significantly higher in the study

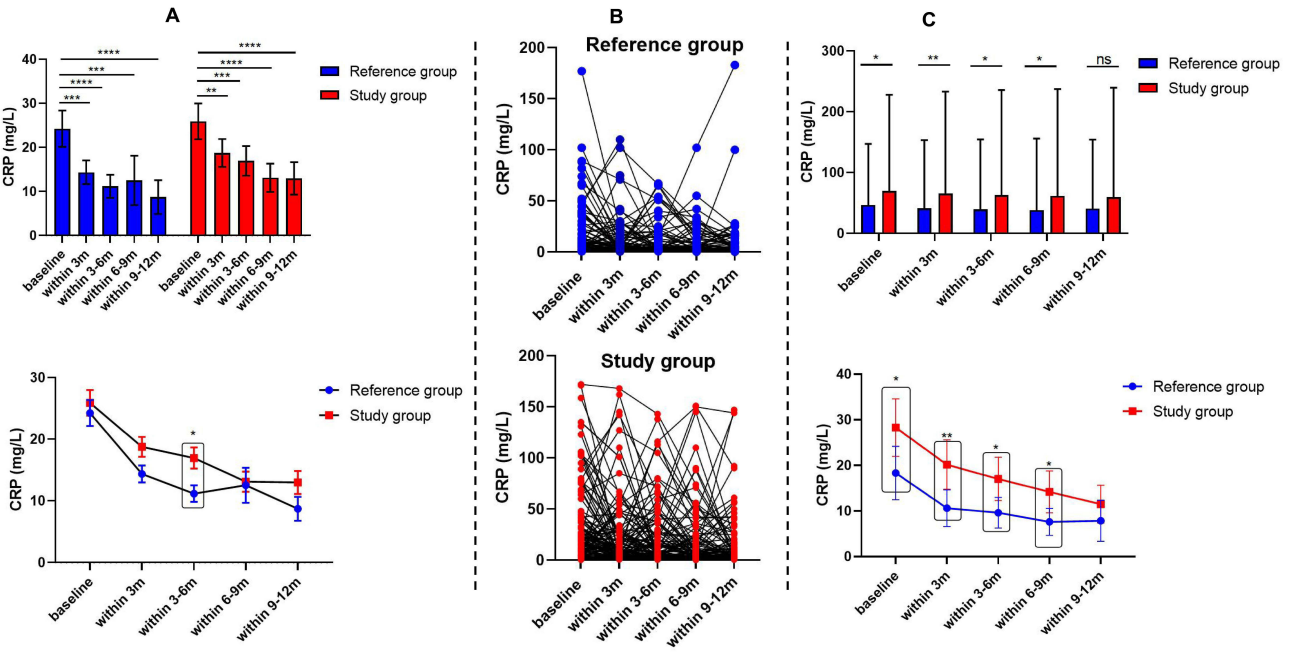


**Figure 4** The reference and the study groups' CRP levels in the one-year follow-up. (**A**) Both the reference and the study groups showed a significant decrease in ESR levels within one year following up, and at time points of 3–6m, the CRP levels in the reference group were lower than the study groups (**B** and **C**) For the patients with CRP results of all five consecutive time nodes in each group showed the study group always higher than the reference group (n = 93 in the reference group, and n = 143 in the study group).
**Notes**: *P < 0.05; **P<0.01; ***P < 0.001; ****P<0.0001.
**Abbreviation**: CRP, C-reactive protein.

group, and GC use was slightly higher but without any statistical significance (Figure 5B and Table 4). The application of csDMARDs had no significant difference between the two groups (Figure 5C).

## Validation of the Research methods

The csDMARD of HCQ was chosen to repeat the above study to validate whether this real-world study protocol was applicable or not. The RA patients were divided into two groups: without HCQ (n = 718) and with HCQ (n = 360) based on whether they received HCQ in their therapeutic regimen during one-year treatment.

