

# Improved Fatigue Management in Primary Sjögren's Syndrome: A Retrospective Analysis of the Efficacy of Methotrexate in Chinese Patients

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**Objective:** To assess the efficacy of methotrexate (MTX) and hydroxychloroquine (HCQ) in improving fatigue symptoms in patients with primary Sjögren's syndrome (pSS).

**Methods:** A single-center retrospective study was conducted on pSS patients experiencing fatigue symptoms. All patients received either MTX, HCQ, or a combination of MTX + HCQ for a period of six months. Clinical efficacy was measured using the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI), EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), fatigue severity scale (FSS), and visual analog scale (VAS) score. These measures were assessed at baseline and at 1, 2, 3, and 6 months.

**Results:** A total of 86 pSS patients with fatigue symptoms were enrolled (27 received MTX, 29 received HCQ, and 30 received MTX + HCQ). Patients receiving MTX and MTX + HCQ showed significant improvements at 6<sup>th</sup> month in ESSDAI, ESSPRI, FSS, FACIT-F, and VAS scores (all  $P < 0.01$ ) compared with baseline. Repeated-measures analysis of variance revealed that patients treated with MTX and MTX + HCQ experienced significant improvements in ESSDAI, FSS, FACIT-F, and VAS scores (all  $P < 0.01$ ) from baseline to the 6<sup>th</sup> month. The HCQ group did not show significant improvement in FSS, FACIT-F, and VAS scores (all  $P > 0.05$ ), although their ESSDAI and ESSPRI scores did improve significantly (all  $P < 0.01$ ). Patients in the MTX group showed the most improvement in mean changes of ESSDAI score, FSS score, FACIT-F score, and VAS score from baseline to the 6<sup>th</sup> month. And patients received MTX treatment significantly had more fatigue remission numbers (all  $P < 0.05$ ).

**Conclusion:** In clinical practice, methotrexate is more effective than hydroxychloroquine in improving fatigue symptoms, as measured by patient-reported fatigue scales (FSS, FACIT-F, and VAS scores) in patients with pSS.

**Keywords:** primary Sjögren's syndrome, fatigue, methotrexate, hydroxychloroquine

## Introduction

Primary Sjögren's syndrome (pSS) is a multisystemic autoimmune disease, second only to rheumatoid arthritis in frequency.<sup>1</sup> Typical symptoms of pSS include oral and ocular dryness, fatigue, and pain. These symptoms are characterized by hypofunction of the salivary and lacrimal glands, and possible systemic multi-organ manifestations that primarily affect women.<sup>2,3</sup> Current evidence suggests that approximately 75% of pSS patients produce autoantibodies of the Sjögren's Syndrome A (SSA/Ro) and -B (SSB/La) type.<sup>4</sup> The majority of pSS patients experience persistent pain, fatigue, and ocular and/or oral dryness.<sup>5</sup>

Fatigue is a complex and disabling symptom affecting between 22 and 30% of the general population, resulting in reduced quality of life.<sup>6</sup> Nearly 70% of patients with pSS report profound, debilitating fatigue as the single symptom with the most significant negative impact on their quality of life.<sup>7</sup> The prevalence of fatigue in pSS patients is reported to range from 67%<sup>8</sup> to 85%.<sup>9</sup> It is now understood that pSS-related fatigue differs from general fatigue in that it is constant, unrelenting, and volatile. Patients with pSS describe fatigue as "an ever-present, fluctuating, and non-relievable lack of vitality beyond one's own control".<sup>10</sup> This symptom is reported as the most challenging to manage.<sup>11</sup> This underscores the importance of identifying effective treatment strategies to improve fatigue in patients with pSS.<sup>12</sup>

However, the mechanisms that lead to and regulate fatigue are debated. The etiology of fatigue is very complex and unclear, and may be multifactorial, including biological and psychosocial elements contributing to the perception of fatigue. Fatigue symptoms are frequently observed in immune-mediated inflammatory conditions and consistently follow autoimmune diseases, tumors, and infections. This is part of a constellation of symptoms termed “sickness behavior”.<sup>6,13</sup> As reported by S.V. Arnett et al, proinflammatory cytokines may play a critical role as the biological basis of fatigue.<sup>13</sup> Evidence suggests that genetic and molecular mechanisms are activated during inflammation and cellular stress conditions, and signaled via neuro-immune and oxidative / nitrosative stress pathways.<sup>14</sup>

Currently, treatment for pSS focuses on relieving symptoms and altering the course of the disease. For glandular symptoms, artificial tears are reasonably effective for xerophthalmia. However, symptomatic treatments like sprays, lozenges, pastilles, and artificial saliva have limited efficacy in relieving xerostomia.<sup>15</sup> Similarly, glucocorticoids and immunosuppressants, such as methotrexate (MTX), leflunomide (LEF), and hydroxychloroquine (HCQ), as well as biological agents, have not been shown to improve dryness symptoms in patients with pSS.<sup>2,16,17</sup> Evidence supporting the use of disease-modifying anti-rheumatic drugs for pSS is also limited.

