

## Original Research Article

# Prevalence and clinical predictors of fibromyalgia in patients with rheumatoid arthritis

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## ABSTRACT

**Background:** Fibromyalgia (FM) is a common disorder in patients with rheumatoid arthritis (RA) and contributes to the inflation of disease activity scores because of a high symptom similarity. Objective of the study was to estimate the prevalence of FM in patients with RA and to identify clinical predictors.

**Methods:** A total of 150 RA patients were enrolled in this cross-sectional study. FM status was determined by WPI and SSS. Sociodemographic, clinical, laboratory and disease activity parameters were evaluated.

**Results:** The prevalence of fibromyalgia in patients with RA was 24%. The participants had a mean age of 52.02±12.13 years and were predominantly female at an 81.3% rate. Patients with both RA and FM presented with more swollen joint count, higher patient VAS scores, DAS28 scores, CDAI scores and SDAI compared to those without FM. Depression and fatigue were more common in FM-positive patients.

**Conclusions:** Nearly one fourth of patients with RA had FM diagnosed concurrently. Psychological and subjective disease components were strongly correlated with FM in this study, indicating that higher disease activity scores may not always represent an active inflammation.

**Keywords:** Rheumatoid arthritis, Fibromyalgia, DAS28, Depression, Disease activity

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by persistent synovitis, progressive joint destruction and significant functional disability. It occurs in around 0.5–1% of the population and is more frequent among women, especially middle-aged women. Chronic inflammation leads to articular destruction and cardiovascular and systemic

comorbidities. Early treat-to-target strategies have revolutionized disease outcome but optimal treatment still relies on appropriate assessment of disease activity.<sup>1,2</sup> Using composite disease activity measures, such as the disease activity score in 28 joints (DAS28) and clinical disease activity index (CDAI), simplified disease activity index (SDAI) for RA patients can help evaluate disease activity. TJC, SJC and patient global assessments are among these measures. These instruments, are however

subjective and might be biased by non-inflammatory causes even if they are easy to administer and highly validated.<sup>3,4</sup> Here is where the story has clinical implications. It's not like RA is operating in a vacuum." The overlap of both of them: both are overlapping pain syndromes, with FM being the most common. Introduction Fibromyalgia is a pain syndrome of long (chronic) duration character`ed by chronic widespread musculoskeletal pain, fatigue, sleep disturbances, cognitive dysfunction and increased pain sensitivity. Different from RA, fibromyalgia is not a peripheral inflammation disease but related to central pain amplification mechanisms.<sup>5,6</sup> Comorbidities of fibromyalgia in RA patients are clinically and therapeutically challenging. Composite RA activity scores contain tender joint count and patient global assessment, but patients with concomitant fibromyalgia (FM) may thus display disproportionately high disease activity scores despite normal inflammation. In other words, high DAS28 may be suggestive of central sensitization instead of the presence of active synovitis. This is an important differentiation, because it affects management decisions, altering the threshold for attempting biologic agents.<sup>7</sup> The prevalence of FM in patients with RA has been reported to vary greatly (15-30%) and is significantly higher than that observed in the general population. The prevalence of female, higher TJC, fatigue and psychological comorbidities such as depression is consistently associated to this overlap syndrome.<sup>8</sup> Furthermore, RA patients with prevalent fibromyalgia commonly describe more disability and worse health status than subjects without concomitant FM. What this actually tells us is that not all high disease activity scores equate with uncontrolled inflammation. Some represent amplified pain perception. Failing to appreciate this may lead to physicians to add immunosuppression empirically, and place patients at higher risk of harm while failing to treat the real underlying etiology of symptoms. Although more importance is now being attached to this problem, regional data are still scarce in South-Asian region. Sociocultural determinants, health-system accessibility and psychosocial factors can condition symptom reporting and perception of illness. Therefore, it is important to know the prevalence and predictors of FM in RA in the local population to give rational patient-applied care. The objective of this study is to detect the prevalence of FM in our patient population with RA, and identify clinical and laboratory predictors of its prevalence. The differentiation between inflammatory activity and central pain amplification will be addressed in order to refine the interpretation of composite disease activity indices, thereby contributing to a better informed clinical decision making process in the RA care.