The IgM-RF levels in the HCQ-treated patients were significantly higher than the patients without HCQ treatment at most of the time and showed a pair of parallel lines in the graph (Figure 6A). Although, at baseline, the ESR levels in

**Table 2** Comparison of SF-36 Between the Reference and the Study Groups

| Comparison items | Reference Group (n=481) | Study Group (n=547) | Statistic | P value |
|---|---|---|---|---|
| reported health transition | 70 ± 21.71 | 71.99 ± 20.36 | t = 1.52 | 0.065 |
| physical functioning | 70.80 (55, 90) | 69.86 (55, 90) | U = 130,309 | 0.396 |
| role-physical | 44.98 ± 41.93 | 46.44 ± 41.28 | t = 0.560 | 0.288 |
| role-emotional | 68.73 (66.7, 100) | 73.16 (66.7, 100) | U = 125,194 | 0.081 |
| **bodily pain** | **62.34 ± 15.45** | **64.19 ± 14.63** | **t = 1.98** | **0.024** |
| **mental health** | **75.00 (72, 80)** | **75.03 (72, 80)** | **t = 120,359** | **0.005** |
| **vitality** | **70.94 ± 11.34** | **72.47 ± 10.46** | **t = 2.24** | **0.013** |
| **social functioning** | **79.95 ± 17.76** | **81.9 ± 17.17** | **t = 1.78** | **0.038** |
| general health | 48.63 (35, 65) | 49.73 (35, 65) | U = 128,894 | 0.268 |
| SF-36 (overall score) | 109.3 (99.2, 118.8) | 111.2 (100.2, 119.4) | U = 124,513 | 0.126 |

**Notes**: The rows with bold characters were statistically significant.
**Abbreviation**: SF-36, 36-Item Short Form Health Survey.

**Table 3** Incidence of GI Symptoms and Infections Between the Reference and the Study Groups

| Grouping | GI symptomes | No GI symptome | Chi-square (and Fisher's exact) test |
|---|---|---|---|
| Reference group | 173 (35.82%) | 310 (64.18%) | RR = 0.96, 95% CI: (0.82, 1.13), P = 0.651 |
| Study group | 205 (37.34%) | 344 (62.66%) | |
| | LTBI | No LTBI | |
| Reference group | 21 (4.35%) | 462 (95.65%) | RR = 1.34, 95% CI: (0.63, 2.04), P = 0.394 |
| Study group | 21 (3.83%) | 528 (96.17%) | |
| | Pneumonia | No pneumonia | |
| Reference group | 91 (18.84%) | 392 (81.16%) | RR = 1.03, 95% CI: (0.80, 1.34), P = 0.810 |
| Study group | 100 (18.21%) | 449 (81.79%) | |
| | Frequent URTIs | No frequent URTIs | |
| Reference group | 124 (25.67%) | 359 (74.33%) | RR = 1.17, 95% CI: (0.94, 1.45), P = 0.187 |
| Study group | 121 (22.04%) | 428 (77.96%) | |
| | Herpes zoster | No herpes zoster | |
| Reference group | 38 (7.87%) | 445 (92.13%) | RR = 0.98, 95% CI: (0.65, 1.48), P = 0.999 |
| Study group | 44 (8.01%) | 505 (91.99%) | |
| | UTIs | No UTI | |
| Reference group | 8 (1.66%) | 475 (98.34%) | RR = 0.53, 95% CI: (0.24, 1.20), P = 0.158 |
| Study group | 17 (3.10%) | 532 (96.90%) | |

**Abbreviations**: GI, gastrointestinal; LTBI, latent tuberculosis infection; URTIs, upper respiratory tract infections; UTIs, urinary tract infections.

HCQ-treated patients were significantly higher than the HCQ untreated patients, but it went gradually to similar levels after 6m of treatment (Figure 6B). The CRP levels in patients with HCQ treatment were decreasing faster (Figure 6C). RA patients treated with HCQ received other anti-rheumatic drugs similar to HCQ untreated patients, but with a significantly lower application ratio of NSAIDs (Figure 6D and Table 5).

## Discussion

Besides investigating the protective effect on RA by inhibiting inflammation via the IL-17/NF-κB pathway, JGL also showed the impact against neurotoxicity via modulating oxidative stress, preventing abnormality of neurotransmitters,

