International Journal of General Medicine

Dovepress
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CLINICAL TRIAL REPORT

# Osteoarthritis and Degree of Fatigue are Associated with Pain Levels in Patients with Fibromyalgia Syndrome: A Cross-Sectional Study of 394 Patients

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**Objective:** To observe how osteoarthritis (OA) and degree of fatigue affect are associated with pain levels in patients with fibromyalgia syndrome (FMS).

**Methods:** A cross-sectional study was conducted involving FMS patients. Data regarding the clinical features of the patients, including scores for pain-Visual Analogue Scale (VAS), Fatigue Scale-14 (FS-14) and other patient information, was collected. A multivariable logistic regression model was constructed to determine whether there is a true association between OA, degree of fatigue, and pain level in FMS patients. Restricted cubic spline (RCS) analysis was used to explore a potential non-linear relationship between degree of fatigue scores and pain levels in FMS patients. An interaction analysis based on the main regression model was performed to examine the interaction between OA and degree of fatigue.

**Results:** Among the FMS patients, the presence of OA was identified as a risk factor associated with higher pain-VAS scores (OR=2.777, 95% CI=1.377–5.601, P=0.004); furthermore, higher degree of fatigue scores on the FS-14 were found to be significantly associated with high pain level (OR=1.145, 95% CI=1.054–1.243, P=0.001). The RCS analysis demonstrated a linear relationship between increasing FS-14 scores and an elevated risk of high pain levels among FMS patients (P-non-linear=0.119, P-overall=0.008). The interaction analyses revealed a significant association between OA and degree of fatigue, which were related to the pain level of patients with FMS synergistically.

**Conclusion:** Patients with FMS experience coexisting OA and a high degree of fatigue, which interact synergistically, being correlated with increased pain levels.

**Trial Registration:** The study was approved by the Clinical Research Ethics Committee of the China-Japan Friendship Hospital (2022-KY-079) and registered on ClinicalTrials.gov (NCT05508516) on August 17th, 2022.

**Keywords:** fibromyalgia syndrome, osteoarthritis, fatigue, pain, correlation analysis

## Introduction

Fibromyalgia syndrome (FMS) is a complex syndrome characterized by persistent and widespread pain, accompanied by a series of systemic symptoms such as fatigue, emotional abnormalities, and sleep disorders.[1] The global mean prevalence of FMS is about 2–3%, and is more prevalent in women.[2] The etiology and pathogenesis of FMS are not fully understood, and it is often suggested to be related to increased sensitivity of the central nervous system.[3] Current

Received: 31 October 2024
Accepted: 24 January 2025
Published: 31 January 2025

treatments for FMS remain limited, with unsatisfactory efficacy, and patients' quality of life progressively deteriorates as the disease advances.

Some studies have proposed that the presence of FMS as a comorbidity is associated with diminished functional activity and a lower quality of life in patients, such as in patients with osteoarthritis (OA).[4] As a degenerative joint disease, OA often co-occurs with FMS, and the resulting joint pain is usually more difficult for the patient to tolerate. Although OA may be related to the functional status of FMS, there is a lack of research specifically addressing their relationship. Meanwhile, fatigue, one of the typical symptoms of FMS, is closely related to pain.[5] It can be utilized jointly with pain as two independent symptoms to differentiate subgroups of FMS patients.[6] It is supposed that a common feedback mechanism exists between fatigue and pain, although more clinical evidence is necessary to support this notion.

Based on extant findings and unclarified clinical questions, we hypothesized that OA and degree of fatigue are key factors that correlate with pain level in FMS patients, and that OA and fatigue may exhibit synergistic interactions in this context. This study illustrates the associations between pain, OA, and degree of fatigue in FMS.

# Materials and Methods

## Patient Selection

This is a cross-sectional study based on prospectively collected data from patients with FMS. We enrolled a population who attended the Traditional Chinese Medicine Department of Rheumatism at the China-Japan Friendship Hospital between September 2022 to September 2023. The study included patients aged 18–75 years for whom complete case data could be obtained. These patients had not been previously diagnosed with FMS and received a diagnosis of FMS during this medical visit in accordance with 2016 American College of Rheumatology (ACR) criteria.[7] Patients with comorbidities relating to other rheumatic immunological diseases (eg, rheumatoid arthritis, ankylosing spondylitis, and systemic lupus erythematosus); acute infections; severe cardiovascular, cerebrovascular, and respiratory diseases; hepatic or renal failure; presence of neoplasms; severe hematopoietic dysfunction; severe mental disorders; or those for whom data collection was difficult due to psycho-linguistic and other factors were excluded from the study. Patients using glucocorticoid, non-steroidal anti-inflammatory drugs (NSAIDs), or psychotherapeutic drugs such as anxiolytics, antidepressants, and cannabinoids were also excluded. None of the patients had undergone any treatment related to FMS when they were included. The study was approved by the Clinical Research Ethics Committee of the China-Japan Friendship Hospital (2022-KY-079) and registered on ClinicalTrials.gov (NCT05508516) on August 17th, 2022. The study was conducted in accordance with the Declaration of Helsinki. Each patient provided written informed consent to allow the use of their clinical records for further scientific reporting.

