# International Journal of Medical Arts

Volume 4, Issue 7, July 2022

https://ijma.journals.ekb.eg/

Print ISSN: 2636-4174

Online ISSN: 2682-3780

Available online at Journal Website
https://ijma.journals.ekb.eg/
Main Subject [Rheumatology and Rehabilitation]

## Original Article

# The Prevalence of Fibromyalgia in Patients with Rheumatoid Arthritis and its Impact on Disease Activity, Functional Level, and Psychological Status

**Adel Ibrahim Azzam [1]*, Mohamed Lamlom [2], Ahmed Mohamed Khalifa [2], Hatem Galal Abdallah Ibrahim [1]**

[1] Department of Rheumatology and Rehabilitation, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

[2] Department of Psychiatry, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

**Article information**

**Received:** 25-07-2022

**Accepted:** 29-08-2022

DOI: 10.21608/IJMA.2022.152399.1486

*Corresponding author

**Email:** adelazzam25@yahoo.com

**Citation:** Azzam AI, Lamlom M, Khalifa AM, Ibrahim HGA. The Prevalence of Fibromyalgia in Patients with Rheumatoid Arthritis and its Impact on Disease Activity, Functional Level, and Psychological Status. IJMA 2022 July; 4 [7]: 2514-2521. doi: 10.21608/IJMA. 2022.152399.1486

## ABSTRACT

**Background:** Rheumatoid arthritis [RA] is a type of progressive disease characterised by inflammation in the synovial tissues resulting in deformity and functional impairment. Fibromyalgia [FM] is a well-known comorbidity in RA which may change the physical evaluation and incorrectly affect the degree of RA treatment.

**The Aim of the work:** To evaluate FM in patients with RA and its impact on disease activity, functional, and psychological status.

**Patients and methods:** The study included 1200 patients with RA. Individuals were divided based on their FM status. All patients were assessed clinically and evaluated by the Health Assessment Questionnaire for pain [HAQ-pain], the Multidimensional Assessment of Fatigue [MAF], the Pittsburgh Sleep Quality Index [PSQI], the Beck Depression Inventory-II [BDI-II], and the Modified Health Assessment Questionnaire for functional disability [MHAQ]. The Disease Activity Score with ESR [DAS28-ESR] was used to assess RA disease activity in 28 joints. FM and RA were diagnosed using the criteria of the American College of Rheumatology [ACR].

**Results:** Among our patients with RA, the prevalence of FM was 37%. Patients with FM had an increased proportion of females, were older, had a more prolonged disease duration, and had more protracted morning stiffness than patients without FM. Scores of DAS28 were considerably higher in RA patients with FM in comparison to those with only RA [5.70 ±1.19, 4.48 ± 1.26; $P < 0.001$] respectively. Concurrent FM also had worse HAQ-pain, MHAQ, fatigue, and depression scores, as well as more frequent sleep problems.

**Conclusion:** In patients with RA, coexisting FM was associated with greater activity of the disease and impairments in functional level. FM was linked to higher rates of depression and fatigue, as well as an increased prevalence of sleep problems. The recognition and evaluation of such psychiatric disorders may help patients with RA achieve therapeutic improvement or remission.

**Keywords:** Rheumatoid arthritis; Disease activity score; Fibromyalgia, Depression; Sleep problems.

## INTRODUCTION

Rheumatoid arthritis [RA] is a form of inflammatory illness that affects the synovial lined joints, inducing erosive changes and destruction of bone and cartilage that result in impaired physical function. Extra-articular manifestations are commonly seen in RA patients and can affect most of the body's organs and result in high mortality and morbidity rates [1]. In most regions of the world, the prevalence rate is 1%, with an incidence of 40/100,000 for those fulfilling the 2010 American College of Rheumatology [ACR]/EULAR criteria [2]. Despite strict disease control strategies aiming at remission or low active disease [3], some patients continue to have increased RA disease activity [4].