Otherwise, pain, depression, and daytime sleepiness scores were closely associated with both physical and mental fatigue in pSS patients, which was observed even after adjustment for comorbidities associated with fatigue or medications associated with drowsiness.<sup>18</sup>

While immunosuppressants like MTX, cyclophosphamide, corticosteroids, and others are often used to manage organ involvement in Sjögren’s syndrome, they can also be effective in addressing extra-glandular manifestations of the disease. However, their use comes with some uncertainty regarding efficacy and the potential for adverse effects.<sup>19</sup>

There is currently no effective treatment for fatigue symptoms in pSS. While evidence from small, uncontrolled, open-label studies suggests rituximab may improve patient-reported dryness, pain, fatigue, global assessment, stimulated salivary flow, and physician global assessment,<sup>20–22</sup> a larger, multicenter, randomized, double-blind, placebo-controlled trial by Simon J Bowman et al found rituximab to be ineffective in pSS patients.<sup>2</sup>

However, no large, systemic, randomized controlled studies have been conducted on the effect of MTX on fatigue in pSS patients. Previous study showed improvement of MTX for the main subjective symptoms (dry mouth and eyes) as well as in the frequency of parotid gland enlargement, dry cough and purpura, however, no improvement in the objective parameters of dry eyes and dry mouth were observed. But regrettably, fatigue symptom was not observed.<sup>16</sup>

Systematic review showed that there is no significant difference between HCQ and placebo in the treatment of dry mouth, dry eye, and fatigue in pSS, and the effectiveness of HCQ was lower than placebo.<sup>23</sup>

This single-center, retrospective clinical study aimed to evaluate the efficacy of MTX in improving fatigue symptoms in pSS patients. All participants were diagnosed with pSS.

## Method

### Inclusion and Exclusion Criteria

Participants were enrolled from the Department of Rheumatology and Immunology, Zhejiang Hospital between January 2019 and December 2023.

Inclusion criteria: All patients fulfilled the 2016 classification criteria for pSS,<sup>24</sup> and were followed up for at least 6 months. During the follow-up period, none of the patients received corticosteroids or immunosuppressants other than methotrexate and hydroxychloroquine.

Exclusion criteria: We excluded patients with a history of other rheumatic diseases, tumors, infectious diseases, malnutrition, chronic kidney disease, graft-versus-host disease, head or neck radiation therapy, or psychiatric disorders.

## Study Design

### Patients

All patients received MTX or HCQ treatment for at least 6 months, and oral MTX 10 mg/week, oral HCQ 400 mg/day. Efficacy endpoints were assessed at 6 months. Efficacy and safety were evaluated at baseline and at 1, 2, 3, and 6 months. Demographic, clinical, and laboratory data were collected from the electronic hospital information system. The study was

approved by the Ethics Committee of Zhejiang Hospital (2020101K) and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects before participation in the study.

## Efficacy Evaluations

Clinical efficacy measures included the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI),<sup>25</sup> EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI),<sup>26</sup> Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F),<sup>27</sup> fatigue severity scale (FSS),<sup>28</sup> and visual analog scale (VAS).<sup>29</sup> The ESSDAI scores were assessed by rheumatologists, and ESSPRI scores, FACIT-F scores, FSS scores, VAS scores were conducted by patients.

## Statistical Analysis

Data were analyzed using SPSS version 23.0 for Windows. All analyses were two-sided, with  $P < 0.05$  considered statistically significant. Continuous variables were presented as mean  $\pm$  standard deviation (SD). One-way analysis of variance (ANOVA) with Scheffé or LSD post-hoc tests were used to evaluate differences between groups for continuous variables. Repeated-measures ANOVA was used for within-group comparisons over time. Qualitative variables were expressed as frequencies (%). The chi-square test with Bonferroni correction was used to evaluate the significance of associations between categorical variables.