## Diagnostic Criteria

The diagnosis of FMS was based on the modified FMS diagnostic criteria (2016 version) from the ACR. These criteria include a widespread pain index (WPI) score≥7 and symptom severity scale (SSS) score≥5, or a WPI score of 4–6 and SSS score≥9. Additionally, there should be presence of generalized pain in at least 4 out of 5 regions of the body, along with the persistence of symptoms for at least 3 months. The diagnosis of OA[8] was based on the modified OA diagnostic criteria from the American Rheumatism Association (1986 version). All diagnoses were performed by experienced rheumatologists.

## Research Methods

### Demographic Information

Patients' information was collected through web-based consultations or face-to-face meetings. Data included demographic characteristics of the study population, including sex, age, body mass index (BMI), duration of illness (since the first definitive diagnosis), smoking (patients who have been actively smoking for more than three months, with at least one cigarette per day, are recorded as having a smoking habit) and drinking (patients who are still consuming alcohol for more than three months, with no less than one drinking session per week, are recorded as having a drinking habit), level of education (categorized into low and high levels based on attainment of a bachelor's degree, patients with a bachelor's

degree or above were considered highly educated while those with lower qualifications considered to have a low level of educational attainment), job (government employees and professional/technical staff were classified as professional-type jobs, while production and service occupations were classified as non-professional-type jobs), daily physical activity (categorized into low and high levels based on achieving 60 minutes per day of moderate-intensity exercise), and documentation of the primary symptoms experienced by the patients.

### Functional Status of FMS Patients

Pain levels associated with FMS were measured using the Visual Analogue Scale (VAS), which is a ten-point scale used to gauge pain intensity.[9] In this study, the pain-VAS was employed to characterize the patient's average pain level during a recent month. The Revised Fibromyalgia Impact Questionnaire (FIQR) was utilized to evaluate the overall functional status of FMS patients, encompassing aspects such as their physical functions, general well-being, and symptom severity.[10] Higher scores on the FIQR indicate a poorer overall functional status.

### Emotional Disorders

The Perceived Stress Scale (PSS) was utilized to evaluate recent exposure to stress among patients.[11] The comprehensive version of the PSS comprises 14 items, for which higher scores indicate greater perceived stress levels. The short Beck Depression Inventory (BDI), consisting of validated 13 items—with higher scores indicating a more pronounced state of depression—was employed to gauge the extent of depressive tendencies in patients.[12] The Beck Anxiety Inventory (BAI) — encompassing 21 items, where higher scores suggest a more severe state of anxiety—was administered to assess the severity of anxiety symptoms experienced by patients.[13]

### Quality of Life

The Fatigue Scale-14 (FS-14) was utilized to measure patients' level of fatigue,[14] which was categorized into two dimensions: physical fatigue (8 items) and mental fatigue (6 items). Higher scores indicate a higher degree of fatigue. The Medical Outcomes Study Short Form Health Survey (SF-36) was employed to evaluate the general health status of the patients.[15] The SF-36 consists of 36 items, where lower scores indicate poorer health. Physical discomfort and behavioral and cognitive disorders were evaluated using the Symptom Checklist 90 (SCL-90), comprising 9 factors, with higher scores indicating poorer somatic-psychological condition.[16] The Pittsburgh Sleep Quality Index (PSQI), used to assess the sleep quality of the patients,[17] included 19 items, where higher scores represent poorer sleep quality.

### Sample Size Calculation

With the inclusion of indicators, it was hypothesized that there would be approximately 5–10 variables associated with the pain levels of FMS patients. To ensure a sufficient sample size for regression analysis, a minimum of 50–100 FMS patients was deemed necessary, with each variable corresponding to approximately 10 events.[18] The final study included a total of 394 FMS patients, meeting the expected minimum sample size.