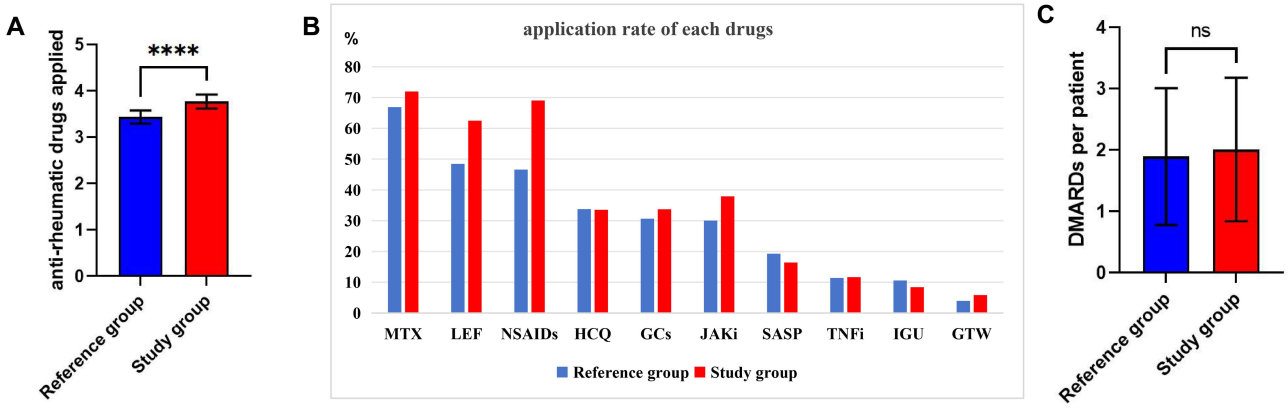


**Figure 5** The anti-rheumatic drugs applied in the reference and the study groups. (**A**) The kinds of anti-rheumatic medications applied in the patients of the study group (n = 483) were significantly more than the reference group (n = 549) patients; (**B**) The application rates of the anti-rheumatic drugs used in the reference and the study groups; (**C**) No significant differences of csDMARDs per patient between the reference and the study groups.

**Notes**: ****P < 0.0001;

**Abbreviations**: ns, no significant, MTX, methotrexate; LEF, Leflunomide; NSAID, non-steroidal anti-inflammatory drug; HCQ, hydroxychloroquine; GC, glucocorticoid; JAKi, JAK inhibitors; SASP, Salazosulfapyridine; TNFi: TNF inhibitors; IGU, iguratimod; GTW, glucosidorum tripterygll totorum.

**Table 4** The Difference Between Anti-Rheumatic Drugs Applied in the Reference and the Study Groups

| Grouping | GCs | Without GC | Chi-Square (and Fisher's exact) test |
|---|---|---|---|
| Reference group<br>Study group | 148 (30.64%)<br>185 (33.70%) | 335 (69.36%)<br>364 (66.30%) | RR = 0.91, 95% CI: (0.76, 1.09),<br>P = 0.317 |
| **NSAIDs**<br>Reference group<br>Study group | **225 (46.58%)**<br>**379 (69.03%)** | **without NSAID**<br>**258 (53.42%)**<br>**170 (30.97%)** | **RR = 0.64, 95% CI: (0.60, 0.75),**<br>**P <0.0001** |
| **JAKi**<br>Reference group<br>Study group | **145 (30.02%)**<br>**208 (37.89%)** | **without JAKi**<br>**338 (69.98%)**<br>**341 (62.11%)** | **RR = 0.79, 95% CI: (0.67, 0.94),**<br>**P = 0.009** |
| TNFi<br>Reference group<br>Study group | 55 (11.39%)<br>64 (11.66%) | without TNFi<br>428 (88.61%)<br>485 (88.34%) | RR = 0.97, 95% CI: (0.69, 1.37),<br>P =0.922 |
| **LEF**<br>Reference group<br>Reference group | **234 (40.55%)**<br>**343 (59.45%)** | **without LEF**<br>**249 (54.73%)**<br>**206 (45.27%)** | **RR = 0.97, 95% CI: (0.69, 1.37),**<br>**P <0.0001** |

**Notes**: The rows with bold characters were statistically significant.
**Abbreviations**: GC, Glucocorticoid; NSAID, Nonsteroidal anti-inflammatory drug; JAKi, JAK inhibitors; TNFi, TNF inhibitors; LEF, Leflunomide.

and modulating pharmacokinetics such as reducing the expression of cytochrome P450 enzymes.[15] As an OTC-approved drug, the functions of JGL are to treat conditions like limited movement, joint swelling, and pain by expelling wind, and eliminating dampness (wind and dampness are pathogenic factors in traditional Chinese medicine theory[16,17]), reducing swelling, and relieving pain. However, its clinical effect has not been strictly verified. In China, Phase III clinical studies may not be needed to confirm the efficacy of a classic folk prescription such as JGL. These recipes are usually the result of a long period of clinical practice and experience, and are believed to be effective in treating specific symptoms or diseases in some cases. However, conducting Phase III clinical studies is a standard practice to verify the safety and effectiveness of a drug or treatment.[18] Therefore, even if some folk classic recipes are widely used in practice, more rigorous scientific studies may be needed to confirm their efficacy and safety.