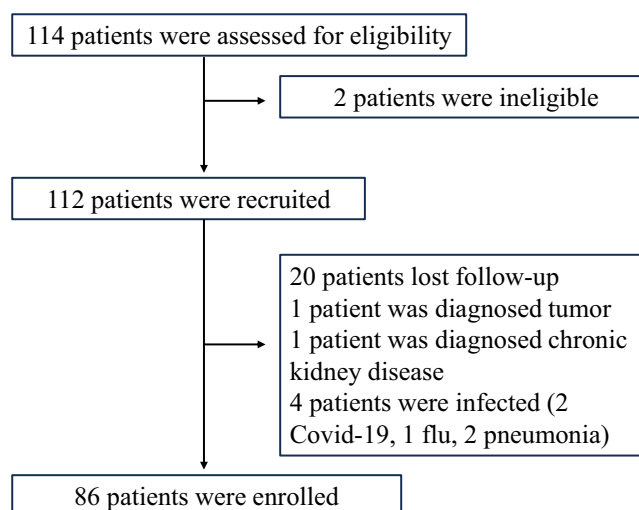
## Results

### Participant Characteristics

A total of 114 patients were assessed for eligibility. After screening clinical information and follow-up, 28 patients were excluded. Two patients were ineligible due to discontinued treatment, and 20 patients were lost to follow-up. One patient was diagnosed with a tumor, one with chronic kidney disease, and four developed infections. Therefore, 86 patients were included in the final analysis. The patient selection process of this study is shown in Figure 1.

Table 1 presents the baseline characteristics of the 86 pSS patients. Among these patients, 27 (31.4%) received MTX, 29 (33.7%) received HCQ, and 30 (34.9%) received both MTX and HCQ. There were no significant differences in gender, age, ESSDAI score, ESSPRI score, FSS score, FACIT-F score, VAS score, or presence of extra-glandular involvement between the MTX, HCQ, and MTX + HCQ groups at baseline (all  $P > 0.05$ ).

Table 2 shows the serological parameters of pSS patients at baseline. There were significant differences in the proportions of patients with hyper-immunoglobulin G (IgG), hypocomplementemia C3, hypocomplementemia C4, leukopenia, anemia, and thrombocytopenia among the three groups at baseline (all  $P < 0.01$ ). Interestingly, ANOVA



**Figure 1** Flow diagram depicting the selection process of study participants.

**Table 1** Baseline Characteristics of Subjects

	All N = 86	MTX N = 27	HCQ N = 29	MTX+HCQ N = 30	P
Age (years)	52.4±12.7	51±12.1	52.8±12.3	53.2±14	0.700
Female, n (%)	78 (90.7%)	25 (92.6%)	27 (93.1%)	27 (90%)	0.218
BMI (kg/m <sup>2</sup> )	21.8±3.4	21.8±2.9	21.3±3.3	22.2±3.9	0.797
Disease duration (years)	3.9±4.7	3.8±5.9	4.3±4.5	3.8±3.5	0.394
ESSDAI score	4.8±0.9	5.1±1	4.6±1	4.8±0.8	0.076
ESSPRI score	6.5±1.2	6.6±1.2	6.5±1.1	6.4±1.3	0.701
FSS score	44.2±7.5	46.2±9.2	42.3±4.7	44.1±7.9	0.149
FACIT-F score	25.8±4	25.7±4.6	26.8±2.5	25±4.6	0.230
VAS score	3.4±1	3.5±1.1	3.4±0.9	3.5±0.9	0.803
Dry eyes, n (%)	52 (60.5%)	13 (48.2%)	18 (62.1%)	21 (70%)	0.236
Dry mouth, n (%)	61 (70.9%)	17 (63%)	21 (72.4%)	23 (76.7%)	0.341
Interstitial lung disease, n (%)	11 (12.8%)	4 (14.8%)	3 (10.3%)	4 (13.3%)	0.263
Articular involvement, n (%)	46 (53.5%)	17 (63%)	13 (44.8%)	16 (53.3%)	0.849
Skin involvement, n (%)	9 (10.5%)	0 (0)	4 (13.8%)	5 (16.7%)	0.083
Hematological involvement, n (%)	46 (53.5%)	17 (63%)	18 (62.1%)	11 (36.7%)	0.073
Lymphadenopathy, n (%)	27 (31.4%)	11 (40.7%)	10 (34.5%)	6 (20%)	0.220

**Abbreviations:** BMI, Body Mass Index; ESSDAI, European League Against Rheumatism (EULAR) Sjögren's syndrome disease activity index; ESSPRI, European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index; FSS, fatigue severity scale; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; VAS, visual analog scale.