## Statistical Analysis

The data were analyzed and visualized using IBM SPSS (Version 25.0) and R (Version 4.1.1). Descriptive statistics, including means, standard deviation (SD), median, first quartile (Q1), third quartile (Q3) and proportions, were employed to present the baseline data. Normally distributed data are characterized by the mean±SD, while non-normally distributed data are represented by the median along with the Q1 and Q3. To compare variable values, independent samples *T*-test was utilized for normally distributed data; rank sum test (Mann–Whitney U) was performed for non-normally distributed data; and chi-square tests were used for count data.

The Pearson correlation test was utilized to assess the relationship between two continuous variables when exploring their correlation. This test measures the strength of the correlation ($r$, $-1<r<1$), with a value closer to 0 indicating a weaker correlation.[19] A multivariable logistic regression model was primarily constructed to examine the pain levels of FMS patients. The pain-VAS scores, categorized as indicating mild or severe pain, served as the outcome measure. This model focused on determining which factors, including OA and degree of fatigue, were truly associated with FMS pain levels. Further sensitivity analyses were conducted by stratifying for other significant variables to demonstrate the

relationship between OA and pain levels among FMS patients. Finally, an interaction analysis based on the main logistic regression model was performed to examine how OA interacts with degree of fatigue.

The restricted cubic spline (RCS) was utilized to investigate potential linear or non-linear associations between degree of fatigue and pain levels in FMS. Knots were selected based on the Akaike information criterion within a range from the 3rd percentile to the 7th percentile, inclusively set at a reference value of odds ratio (OR)=1 corresponding to the median score. Additional knots were placed at the 10th percentile, 50th percentile, and 90th percentile of ln-transformed scores, excluding values outside the 5th and 95th percentiles.[20]

If any variable contained no more than 20% missing values, the MICE package in R was utilized for multiple imputation to replace them. For statistical analysis, a significance level of $P<0.05$ was considered to indicate statistical significance.

# Results

## Demographic Characteristics

A total of 394 patients were enrolled in the study. Of the 394 patients diagnosed with FMS, 62 patients were also diagnosed with OA. These 394 patients were further categorized into two groups based on the absence or presence of concurrent OA, namely, "FMS without OA" and "FMS with OA", respectively. The detailed patient inclusion process is illustrated in Figure S1.

As presented in Table 1. The two patient groups (FMS without OA and FMS with OA) exhibited similar characteristics in terms of age, sex, BMI, smoking and drinking habits, duration of illness, educational level, employment, and daily physical activity without any statistically significant differences (all $P>0.05$).

## Disease-Related Clinical Features

The disease status of patients with FMS was assessed using pain-VAS scores and FIQR. The findings revealed that patients with FMS accompanied by OA exhibited higher scores for both pain-VAS and FIQR than patients who had FMS without OA (Table 2).

Next, we performed assessment of several indicators related to emotional disorders, such as PSS, BAI, and BDI, which show worse performance when OA coexisted in patients with FMS. We additionally conducted corresponding assessments for different aspects of patients' overall living conditions. The SF-36 scores were significantly lower in "FMS with OA" ($P<0.05$), revealing that the presence of OA is associated with poorer quality of life of patients with FMS. The SCL scores significantly increased in "FMS with OA" ($P<0.05$), revealing that the worse somatization

**Table 1** Analysis of the Basic Characteristics of Patients

| | FMS Without OA (n=332) | FMS with OA (n=62) | *P* values* |
|---|---|---|---|
| Age (years), mean±SD | 49.23±9.41 | 50.87±11.24 | 0.224 |
| Sex, N (%) | | | |
| Female | 270 (81.3) | 47 (75.8) | 0.301 |
| BMI (kg/m^2), mean±SD | 23.36±3.69 | 22.70±3.50 | 0.134 |
| Smoking, N (%) | 53 (16.0) | 4 (6.5) | 0.051 |
| Drinking, N (%) | 41 (12.3) | 7 (11.3) | 0.999 |
| Duration (months), median (Q1, Q3) | 4.00 (1.00, 10.00) | 3.00 (1.00, 10.00) | 0.078 |
| Educational level, N (%) | | | |
| High level | 196 (59.0) | 34 (54.8) | 0.576 |
| Employment, N (%) | | | |
| Professional work | 78 (23.5) | 16 (25.8) | 0.746 |
| Daily physical activity, N (%) | | | |
| Low level | 177 (53.3) | 27 (43.5) | 0.168 |

**Notes:** * The *P*-value represents the statistical significance of the difference between the groups.The presence of statistical significance is indicated by bolded *P* values.