Fibromyalgia [FM] is a persistently painful disorder that impacts mostly women [5]. In individuals with RA, the prevalence of FM is roughly 21%, with a range of 4.9–52.4 %, compared to 2–8% in the general population [6]. Fibromyalgia may be a coexisting condition or a broad clinical spectrum linked to changes in the central nervous system's pain processing [7]. As a result, non-inflammatory pain pathways in RA may contribute to increased pain sensitivity at both articular and peri-articular locations, indicating enhanced central pain processing and thus an increase in FM prevalence [8].

FM is typically linked to many cognitive and psychological disorders, such as fatigue and depression [9]. Disabilities caused by FM are commonly noted [10], resulting in subsequent impaired physical and mental health [11, 12].

The presence of FM in RA may impact disease evaluation and assessment, resulting in an overestimation of disease severity and subsequent increase in treatment intensity with frequent prescription of unnecessary and costly medical treatments like biologics [13].

## THE AIM OF THE WORK

The goal of this study is to evaluate FM in patients with RA and its relationship to disease activity, functional, and psychological status.

## PATIENTS AND METHODS

Patients were enrolled from outpatient clinics at Al-Azhar University Hospitals' Rheumatology and Rehabilitation department. A total of 1,200 patients were requested to participate in this cross-sectional study from April 2021 to March 2022. To be included in this study, patients had to meet the European League Against Rheumatism/American College of Rheumatology [EULAR/ACR 2010] criteria for RA diagnosis [14].

Exclusion criteria included refusing to sign the informed written consent; the presence of infection detected by clinical or lab work; overlap with other rheumatic disorders; and a history of or recent inflammatory joint disease other than RA [e.g., gout]. Individuals were divided into two groups based on their FM status. Patients in Group 1 had both RA and FM, while patients in Group 2 had RA but no FM.

The RA disease activity in 28 joints was assessed by the Disease Activity Score [DAS28] [15]. FM was diagnosed according to the 1990 ACR classification criteria, which revealed widespread pain as well as axial skeletal pain and the presence of 11 out of 18 tender point sites on digital palpation [16].

The Health Assessment Questionnaire for pain [HAQ] is a visual analogue scale with 0 [no discomfort] and 100 [extreme pain] [17]. Functional abilities were assessed by the Modified Health Assessment Questionnaire [MHAQ]. On a scale of 0 to 3, it asks eight questions on eight different functions [dressing, rising, walking, bathing, bending, lifting a cup, gripping, and getting in and out of a car] [18].

The Beck Depression Inventory-II [BDI-II] is a 21-item questionnaire that has been well-validated for the screening and rating severity of the depressive manifestations. The range from 0 to 13 is considered minor, 14 to 19 is mild, 20 to 28 is moderate, and 29 to 63 is severe [19].

Fatigue was evaluated by the Multidimensional assessment of fatigue [MAF] scale. The MAF addresses four aspects: intensity, distress, interference in daily activities, and frequency and change during the past week [20].

The quality of sleep was assessed by the Pittsburgh Sleep Quality Index [PSQI], which evaluates sleep disruptions in the preceding one-month and contains 19 items. The total score separates "good sleep"[PSQI total score $\leq$ 5] from "poor or worse sleep" [PSQI > 5] [21].

The Research Ethics Committee of the Rheumatology and Rehabilitation Department at Al-Azhar University Hospitals authorized this study, and all patients gave written informed permission before participating. It adheres to the legal principles outlined in the Helsinki Declaration. Because each medical file comprising all enquiries carried a code number, all patient details were kept private.

**Statistical Methodology:** Data were coded and entered using IBM Corp.'s statistical package for the Social Sciences [SPSS] version 26 [Armonk, NY, USA]. In quantitative data, mean, standard deviation, median, minimum, and maximum were used, while frequency [count] and relative frequency [percentage] were used in categorical data. Comparisons between quantitative variables were made using the non-parametric Mann-Whitney test. A Chi-square test was performed for comparing categorical data. An exact test was used instead when the expected frequency is less than 5. p values of less than 0.05 were considered statistically significant.