In this RWS, it was hypothesized that adding JGL to regular Western medical treatment might benefit RA patients with better results in controlling the disease activity or improving QoL. However, the results were not satisfactory. At baseline, the patients in the reference and study groups had a difference in age and IgM-RF levels, the level of inflammation markers ESR and CRP showed no significant differences. In this RWS, the data reflected a general phenomenon that Traditional Chinese Medicine (TCM) tends to be more popular among older generations compared to younger people.[19] However, age is considered to be one of the factors that affects disease activity and treatment outcome.[20] Thus, the rejection part of the cases in the study group based on the results of stratification analysis was applied and generated baseline consistency of RF levels. Within one year of treatment, the patients taking Western medicine plus JGL (study group) showed higher levels of ESR and CRP in 3–6m, indicates the addition of JGL might not be beneficial for controlling the disease development.

The study group showed lower levels of compliance level than the reference group. The cause and effect of the compliance and treatment outcome are unclear. It is assumed that non-adherence to treatment would be detrimental in the majority of rheumatic patients.[21] But inferior effectiveness may also lead to poor compliance. Interestingly, by adjusting cases with IgM-RF consistency, the compliance showed no further difference between the two groups. This confirmed that patients' compliance was associated with treatment effectiveness.

Adding JGL to the treatment was hypothesized to reduce the application of GCs or immunosuppressors, and contribute to the patient's management. However, as we recorded every patient's treatment drugs in one year, we