**Abbreviations**: OA, Osteoarthritis; SD, standard deviation; BMI, Body Mass Index.

**Table 2** Analysis of Disease-Related Clinical Features in Patients

| | FMS Without OA (n=332) | FMS with OA (n=62) | *P* value* |
|---|---|---|---|
| Pain-VAS (0–10), mean±SD | 5.12±2.31 | 6.87±2.29 | **<0.001** |
| FIQR (0–100), mean±SD | 56.07±22.92 | 69.60±15.77 | **<0.001** |
| PSS (0–56), median (Q1, Q3) | 27.60 (10.80, 44.40) | 42.00 (19.75, 53.00) | **<0.001** |
| BDI (0–39), median (Q1, Q3) | 11.50 (6.00, 19.80) | 19.00 (13.50, 25.00) | **<0.001** |
| BAI (0–63), median (Q1, Q3) | 48.00 (32.00, 56.00) | 54.00 (42.00, 58.00) | **0.005** |
| SF-36 (0–100), mean±SD | 48.53±16.80 | 41.56±15.62 | **0.006** |
| FS-14 (0–14), median (Q1, Q3) | 8.40 (4.20, 12.60) | 9.00 (4.80, 11.80) | 0.425 |
| SCL scores (0–269), mean±SD | 147.32±51.05 | 163.66±46.34 | **0.046** |
| PSQI (0–21), mean±SD | 10.92±3.37 | 11.14±3.48 | 0.640 |

**Notes:** * The *P*-value represents the statistical significance of the difference between the groups.The presence of statistical significance is indicated by bolded *P* values.

**Abbreviations**: FMS, Fibromyalgia Syndrome; OA, Osteoarthritis; FIQR, The Revised Fibromyalgia Impact Questionnaire; VAS, Visual Analogue Scale; PSS, Perceived Stress Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; SF-36, Medical Outcomes Study Short Form Health Survey; FS-14, Fatigue Scale-14; SCL, Symptom Checklist; PSQI, Pittsburgh Sleep Quality Index.

symptoms of FMS patients were associated with the presence of OA. However, the FS-14 assessment revealed that the presence of OA was not associated with varying degrees of fatigue symptoms in FMS ($P>0.05$), while the PSQI assessment demonstrated no significant alteration in sleep quality between two groups ($P>0.05$).

## The Factors Associated with the Pain Level of Patients with FMS

We investigated the potential factors influencing the pain level of individuals with FMS. The findings revealed significant correlations between presence of OA, disease duration, FIQR, BAI, BDI, PSS, FS-14, SCL scores, PSQI, and pain-VAS scores in all individuals diagnosed with FMS (*Table S1*).

To account for potential confounding factors, a multivariable logistic regression analysis was performed to examine the associations between variables (Table 3). The outcome variable "pain-VAS scores" was preprocessed. To better capture the trend, we categorized the continuous variables and grouped the pain levels into two categories based on the average pain-

**Table 3** Multivariable Logistic Regression Analysis of the Correlations of OA, FS-14 Scores, and Other Variables with Pain-VAS Scores[Δ]

| | Model 1 | | Model 2 | |
|---|---|---|---|---|
| | OR (95% CI) | *P* value | OR (95% CI) | *P* value |
| Disease classification | | | | |
| FMS | *Ref.* | | *Ref.* | |
| FMS with OA | 2.684 (1.341–5.374) | **0.005** | 2.777 (1.377–5.601) | **0.004** |
| FS-14 | 1.152 (1.061–1.250) | **0.001** | 1.145 (1.054–1.243) | **0.001** |
| Duration | 0.968 (0.940–0.996) | **0.027** | 0.968 (0.940–0.997) | **0.028** |
| FIQR | *N/A* | 0.429 | *N/A* | 0.546 |
| PSQI | *N/A* | 0.678 | *N/A* | 0.666 |
| SCL scores | 1.011 (1.005–1.017) | **<0.001** | 1.011 (1.005–1.017) | **<0.001** |
| PSS | 1.037 (1.015–1.059) | **0.001** | 1.039 (1.017–1.061) | **<0.001** |
| BDI | *N/A* | 0.322 | *N/A* | 0.320 |
| BAI | *N/A* | 0.286 | *N/A* | 0.300 |

**Notes:** [Δ] The main outcome variable, pain-VAS scores, was modeled using separate regression models.The presence of statistical significance is indicated by bolded *P* values.Model 1 was adjusted for sex, educational level, employment, daily physical activity, and smoking and drinking as separate variables. Model 2 built upon Model 1 by additionally adjusting for age, BMI, and SF-36.