**Table 2** Baseline Serological Parameters of pSS Patients

	All N = 86	MTX N = 27	HCQ N = 29	MTX+HCQ N = 30	P
IgG(g/L)	16.8±5.6	19.7±6	15.6±4.7	15.2±5.1	0.006
Hyper IgG, n (%)	48 (55.8%)	22 (81.5%)	16 (55.2%)	10 (33.3%)	0.001
C3	1.1±0.4	0.9±0.3	1.2±0.2	1.1±0.3	<0.001
Low C3, n (%)	19 (22.1%)	14 (63%)	3 (10.3%)	2 (6.7%)	<0.001
C4	0.2±0.1	0.2±0.1	0.3±0.1	0.3±0.1	0.007
Low C4, n (%)	19 (22.1%)	12 (44.4%)	4 (13.8%)	3 (10%)	0.003
WBC (*10 <sup>9</sup> /L)	4.7±1.8	2.8±0.9	5.6±1.4	5.5±1.7	<0.001
Leukopenia, n (%)	27 (31.4%)	27 (100%)	0 (0%)	0 (0%)	<0.001
Hemoglobin	121.5±12.2	115±25.6	124.1±18.4	124.9±10.8	0.017
Anemia, n (%)	25 (29.1%)	14 (63%)	7 (24.1%)	4 (13.3%)	<0.001
Platelet	171.3±62.9	131.2±56.4	196±56.5	183.4±53.8	<0.001
Thrombocytopenia, n (%)	17 (19.8%)	11 (40.7%)	2 (6.9%)	4 (13.3%)	0.004
Anti-SSA+, n (%)	74 (86%)	25 (92.6%)	27 (93.1%)	22 (73.3%)	0.05
Anti-SSB+, n (%)	30 (34.9%)	9(33.3%)	14 (48.3%)	7(23.3%)	0.130
Anti-RO52+, n (%)	70 (81.4%)	25 (92.6%)	23 (79.3%)	22 (73.3%)	0.165
RF+, n (%)	54 (62.8%)	19 (70.4%)	17 (58.6%)	18 (60%)	0.613

**Abbreviations:** IgG, immunoglobulin G; C3, complement 3; C4, complement 4; WBC, white blood cell; SSA, Sjögren's syndrome A; SSB, Sjögren's syndrome B; RF, rheumatoid factor.

analysis revealed significant differences in the levels of IgG, complement C3, complement C4, white blood cells, hemoglobin, and platelets among the three groups (all  $P < 0.05$ ). However, no significant differences were found in autoantibodies among the three groups at baseline (all  $P > 0.05$ ).