## RESULTS

Of 1200 individuals with RA, 444 [37.0 %] met the criteria for FM diagnosis. Table 1 shows the demographic and clinical features related to the study participants. In the group with RA and FM, the average age was greater, and female sex were more abundant. Concurrent FM patients had a protracted duration of the RA illness, were widowed or divorced, had more joint erosions, and had anti-cyclic citrullinated peptide [anti-CCP] antibodies than RA-only patients. Regarding the current use of methotrexate and steroid medications, no statistically significant difference was found between RA patients with and without FM.

This study revealed a statistically significant difference in the DAS28 score between the RA groups. The mean DAS28 was greater in the RA with FM group than in the RA only group [Table 2]. The components of the DAS28 [ESR, tender and swollen count of the joints] were statistically higher in the group of RA with FM [$p<0.05$]. Furthermore, a high incidence of active RA disease was more common in the concurrent FM group [70.3 %], with a relatively low incidence of remission and low disease activity [1.8% and 0.9%], respectively. The RA with FM group had greater HAQ-pain and MHAQ functional impairment scores than the other groups.

There was also a statistically significant difference between the two groups regarding sleep score, fatigue, and depression [Table 3]. The PASQI score revealed a statistically significant difference between RA patients who had FM and those who did not. Poor sleep was more frequently encountered by RA with FM [87.4 %] than in the RA only group [52.4 %] [$p<0.05$]. The MAF fatigue rating was greater in RA patients with concurrent FM than in the RA only group. The reported frequency of depressive symptoms among RA with FM patients attracted attention since all RA with concurrent FM [100%] were found to have depressive symptoms of varying severity.

**Table [1]:** Clinical and demographic data of the studied patients

| | | RA+FM [n:444] | RA only [n:756] | P value |
|---|---|---|---|---|
| **Age in years, mean ± SD** | | 40.19 ± 7.46 [20-49] | 37.29 ± 9.34 [20-50] | **< 0.001** |
| **Disease duration in years, mean ± SD** | | 4.63± 4.00 [0.20-20] | 4.18 ± 3.60 [0.17-20] | 0.037 |
| **Sex** | Males | 12 [2.7%] | 84 [11.1%] | **< 0.001** |
| | Females | 432 [97.3%] | 672 [88.9%] | |
| **Marital status** | Married | 376 [84.7%] | 640 [84.7%] | **0.001** |
| | Widow | 32 [7.2%] | 32 [4.2%] | |
| | Divorced | 20 [4.5%] | 20 [2.6%] | |
| | Single | 16 [3.6%] | 64 [8.5%] | |
| **Current MTX use** | | 344 [77.5%] | 580 [76.7%] | 0.763 |
| **Current use of GC** | | 248 [55.9%] | 424 [56.1%] | 0.939 |
| **Anti CCP positive** | | 340 [76.6%] | 496 [65.6%] | **< 0.001** |
| **Larsen score, mean ± SD** | | 11.42 ± 13.29 | 9.90 ± 13.12 | **< 0.001** |
| **Morning stiffness for≥60 minutes, mean ± SD** | | 59.73 ± 50.15 | 24.55 ± 37.07 | **< 0.001** |

MTX: Methotrexate; GC: Glucocorticoids; CCP: cyclic citrullinated peptide

**Table [2]:** The assessment tools [DAS28, HAQ-pain and MHAQ] in the studied groups

| | | RA+FM [n:444] | RA only [n:756] | P value |
|---|---|---|---|---|
| **DAS28, mean ± SD** | | 5.70 ± 1.19 | 4.48 ± 1.26 | < **0.001** |
| **ESR, mean ± SD** | | 51.46 ± 26.80 | 44.20 ± 23.30 | < **0.001** |
| **Swollen joints, mean ± SD** | | 8.42 ± 6.04 | 4.15 ± 4.64 | < **0.001** |
| **Tender joints, mean ± SD** | | 11.83 ± 7.11 | 5.69 ± 5.03 | < **0.001** |
| **DAS28** | High [DAS28>5.1] | 312 [70.3%] | 272 [36.0%] | < **0.001** |
| | Moderate [DAS28>3.2 to≤5.1] | 120 [27.0%] | 320 [42.3%] | |
| | Low [DAS28≤3.2] | 4 [0.9%] | 108 [14.3%] | |
| | Remission [DAS28<2.6] | 8 [1.8%] | 56 [7.4%] | |
| **HAQ-pain score, mean ± SD** | | 70.00 ± 17.42 | 32.70 ± 19.92 | < **0.001** |
| **MHAQ score, mean ± SD** | | 1.39 ± 0.75 | 0.60 ± 0.61 | < **0.001** |

DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate HAQ: Health Assessment Questionnaire; MHAQ: Modified Health Assessment Questionnaire.

**Table [3]:** Frequency of symptomatology associated with FM in both groups

| | | RA+FM [n:444] | RA only [n:756] | P value |
|---|---|---|---|---|
| **Sleep quality** | Good sleep<br>Poor sleep | 56 [12.6%]<br>388 [87.4%] | 360 [47.6%]<br>396 [52.4%] | < **0.001** |
| **Fatigue, MAF** | No. (%)<br>MAF, mean ± SD | 420 [94.6%]<br>30.61 ± 10.85 | 564 [74.6%]<br>19.86 ± 13.53 | < **0.001** |
| **Depression** | No. (%)<br>BDI-II, mean ± SD | 444 [100.0%]<br>22.13 ± 10.84 | 708 [93.7%]<br>12.71 ± 8.76 | < **0.001** |

MAF: multidimensional –assessment of fatigue; BDI-II: The Beck Depression Inventory-II

## DISCUSSION

In the current research, we found an increased frequency of FM among RA patients. The presence of FM was linked to higher RA disease activity with worsened functional and quality of life scores.

Globally, the prevalence of FM has been estimated to be between 2.2% and 6.6% [22–24]. However, its prevalence among RA patients ranged between 6.6% and 22.4% [25–27].

The FM frequency may vary depending on the diagnostic criteria. A study by **Vincent *et al.*** [28] found a 1.1% prevalence of FM using 1990 criteria; however, a random sampling from the same patient group indicated a frequency of 6.36% when considering 2010 ACR criteria. **Wolfe *et al.*** [29] reported a 21.1% FM incidence in RA patients utilizing the modified 2010 ACR FM diagnostic criteria.

In this study, FM was observed in 37% of RA patients, which was in accordance with the previously reported data. In line with our findings, **Bazzichi *et al.*** [6] showed that FM prevalence in RA patients is about 21%, with a range of 4.9–52.4%. In another study, **Klçarslan *et al.*** [30] found that FM frequency was higher in patients with RA [35.1%] compared to the control group [19.5%].

As opposed to the previous research, RA patients with FM had an increased mean age, which was consistent with **Ranzolin *et al.*** [31]. However, as anticipated from fibromyalgia epidemiological studies, the group with concurrent FM had a higher proportion of women [5, 22, 32].

Our findings reveal that FM is associated with a protracted RA disease course and a higher HAQ-pain score. According to **Shresher *et al.*** [33], RA patients with FM have a longer disease duration and higher pain evaluated by VAS than patients without FM. The higher HAQ-pain score associated with FM may be attributed to the systemic inflammatory response and the increased levels of the

mediators of inflammation such as tumor necrosis factor [TNF] and IL-6, which are implicated in central pain processing and increased generalized sensitivity and persistent pain.

Our findings demonstrated that FM was associated with prolonged morning stiffness, articular erosions, and positive anti-CCP. Several factors are implicated in the prolonged morning stiffness that is commonly experienced in RA patients, such as pain, fatigue, and sleep disturbances, all of which are prevalent in FM patients [31].

Our study revealed that the DAS28 mean score in the concomitant FM group was higher than in patients with isolated RA [5.7 vs 4.48], indicating that the coexistence of FM is associated with an increase in the RA disease activity. The DAS28 variables [swollen, tender count of the affected joints, and ESR] were also shown to be considerably different in the two groups. This was supported by a number of studies [25, 27, 34, 35].