**Abbreviations**: OR, Odds Ratio; FMS, Fibromyalgia Syndrome; OA, Osteoarthritis; FIQR, The Revised Fibromyalgia Impact Questionnaire; PSQI, Pittsburgh Sleep Quality Index; VAS, Visual Analogue Scale; PSS, Perceived Stress Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; FS-14, Fatigue Scale-14; SCL, Symptom Checklist.

VAS scores of all FMS patients (mean pain-VAS scores=5.40). In the logistic regression test, the variable coding was defined as follows: mild pain level was coded as 0 and severe pain level was coded as 1. Our focus was to investigate the true correlation of the 9 related variables previously identified (with particular emphasis on concurrent OA and degree of fatigue) on the pain level of FMS patients. The findings revealed that in individuals with FMS, the presence of OA was a risk factor for more severe level of pain (OR=2.777, 95% CI=1.377–5.601, *P*=0.004); furthermore, higher degree of fatigue (according to FS-14) were associated with a severe pain level (OR=1.145, 95% CI=1.054–1.243, *P*=0.001).

The analyses also yielded supplementary findings. Some measures related to emotional disorders, such as SCL scores (OR=1.011, 95% CI=1.005–1.017, *P*<0.001) and PSS (OR=1.039, 95% CI=1.017–1.061, *P*<0.001), have also been found to correlate with increased pain levels. Meanwhile, shorter disease duration of FMS was found to correlate with the higher level of pain (OR=0.968, 95% CI=0.940–0.997, *P*=0.028).

## Subgroup Analysis of the Correlation of Co-Existence of OA with Pain Level in FMS

The multivariable logistic regression clearly demonstrated that in addition to OA, duration of the disease, level of fatigue (FS-14), and emotional symptoms (PSS and SCL scores) also were related to pain level in patients with FMS, thus providing a basis for subgroup classification.

The duration of the disease (median=4.00), FS-14 (median=8.00), PSS (median=33.00), and SCL scores (median=150.00) of all FMS patients were used as the basis for categorization of patients. The relation of coexisting OA on FMS was observed more realistically under varying conditions. The results presented in Table 4 indicate that stratification of subgroups by disease duration did not alter the finding of increased pain levels associated with OA; furthermore, among patients exhibiting lower scores on both the PSS and SCL, a significant association was still observed between OA and pain levels.

## The Correlation of Fatigue on Pain in FMS and Interaction of Fatigue and OA

The subsequent investigation focused on exploring the correlation between fatigue and pain in individuals with FMS. RCS analysis was employed to examine a potential association between FS-14 scores and pain-VAS scores. The RCS model (Figure 1A) demonstrated a more consistent linear relationship (*P*-non-linear=0.119) between higher FS-14 scores and elevated risk of severe pain level, with the overall curve indicating statistical significance (*P*-overall=0.008).

Previous subgroup analysis results indicate a plausible association between levels of fatigue, OA, and pain. We determined the distribution frequency of the FS-14 integral among FMS patients, distinguishing them based on the

**Table 4** Subgroup Analysis Examining the Correlations of OA Co-Existence with Pain Level in FMS Patients[Δ]

| | | FMS with OA (all n=62) | OR (95% CI) | *P* values* |
|---|---|---|---|---|
| Duration | | | | |
| | ≥ 4.00 months | 28 | 2.875 (1.059–7.802) | **0.038** |
| | < 4.00 months | 34 | 2.921 (1.058–8.064) | **0.039** |
| FS-14 | | | | |
| | ≥ 8.00 | 32 | 2.304 (0.740–7.174) | 0.150 |
| | < 8.00 | 30 | 2.227 (0.832–5.961) | 0.111 |
| PSS | | | | |
| | ≥ 33.00 | 39 | 1.779 (0.709–4.465) | 0.220 |
| | < 33.00 | 23 | 3.902 (1.389–10.963) | **0.010** |
| SCL scores | | | | |
| | ≥ 150.00 | 33 | 1.969 (0.707–5.481) | 0.195 |
| | < 150.00 | 29 | 6.375 (1.898–21.408) | **0.003** |

**Notes:** [Δ] Based on multivariable logistic regression model 2.* The *P* value indicates the statistical significance of the difference between the groups.The presence of statistical significance is indicated by bolded *P* values.
**Abbreviations**: OR, Odds Ratio; FMS, Fibromyalgia Syndrome; OA, Osteoarthritis; PSS, Perceived Stress Scale; FS-14, Fatigue Scale-14; SCL, Symptom Checklist.