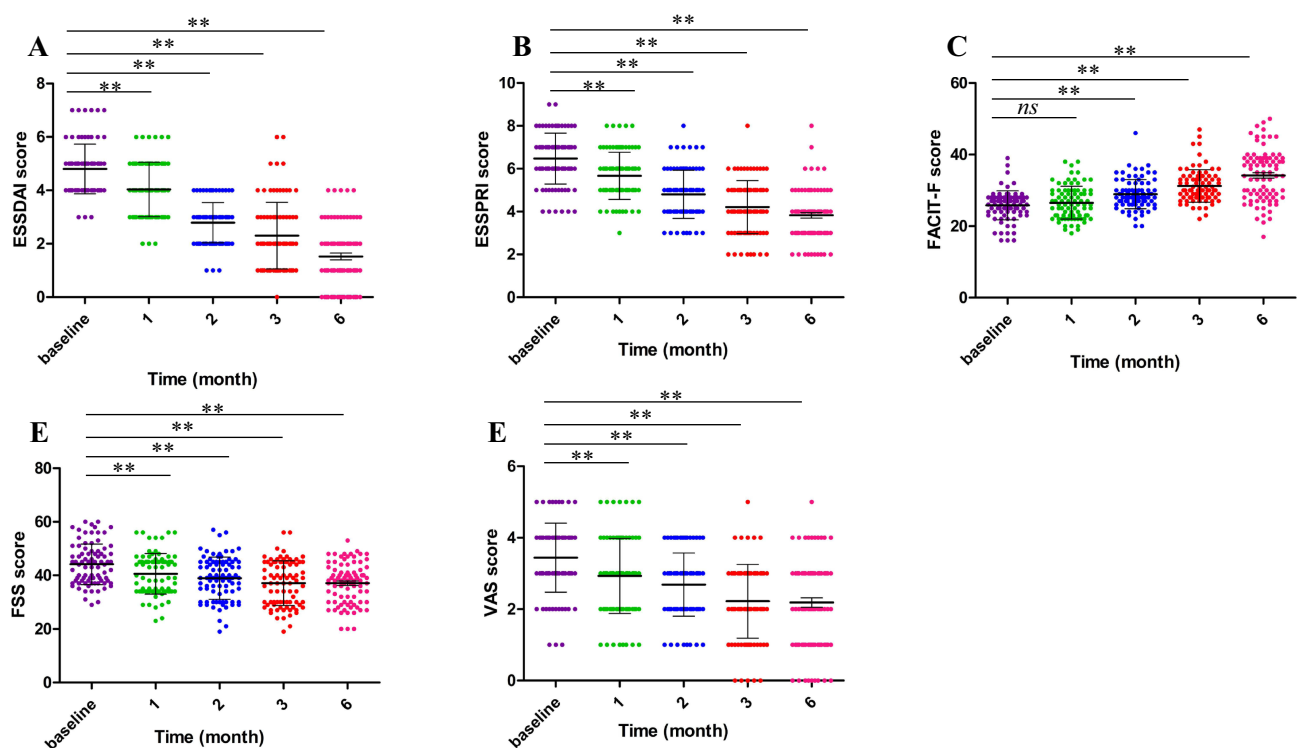
## Clinical Efficacy Measures

A repeated-measures ANOVA analysis was conducted to assess the differences in outcomes among the MTX, HCQ, and MTX + HCQ groups from baseline to the 6<sup>th</sup> month. The MTX and MTX + HCQ groups showed significant improvements of ESSDAI score, FSS score, FACIT-F score and VAS score from baseline to the 6<sup>th</sup> month (all  $P < 0.05$ ). In contrast, the HCQ group did not exhibit significant improvement during the follow-up period (baseline to 6<sup>th</sup> month) ( $P > 0.05$ ) (Figure 2).

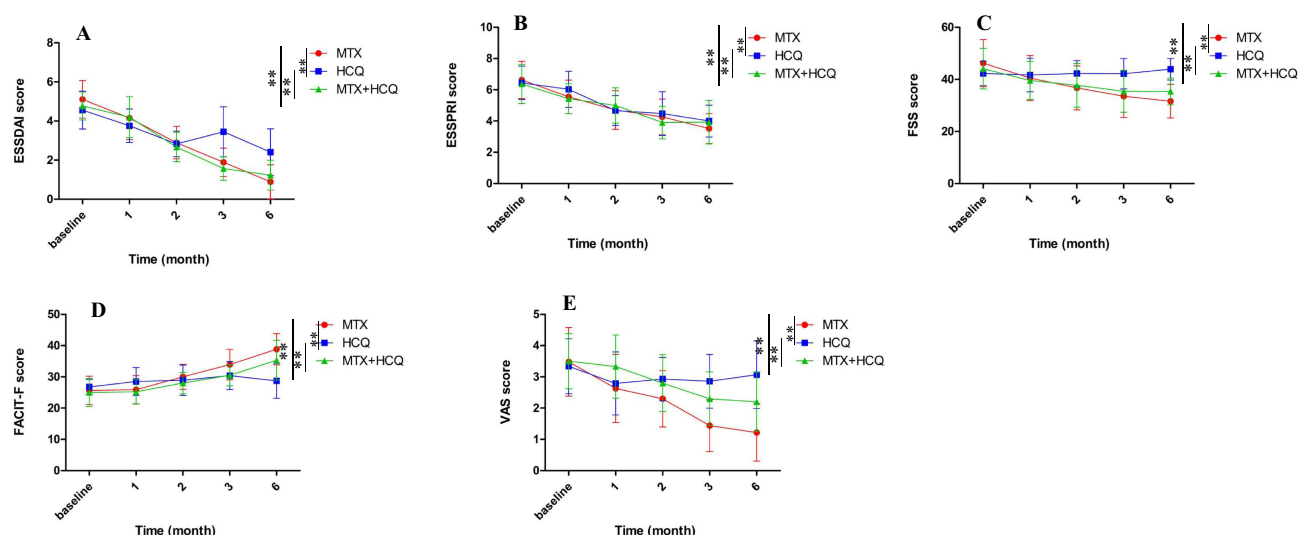
The ESSDAI score ( $5.1 \pm 1.0$ ,  $4.6 \pm 1.0$ ,  $4.8 \pm 0.8$  vs  $0.9 \pm 0.9$ ,  $2.4 \pm 1.2$ ,  $1.2 \pm 0.8$ , respectively;  $P < 0.01$ ), ESSPRI score ( $6.6 \pm 1.2$ ,  $6.5 \pm 1.1$ ,  $6.4 \pm 1.3$  vs  $3.5 \pm 1.0$ ,  $4.0 \pm 1.0$ ,  $3.9 \pm 1.4$ , respectively;  $P < 0.01$ ), FSS score ( $46.2 \pm 9.2$ ,  $42.3 \pm 4.7$ ,  $44.1 \pm 7.9$  vs  $31.6 \pm 6.6$ ,  $43.9 \pm 4.2$ ,  $35.4 \pm 5.7$ , respectively;  $P < 0.01$ ), FACIT-F score ( $25.7 \pm 4.6$ ,  $26.8 \pm 2.5$ ,  $25.0 \pm 4.6$  vs  $38.9 \pm 5.1$ ,  $28.7 \pm 5.7$ ,  $35.2 \pm 6.6$ , respectively;  $P < 0.01$ ), and VAS score ( $3.5 \pm 1.1$ ,  $3.4 \pm 0.9$ ,  $3.5 \pm 0.9$  vs  $1.2 \pm 0.9$ ,  $3.1 \pm 1.1$ ,  $2.2 \pm 1.0$ , respectively;  $P < 0.01$ ) all showed significant improvement for the MTX, HCQ, and MTX + HCQ groups from baseline to the 6<sup>th</sup> month. Scores in the MTX group showed the most significant improvement, while the HCQ group showed the least (Figure 3).