In our study, 70.3 % of RA patients with concurrent FM had high disease activity [DAS28 > 5.1], whereas only 1.8 % were in remission [DAS28<2.6]. This was in line with the findings of **Durán *et al.*** [36], who found that RA patients with FM had more aggressive disease activity and did not achieve remission than those who had only RA.

Long-term RA is known to cause functional impairment due to joint damage; however, FM associated with RA has been shown to influence functional level, alter QoL, and impact MHAQ scores [22,31,32,35,37].

Confirming the findings of prior research [22,31], we found an association between FM and functional impairment. The mean MHAQ score for our RA patients with FM was 1.39, compared to 0.60 for individuals with isolated RA. **Strömbeck *et al.*** [38] demonstrated that patients with FM had more functional impairment and poorer QoL scores than RA patients. Although FM does not cause joint injury or deformity, it may have a greater impact on QoL than RA [35].

Depression is one of the most frequent comorbidities in the FM population, accounting for roughly 63 % [39]. Depression was found to be present in 100% of the FM group in this research. Given the high frequency of depression among FM patients, it is plausible to speculate that depression may have a role in the association between pain and physical function, indicating that there is a bidirectional link between FM and depression [40].

Our findings revealed that poor sleep and worsened fatigue scores were common in the RA with concurrent FM group.

**Nicassio *et al.*** [41] argued that certain parameters, such as disease severity, persistent pain, and exaggerated inflammatory response, directly lead to the development of fatigue, triggering other contributing factors such as changes in mood and lower quality of sleep. In our study, we noted that 94.6 % of concomitant FM patients reported fatigue, with a mean score of 30.61, which was substantially greater than that in patients without FM.

Owing to the high frequency of depression and fatigue in our RA patients with FM, as well as the increased frequency of RA disease activity, sleep quality was found to be altered among these patients. This is confirmed by the findings of **Rezaei *et al.*** [42] who stated that active disease, chronic fatigue, depression, and severe pain occur more commonly in RA patients and can lead to sleep problems. Furthermore, **Westhovens *et al.*** [43] found a strong correlation between inadequate disease management in RA patients and a decline in sleep quality.

It has been shown that patients with RA and FM have different central cytokine profiles, which may reflect the disease pattern. Increased IL-8 levels in cerebrospinal fluid [CSF] have been linked to fibromyalgia's dysfunctional sympathetically mediated pain. Higher levels of IL-1 have been linked to RA, which might also contribute to the inflammatory, prostaglandin-associated pain [44].

This study has some noteworthy points. We recruited a high number of RA patients over the course of a year in the context of clinical practice rather than a sample chosen using strict selection criteria to ensure that our findings were as generalizable as possible. Using a series of standardized questionnaires, we investigated a wide range of possible correlates of FM and its associated conditions on RA, with a focus on disease activity and functional limitations. Finally, the study's design and analysis were

influenced by the rigorous collaboration of a rheumatologist and a psychiatrist, resulting in a multidisciplinary approach to such a potential RA comorbidity.

This study has certain limitations. The first is the absence of a healthy control group with which to compare results. Second, the current results need to be confirmed by longitudinal investigations in order to determine how treatments could affect the underlying FM and subsequently impact RA disease activity status.

**Conclusions:** FM is highly prevalent in RA patients. Our study illustrates the impact of FM on RA disease activity and functional status. The findings of this study showed that the presence of FM is associated with higher DAS28 scores, MHAQ, and established that worse depression, fatigue, and sleep scores in RA patients were also highly associated with FM. Thus, Concomitant FM should be noted while assessing and managing individuals with RA in order to avoid overtreatment and achieve effective disease control.

**Availability of data and material:** The data will be available upon reasonable request.

**Competing interests:** The authors declare that they have no competing interests.

**Funding:** The authors received no financial support for the research, authorship, and/or publication of this article.

**Acknowledgements:** Not applicable

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Print ISSN: 2636-4174
Online ISSN: 2682-3780