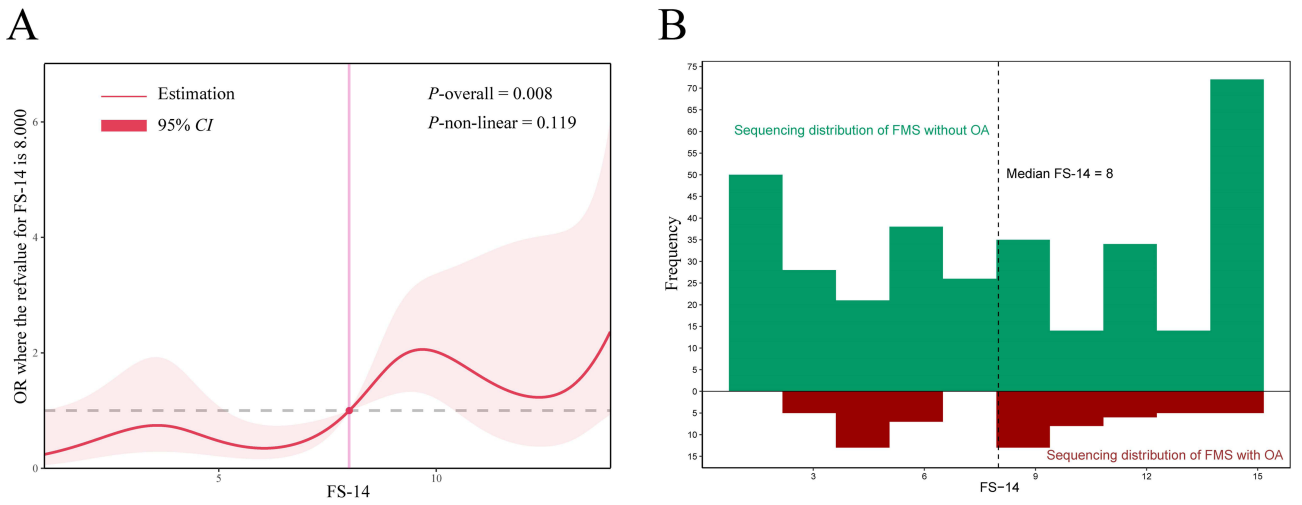


**Figure 1** RCS and frequency distribution histogram based on FS-14 values. (**A**) The results of RCS analysis for modeling FS-14 scores indicate that higher FS-14 scores are associated with an elevated risk of severe pain level. (**B**) Frequency distribution histogram for FS-14 scores. Among patients with FMS categorized based on the presence or absence of concurrent OA, the color "green" represents FMS without OA while the color "red" represents those with FMS accompanied by OA. The histogram illustrates the frequency distribution of FS-14 scores.
**Abbreviations**: FS-14, Fatigue Scale-14; OA, Osteoarthritis; OR, Odds Ratio.

presence or absence of OA (Figure 1B). The results from simultaneous consideration of the difference analysis (FS-14, FMS without OA vs FMS with OA, $P$=0.425) in Table 2 leads us to conclude that the coexistence of OA has no relation with patients' fatigue levels (Supplementary correlation test, r=0.040, $P$=0.431).

The logistic regression results of the main model and subgroup analysis suggest that OA and fatigue, as two independent variables, exhibit a correlation with pain level in FMS. To test this hypothesis, interaction analyses were conducted (*Table S2*) based on the main regression model 2 of Table 3. The results demonstrate that degree of fatigue (as indicated by FS-14 scores) exhibits additive or multiplicative interactions with coexistence of OA, at a statistically level, which jointly correlates with the pain levels in FMS patients.

## The Value of OA and Fatigue in Determining High Pain Levels

We conducted further analysis on the utility of degree of fatigue and OA in assessing pain levels. In our regression model, we separately included the FS-14 scores and OA as predictors, obtaining a combined coefficient Logit($P$), which determined the presence of severe pain level. The differentiation was reported using ROC curves and area under the curve (AUC) index, as shown in Figure 2. The comprehensive coefficient curve had the largest area under it (AUC=0.803, 95% CI=0.759–0.848), followed by the FS-14 scores (AUC=0.783, 95% CI=0.738–0.829), and OA (AUC=0.573, 95% CI=0.517–0.630). Compared with using a single variable, combining both variables resulted in a significantly greater AUC value (all $P_{\text{for DeLong method}} < 0.05$).