Several patient-reported outcome instruments were used in the study to assess changes in fatigue and disease activity. Patients in the MTX group showed the most improvement in mean changes of ESSDAI score, FSS score, FACIT-F score, and VAS score from baseline to the 6<sup>th</sup> month (Figure 4). However, there was no significant difference in ESSPRI scores across the three groups (Table 3).

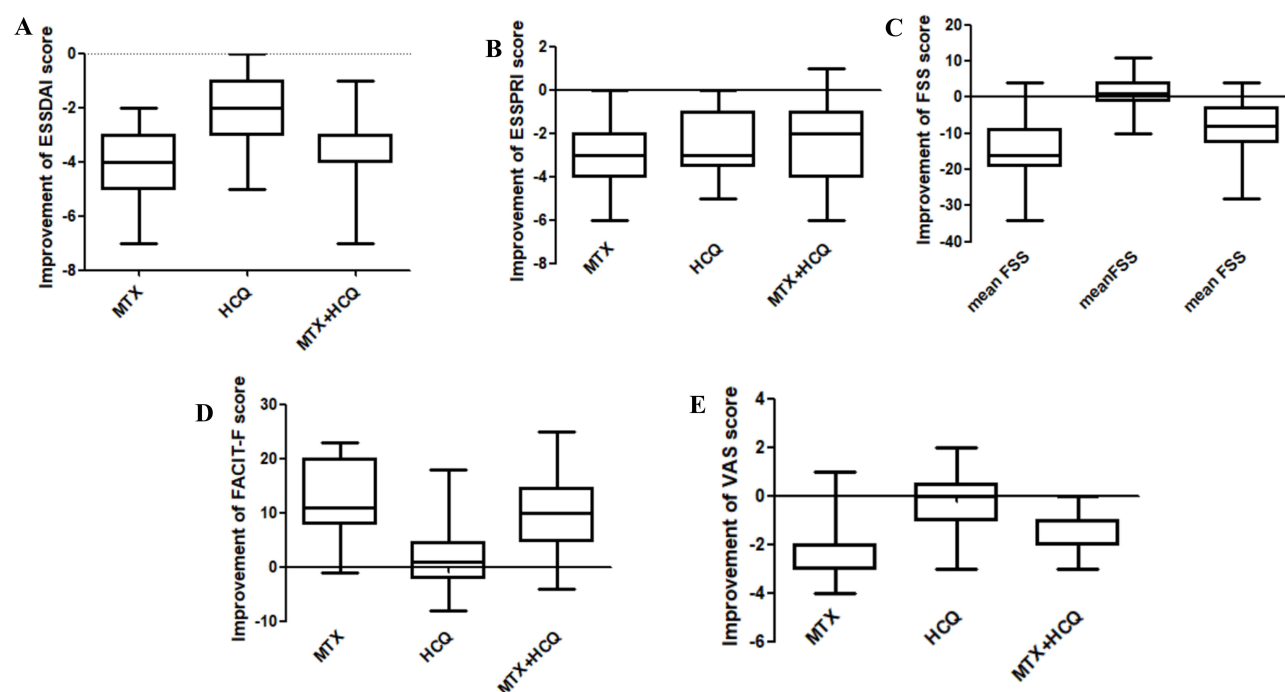
At 6 months, the MTX, HCQ, and MTX+HCQ groups showed significant differences in fatigue remission rates according to FSS score (63%, 3.4%, 13.3%,  $P < 0.01$ ), FACIT-F score (96.3%, 13.8%, 24.8%,  $P < 0.01$ ), and VAS score (25.6%, 3.4%, 30%,  $P = 0.04$ ), respectively (Table 3).



**Figure 2** Changes in Clinical efficacy measures over time. Panels (A–E) show the changes in ESSDAI score (A), ESSPRI score (B), FACIT-F score (C), FSS score (D), and VAS score (E) for all subjects from baseline to the 6<sup>th</sup> month. \*\* $P < 0.01$ . ns, nonsignificant.