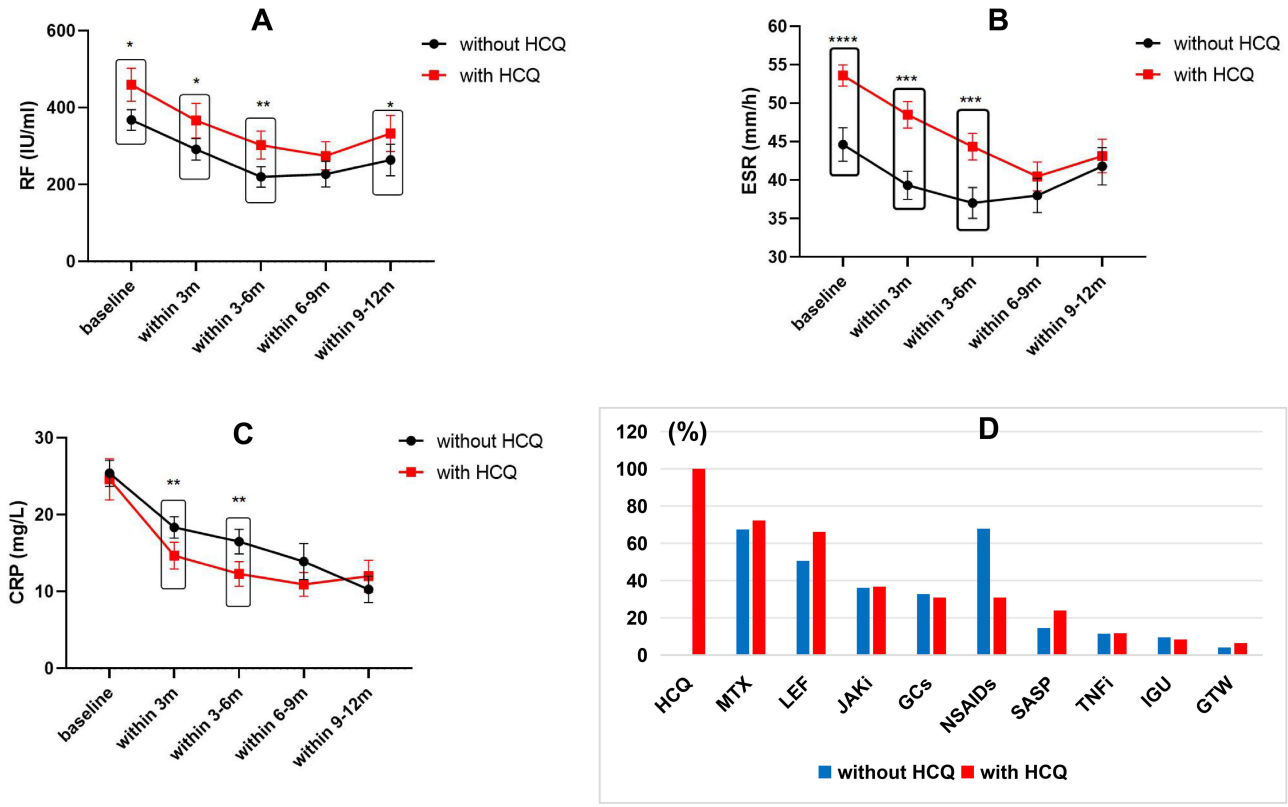


**Figure 6** Validation of the research protocol by investing HCQ. (**A-C**) RA patients treated with HCQ (n = 568) in their regimens seem better at decreasing inflammatory markers of ESR and CRP than those without (n = 296); (**D**) The anti-rheumatic drugs applied in the patients with HCQ group and the without.
**Notes**: *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001.
**Abbreviations**: MTX, methotrexate; LEF, Leflunomide; NSAID, non-steroidal anti-inflammatory drug; HCQ, hydroxychloroquine; GC, glucocorticoid; JAKi, JAK inhibitors; SASP, Salazosulfapyridine; TNFi: TNF inhibitors; IGU, iguratimod; GTW, glucosidorum tripterygll totorum.

found a need for more anti-rheumatic drugs and NSAIDs for the patients in the study group. In addition, they need to switch between different drugs due to the uncontrolled pain suggesting the drug survival rate in the study group might be lower than the reference group. The drug survival rate is a crucial metric for evaluating its long-term treatment effects. A higher drug survival rate is considered beneficial during long-term disease management, effectively controlling the activity of the disease and maintaining a steady remission of the condition.[22]

However, due to a lack of baseline data, the results were not promising because adding JGL did not decrease complications such as GI symptoms and attacks of pneumonia, herpes zoster, URTIs, UTIs, and LTBIs. For QoL, the JGL-treated group showed better performance regarding body pain, mental health, vitality, and social functioning. However, the overall score of SF-36 showed no significant difference.

RWS, also known as real-world evidence study, is an observational study conducted in real-world settings to evaluate the effectiveness, safety, and outcome of medical interventions in a diverse patient population RWS offers valuable insights to help inform clinical decision-making, healthcare policy-making, and regulatory decisions. It is important to note that real-world studies are observational and are subject to various potential sources of bias, such as patient selection

**Table 5** The Difference in Application of NSAIDs Ratio in the Patients with HCQ Group and Those Without

| Grouping | NSAIDs | Without NSAIDs | Chi-square (and Fisher's exact) test |
|---|---|---|---|
| without HCQ | 487 (67.83%) | 231 (32.17%) | RR = 0.775, 95% CI: (0.69, 0.87) |
| with HCQ | 111 (30.83%) | 249 (69.17%) | P<0.0001 |

**Abbreviations**: NSAID, Nonsteroidal anti-inflammatory drug; HCQ, Hydroxychloroquine.

bias, treatment selection bias, etc.[23] Research flow was conducted to validate our results with HCQ, a commonly used csDMARD, widely prescribed to patients with autoimmune diseases, including RA.[24] While HCQ is beneficial, it is generally considered to have a milder impact compared to other more potent immunosuppressive agents.[25] The results indicated that RA patients who received HCQ showed lower CRP levels within 3m of treatment than patients without HCQ. Furthermore, the application ratio of NSAIDs was decreased in the HCQ-treated group. Research on HCQ suggests that the current RWS approach is valuable for evaluating the clinical efficacy of drugs. JGL did not show better benefits for patients with RA in this study, while HCQ did.

Potential limitations of this study include, firstly, the treatment course and dose of each medicine was impossible to figure out due to mobilization of patients and insufficiently detailed outpatients record; secondly, telephone calls were made to retrospectively complete the SF-36 questionnaire of all participants, and this could introduce recall bias. In future, prospective study with disease activity and QoL interviewed face-to-face with patients may release more accurate data. Thirdly, at baseline, patients in the study group with slightly higher age and IgM-RF levels than the reference group. As age might be the factor contributing to RF differences,[20] we adjusted the RF titers by rejection part of the cases in the study group based on the results of stratification analysis. However, a prospective study with a similar baseline would confer more reliable findings.

## Conclusion

However, with limitations, we conducted this RWS and found that adding JGL to RA patients failed to affect inflammatory markers or QoL significantly. Instead, more NSAIDs or other anti-rheumatic drugs were needed to fill the treatment insufficiency. Considering the economic burden to the families of RA patients and governmental health insurance, it is unnecessary to add JGL to RA therapy. Due to unavoidable confounding factors in RWS, a randomized controlled trial (RCT) is also recommended to confirm the findings. More over, folk herbal prescriptions are suggested to undergo strict clinical trials before application.

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## Disclosure

The authors report no conflicts of interest in this work.

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