When these two variables were combined, the sensitivity value was found to be 84.54%, while the specificity value was calculated at 69.00%, with high accuracy indicated by a Jorden Index of 0.5354. After testing for prediction consistency within our model's judgment ability against original data points, Cohen's kappa coefficient was calculated at 0.534 ($P$<0.001), indicating moderately strong agreement. These data suggest that the combined use of FS-14 scores and OA can serve as an effective assessment tool for predicting severe pain levels in patients with FMS.

# Discussion

There are similarity of joint-related symptoms between the FMS and OA, when these two diseases coexist, the resulting stacking effect was related to the worse overall disease status.[21] Individuals with FMS often experience fatigue;[22] yet, the precise impact of fatigue and OA on systemic symptoms remains poorly understood. Given the absence of recognized biomarkers, treatment for FMS primarily focuses on managing specific disease manifestations such as pain. Therefore, in


https://doi.org/10.2147/IJGM.S503902

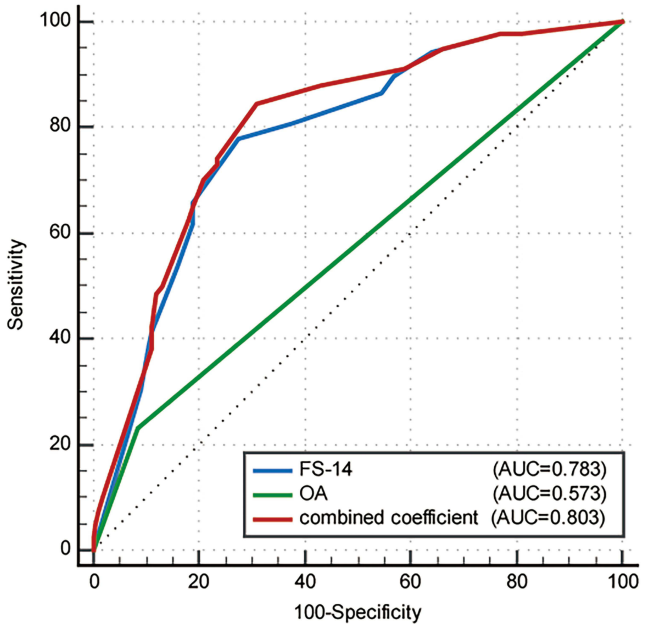


**Figure 2** ROC curve for assessing the risk of severe pain level in patients with FMS. The largest AUC (0.803, 95% CI=0.759–0.848) is observed for the combination of OA with FS-14 scores in evaluating severe pain level risk in patients with FMS.
**Abbreviations**: FS-14, Fatigue Scale-14; OA, Osteoarthritis; AUC, area under the curve.

this study, we aimed to elucidate how OA and fatigue are associated with alterations in pain perception among patients with FMS. The findings potentially provide useful insights to guide future directions of disease research.

FMS and OA are both common chronic musculoskeletal pain disorders that may share similar mechanisms of central nervous sensitization,[23,24] leading to a widespread pain for patients. It is clinical experience that OA is one of frequently comorbid degenerative conditions in FMS patients. In this study, 62 out of 394 FMS patients (15.74%) were found to have concurrent OA, although this percentage should be interpreted with caution owing to limitations of this study such as being conducted at a single center and potential temporal concentration bias. Nonetheless, this finding can provide some reference information. Previous studies have suggested that individuals with FMS experience significantly more pain and fatigue than those with OA alone,[25,26] the systemic symptoms of FMS may add to these burdens.

The findings indicate that patients with FMS exhibit a higher pain level, systemic functional performance, emotional disorders, quality of life, and somatic reactions when co-morbid with OA. It is necessary to explore the relevance between pain experienced in OA and FMS. Our findings shed light significantly elevated pain levels when FMS coexists with OA. This finding emphasizes the pivotal role of OA in the pain level associated with FMS. Furthermore, OA may result in increased financial burden and emotional stress for the patient, leading to anxiety or depression.[27] Conversely, changes in fatigue were less pronounced. We hypothesize that when FMS is involved, patients are already experiencing high levels of fatigue as indicated by their high FS-14 scores, thus approaching a threshold effect. Simultaneously, primary symptoms associated with OA primarily involve knee pain and dysfunction, with less damage to other bodily systems. These findings highlight that the coexistence of OA serves as a key risk factor for worse disease status among individuals with FMS—a notion supported by subsequent regression analyses. Meanwhile, subgroup analysis revealed that the association between OA and pain was no longer evident in individuals with elevated PSS and SCL scores, we suppose high mental stress may obscure the pain response associated with OA. However, further evidence is required to substantiate this potentially interaction.