**Figure 3** Clinical efficacy measures of the MTX group, HCQ group, and MTX + HCQ group. Mean Levels of ESSDAI score (A), ESSPRI score (B), FSS score (C), FACIT-F score (D), and VAS score (E) of the three groups from baseline to the 6<sup>th</sup> month. \*\* $P < 0.01$ .



**Figure 4** Improvement of ESSDAI score (A), ESSPRI score (B), FSS score (C), FACIT-F score (D) and VAS score (E) of the MTX, HCQ and MTX+HCQ group.

## Discussion

Fatigue is a complex and subjective experience, often described as a constant feeling of tiredness, lack of energy, endurance, or vitality that interferes with daily activities. The estimated prevalence of fatigue in pSS patients varies considerably, and there is a lack of standardized instruments specifically designed to measure fatigue in rheumatic diseases. Severe fatigue symptoms are present in 41% to 57% of patients with various inflammatory rheumatic diseases, including rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, Sjögren's syndrome, psoriatic arthritis, and scleroderma. Notably, severe fatigue is least prevalent in patients with osteoarthritis (35%) and most prevalent in patients with fibromyalgia (82%).<sup>30</sup> Studies have identified depression, ESSDAI, and ESSPRI as



**Table 3** Clinical Efficacy Measures

	MTX N = 27	HCQ N = 29	MTX+HCQ N = 30	P
Mean change from baseline to the 6 <sup>th</sup> month, mean (SD)				
ESSDAI score	−4.2 (1.3)	−2.1 (1.5)	−3.5 (1.1)	<0.001
ESSPRI score	−3.1 (1.7)	−2.4 (1.5)	−2.4 (1.8)	0.236
FSS score	−14.6 (8.4)	1.6 (5)	−8.7 (8.1)	<0.001
FACIT-F score	13.2 (6.4)	1.9 (6.1)	10.2 (7.4)	<0.001
VAS score	−2.3 (1.2)	−0.3 (1.1)	−1.3 (0.9)	<0.001
Fatigue remission at 6th month				
FSS remission, n (%)	17 (63%)	1 (3.4%)	4 (13.3%)	<0.001
FACIT-F remission, n (%)	26 (96.3%)	4 (13.8%)	24 (80%)	<0.001
VAS remission, n (%)	7 (25.6%)	1 (3.4%)	9 (30%)	0.037

**Abbreviations:** ESSDAI, European League Against Rheumatism (EULAR) Sjögren's syndrome disease activity index; ESSPRI, European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index; FSS, fatigue severity scale; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; VAS, visual analog scale.

independent risk factors for fatigue in pSS patients.<sup>31</sup> Unfortunately, there is currently no specific and highly effective treatment to completely relieve fatigue symptoms in pSS patients. Based on our clinical experience, we designed this study to explore the efficacy of MTX and HCQ in managing fatigue symptoms in patients with pSS.

The purpose of this study is to evaluate the efficacy of MTX and HCQ for fatigue symptom in pSS patients. In this study, we enrolled 86 patients with pSS who were experiencing fatigue. We found that MTX was more effective than HCQ in improving fatigue symptoms. Hydroxychloroquine may still be considered in certain situations for managing fatigue in pSS. Some reports suggest that HCQ improves fatigue in about one-third of patients treated with the medication.<sup>32</sup>

Although, hydroxychloroquine is one of the most frequently prescribed DMARDs for fatigue symptom in pSS patients. However, evidence regarding its efficacy is limited. Previous study involving a significant number of randomized or non-randomized controlled experiments have reported hydroxychloroquine to exhibit placebo-like effects in the treatment of pSS.<sup>17</sup> Nevertheless, we conducted this substantial workload study and similarly, we did not observe significant improvement in fatigue among patients receiving HCQ. While the overall quality of evidence is considered very low, some experts recommend considering HCQ for pSS patients with fatigue due to its favorable safety profile and established use in clinical practice.<sup>33</sup>

Otherwise, we found MTX presented compelling evidence for a robust therapeutic effect for fatigue in pSS patients, compared with hydroxychloroquine. But considering the potential confounding factors inherent in retrospective studies, the reliability of the conclusion warrants further scrutiny. On the other hand, possibly due to its relatively short duration, we could not get an accurate conclusion. MTX was already recommended for treating inflammatory musculoskeletal pain in pSS, but there was no existing evidence or recommendation for its use in managing fatigue.<sup>34</sup>