## **METHODS**

This cross-sectional analytical study was done in the Department of Medicine, Chittagong Medical College Hospital, Chattogram, Bangladesh from August 2022 to July 2023. During the study period, 150 consecutive cases of patients with a confirmed diagnosis of RA were

included. The goal of the study was to examine the association of psychological factors and overall symptom burden with composite disease activity indices in patients with RA.

### ***Inclusion criteria***

Adult patients ( $\geq 18$  years), confirmed diagnosis of RA, and patients with willingness to take part in the study were included.

### ***Exclusion criteria***

Patients with other diagnosed connective tissue diseases, severe uncontrolled systemic illness, and with incomplete clinical or laboratory data were excluded.

### ***Data collection procedure***

Data were collected by interview, reviewing the medical records, and physical and laboratory investigations (mentioned below) using a structured questionnaire containing all the variables of interest. After selecting eligible participants, the researcher took a brief history and conducted a clinical examination, per the study data collection form. The history included components of the DAS28 score, such as how the patient thinks they are doing on a scale of 0 to 100 (patient global assessment). The clinical examination entailed palpation of the joints for swelling and tenderness as per the DAS28 score and assessment for jaundice, liver size, and splenomegaly. The participant's medical record and file were reviewed to obtain information on disease duration, medication and duration of treatment, and previous liver function tests. This information was then recorded in the data collection form.

### ***Statistical analysis***

All statistical data were processed with the aid of computer software. Quantitative variables were summarized using mean $\pm$ SD, while categorical variables were described as frequency and percentage. RA patients were compared between those with and without fibromyalgia. Continuous variables were compared using independent sample t-test. Categorical variant were compared by Chi-square test. A p value of less than 0.05 was taken to indicate statistical significance.

### ***Ethical implication***

The study was conducted after getting approvals from the ethical and review committee of Chittagong Medical College. Participation was voluntary. Consent was obtained after the attendants or caregivers briefly explained the study. It was clear to them that they were free to participate or refuse any part of the study. Privacy, confidentiality and anonymity were maintained.

**RESULTS**

A total of 150 patients with rheumatoid arthritis were included in the analysis. Among them, 36 patients (24%) had coexisting fibromyalgia (RA±FM), while 114 patients (76%) had RA without fibromyalgia.

The mean age of the study subjects according to the entire population was average 52.02±12.13 years that represents a group mostly in stages middle life cycle. A strong female preponderance was noted at 122 (81.3%) versus 28 males (18.7%), in line with the known gender distribution of RA. The mean disease duration was 6.84±4.91 years, indicating that the majority of patients were not early RA but had established disease (Table 1).

**Table 1: Sociodemographic characteristics of study participants (n=150).**

Variables	Mean±SD/N (%)
Age (years)	52.02±12.13
Female	122 (81.3%)
Male	28 (18.7%)
Disease duration (years)	6.84±4.91

From this screening, FM was diagnosed in 36 patients (24%), and FM criteria were not met in 114 patients (76%). This data demonstrates a large "burden of fibromyalgia" in patients with RA, in that almost one-quarter of them also have FM (Table 2).

**Table 2: Prevalence of fibromyalgia among RA patients.**

Fibromyalgia status	Frequency (n)	Percentage (%)
RA without FM	114	76
RA with FM	36	24

Mean age was slightly higher in the RA with FM subjects (53.78 years SD 12.92) compared to those without FM (51.46 years, SD 11.87); however the difference was not statistically significant (p=0.31). There was a greater female-to-male ratio in the RA with FM group (88.9%) compared to that without (78.9%); however, even this difference did not achieve statistical significance (p=0.18).

Time of disease evolution was higher in RA with FM (7.78±5.42 years) than in RA without FM (6.51±4.73 years); this however, was not significant (p=0.22) (Table 3).

The TJC was significantly higher in patients with RA + FM (13.81±5.27) than those with RA alone (7.62±4.38) and the difference showed highly significant difference of p<0.001. On the other hand, swollen joint count (SJC) were not different between them (6.41±3.89 versus 5.94±3.72; p=0.48) (Table 4).