In the management of FMS, fatigue is a crucial aspect that cannot be overlooked. Degree of fatigue is consistently considered a key indicator in evaluations of disease status in FMS patients.[22] In this study, multi-factor regression analysis revealed a close relationship between the degree of fatigue and patients' pain level, and RCS analysis demonstrated a linear relationship between the fatigue evaluation index FS-14 and pain-VAS. However, when subgroup

analysis was conducted based on fatigue, the impact of OA on pain was no longer evident. We hypothesized that the pain response caused by OA may be influenced by changes in fatigue levels, and the interaction analysis indicated that there were both additive and multiplicative interactions between OA and fatigue. These findings offer complementary explanations and suggest that the combined effect of OA and fatigue relate to pain level in patients with FMS. Additionally, we discovered that the coexistence of OA and high levels of fatigue consistently were associated with a worsened functional state in FMS patients.

Exercise is one of the recommended modalities in the management of FMS.[28] An interaction exists between fatigue and kinesiophobia in patients with FMS,[29] which may be one of the reasons for the challenges associated with treatment of this condition. The presence of OA among FMS patients often poses an even greater impediment to the initiation of exercise in this group,[30] leading to exacerbation of symptoms such as pain. Furthermore, OA has also been linked with central nervous system sensitization, which exacerbates mood disorder symptoms in patients.[31] Therefore, when patients with FMS also have OA, the cycle of "fatigue" and "exercise fear" is further exacerbated. These findings provide a potential explanation for the interaction of OA and fatigue, highlighting the significance of preventing OA and managing fatigue symptoms in FMS patients.

This study employs a multidimensional mode of analysis to provide a comprehensive understanding of the relationship between pain, FMS, OA, and degree of fatigue in FMS patients. However, the subjective nature of reports from patients may introduce potential information bias, as evidenced perhaps by the observed median disease duration of only 4 months. Some factors may have contributed to the relatively short disease duration observed, such as we defined duration as the time since diagnosis and imposed restrictions on the inclusion of patients being administered certain therapies. And we need to be vigilant that some patients may have lacked complete comprehension of questions, leading to the provision of inaccurate answers. Additionally, in the design of this study, the sample size comprised 394 patients with FMS, of whom 62 had OA. Therefore, there may still be potential errors associated with the sample size.

## Conclusions

In summary, we conducted this cross-sectional study to elucidate the interactive effects of OA and degree of fatigue on pain perception in patients with FMS. The findings demonstrate that patients with FMS frequently exhibit comorbid OA and fatigue, and the interaction of these factors collectively associated with the higher pain level.

## Abbreviations

ACR, American College of Rheumatology; AUC, area under the curve; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BMI, Body Mass Index; FS-14, Fatigue Scale-14; FIQR, The Revised Fibromyalgia Impact Questionnaire; FMS, Fibromyalgia Syndrome; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; OA, Osteoarthritis; OR, Odds Ratio; PSS, Perceived Stress Scale; PSQI, Pittsburgh Sleep Quality Index; Q1, first quartile; Q3, third quartile; RCS, Restricted Cubic Spline; SCL-90, Symptom Checklist 90; SD, Standard Deviation; SF-36, Medical Outcomes Study Short Form Health Survey; SSS, Symptom Severity Scale; VAS, Visual Analogue Scale; WPI, Widespread Pain Index.

## Data Sharing Statement

Some, not all, original data may be shown upon request to a limited extent. However, some other data cannot be obtained due to the confidentiality of the patients' personal information. The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Ethics Approval and Consent to Participate

The study was approved by the Clinical Research Ethics Committee of China-Japan Friendship Hospital (2022-KY-079) and registered on ClinicalTrials.gov (NCT05508516) on August 17th, 2022. The study was conducted in accordance with the Declaration of Helsinki. Each patient provided informed consent at the time of investigation to allow use of their clinical records for further scientific reporting.

## Consent for Publication

Written informed consent was obtained from the patients for publication of the research.

## Acknowledgments

The Traditional Chinese Medicine Department of Rheumatism, China-Japan Friendship Hospital provided support with data collection and interpretation, and some of the data analyses were performed with assistance from researchers at the University of Auckland.

## Author Contributions

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

## Funding

This study received funding support from the Chinese Association of Chinese Medicine Youth Reality Seeking Project (2021-QNQS-05).

## Disclosure

The authors declare that they have no competing interests for this work.

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