James Posada et al<sup>7</sup> found that RSLV-132 improved severe fatigue in patients with pSS. This improvement was determined by independent patient-reported measures of fatigue, including the ESSPRI, FACIT-F, Profile of Fatigue (ProF), and Digit Symbol Substitution Test (DSST). They also found a significant correlation between this improvement and increased expression of selected interferon-inducible genes.<sup>7</sup> In contrast, a multicenter, randomized, double-blind, placebo-controlled trial conducted by Simon J Bowman et al<sup>2</sup> recruited 133 pSS patients with fatigue and found that Rituximab was neither clinically nor cost-effective for this patient population. However, a pilot RCT study by another group enrolled 17 pSS patients and reported a significant reduction in fatigue among those randomized to rituximab compared to placebo. This study did not find a significant difference in the proportion of patients achieving either a 20% or 30% reduction in fatigue from baseline at 6 months.<sup>35</sup>

It is widely thought that physiotherapeutics play an important role in managing fatigue. Jessica Tarn et al<sup>36</sup> recruited 15 pSS patients who used a noninvasive vagus nerve stimulation device twice daily for a 26-day period. This study found a reduction in clinical symptoms of fatigue and sleepiness, suggesting that the vagus nerve may be involved in regulating

fatigue and immune responses in pSS. However, a larger placebo-controlled follow-up study is required to confirm these findings. According to the Treatment Guidelines for Rheumatologic Manifestations of Sjögren's Syndrome, experts recommend self-care measures and exercise advice as ways to reduce fatigue.<sup>33</sup>

Herein, we selected three fatigue scales that are currently or have recently been used in rheumatology populations and are considered easy for patients to complete. However, it is important to note that the FSS, developed by Krupp et al in 1989, was originally designed to evaluate fatigue in Parkinson's disease and may not be entirely suitable for pSS patients,<sup>28</sup> despite being simple and easy to understand. Additionally, while all three scales are patient-reported measures of fatigue, self-assessment may not always accurately reflect the true level of fatigue experienced. Due to the subjective of the several assessment scales, the results of the questionnaire may be not very accuracy.

The PROMIS (Patient Reported Outcomes Measurement Information System) scales are available in both a fixed short form as well as a computer-adaptive testing format and have shown robust psychometric properties, and the PROMIS fatigue instruments have been shown to be reliable, well correlated with, and responsive to change in rheumatoid arthritis disease activity.<sup>37,38</sup> But there were not objective assessment tools available. More scientific approach needed to be used to evaluate fatigue severity and degree.

There are no established pharmacological treatment options for fatigue in pSS. So far, exercise and neuromodulation techniques have shown positive effects on fatigue in pSS.<sup>39</sup> Patients with Sjögren's syndrome may have complex comorbidities and be taking medications that contribute to fatigue. And MTX can cause fatigue symptom.<sup>40</sup> These factors may account for a relatively small proportion of the variation observed in fatigue symptoms among the study participants.<sup>18</sup>

The biological mechanisms and pathology involved in pSS fatigue are still not fully understood. In terms of physiology, fatigue is multidimensional and associated with neurocognitive, neuroendocrine, environmental and behavioral components. Fatigue in pSS is multifactorial and clinically related to sleep, mood and physical, and psychological disorders.<sup>18</sup> Additionally, pSS patients developed with low quality of sleep, and this may correlate with fatigue.<sup>41</sup> Sleep quality definitely associated with fatigue symptom, and future studies could address whether such factors could be useful as surrogate markers for fatigue in pSS. But regrettably, in this study, we did not study the correlations between sleep, psychiatric disorders and fatigue.

Several limitations in this study should be acknowledged. First, the retrospective design relies on data obtained from medical records, which can be susceptible to recall bias. Second, a prospective long - time follow-up study with a larger sample size is required to confirm the findings. Finally, differences in education level among participants may have contributed to the heterogeneity observed in fatigue scores, as educational background can influence how patients understand and respond to assessment questions. Well-designed, randomized, controlled trials are needed to provide higher-quality evidence to confirm our findings, and future studies should focus on some extra-glandular measures, such as fatigue symptom to further explore the therapeutic effect of MTX in pSS.

## Conclusion

This retrospective study investigated the efficacy of MTX in managing fatigue symptoms in patients with pSS. Utilizing a limited sample size, the study employed patient-reported fatigue measures to assess the comparative effects of MTX and HCQ. The findings demonstrate that MTX treatment resulted in significantly greater improvements in fatigue symptoms compared to HCQ, and it's the first study to explore the efficacy of MTX and HCQ for fatigue in pSS patients.

## Data Sharing Statement

All data generated or analyzed during this study are included in this article. For further information, please contact the corresponding author, Fang Yuan.

## Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Zhejiang Hospital (2020101K) and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects before participation in the study.



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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception and design, data acquisition, or data analysis and interpretation, participated in the drafting of the article or critically revising it for important intellectual content, agreed to submit to the current journal, gave final approval for the version to be published, and agreed to be accountable for all aspects of the work.

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## Disclosure

The authors have declared no conflicts of interest.

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