**Table 3: Comparison of demographic variables between RA with FM and RA without FM.**

Variables	RA without FM (n=114)	RA with FM (n=36)	P value
Age (years)	51.46±11.87	53.78±12.92	0.31
Female (%)	90 (78.9)	32 (88.9)	0.18
Disease duration (years)	6.51±4.73	7.78±5.42	0.22

**Table 4: Comparison of joint counts between groups.**

Variable	RA without FM	RA with FM	P value
Tender joint count	7.62±4.38	13.81±5.27	<0.001
Swollen joint count	5.94±3.72	6.41±3.89	0.48

DAS28 was significantly greater in the RA with FM group (5.23±1.11) versus the RA without FM group (3.89±1.08), which difference was statistically significant at high level (p<0.001). CDAI was also significantly higher in RA with FM (27.81±9.65) than in those without FM 16.42±8.34 (p<0.001). SDAI scores were also higher in the RA with FM group (30.94±10.12) than the RA without FM group (18.77±9.02), with p<0.001, respectively (Table 5).

**Table 5: Disease activity scores in RA patients with and without fibromyalgia.**

Variable	RA without FM	RA with FM	P value
DAS28	3.89±1.08	5.23±1.11	<0.001
CDAI	16.42±8.34	27.81±9.65	<0.001
SDAI	18.77±9.02	30.94±10.12	<0.001

ESR for RA was 38.26±18.14 mm/hour if FM was not present and there were no significant differences observed in this level when compared to ESR of RA with FM (40.81±17.92 mm/hour) which was found to be p=0.46). CRP was 11.84±6.23 mg/l for RA without FM and 12.39±6.71 mg/l for RA with FM (p=0.63) (Table 6).

**Table 6: Laboratory parameters in RA patients with and without fibromyalgia.**

Variable	RA without FM	RA with FM	P value
ESR (mm/hour)	38.26±18.14	40.81±17.92	0.46
CRP (mg/l)	11.84±6.23	12.39±6.71	0.63

Depression occurred in 58.3% of RA with FM patients, and in 29.8% of those without RA (p=0.003). Fatigue was found in 77.8% of RA with FM compared to 43.0% in RA without FM (p<0.001). Patient visual analog scale (VAS)

scores were significantly increased in RA and FM (7.91±1.42) in comparison to RA alone, p<0.001.

**Table 7: Psychological and symptom variables.**

Variable	RA without FM	RA with FM	P value
<b>Depression (%)</b>	34 (29.8)	21 (58.3)	0.003
<b>Fatigue (%)</b>	49 (43.0)	28 (77.8)	<0.001
<b>Patient VAS</b>	5.12±1.88	7.91±1.42	<0.001

**DISCUSSION**

The objective of this study was to investigate the frequency and clinical predictors of FM in RA, careful comparison being made between demographic, clinical, laboratory, and psychological variables. The findings of increased subjective burden of the disease, in terms of self-perceived health and function and RF activity without concomitant up modulation of the objective measures of inflammation support this. The 24% here is consistent with the known rates of 15–30% reported for RA populations.<sup>7-9</sup> This large amount of overlap gives further evidence to the suggestion that chronic inflammatory pain may act as a trigger in susceptible individuals leading to these central sensitization syndromes. Nociceptive input from the inflamed synovium could alter central pain processing pathways making individuals more susceptible to fibromyalgia.<sup>6</sup> Regarding baseline characteristics, the high female proportion (81.3%) and mean age (52.02 ± 12.13 years) are in line with international RA epidemiology.<sup>12</sup> Patients with RA with and in absence FM did not differ significantly by age (53.78±12.92 versus 51.46±11.87 years; p=0.31), female percentage (88.9% versus 78.9%; p=0.18) and disease duration (7.78±5.42 versus 6.51±4.73 years; p=0.22). A similar finding has also been observed in other cohorts, where demographic factors were not independent predictors for the presence of fibromyalgia.<sup>8</sup> This indicates that FM in patients with RA is not merely an age- or disease duration-related phenomenon. Comparison of joint counts yields a more clinically informative pattern. TJC was significantly higher in RA with FM as compared to RA alone 14.81±5.27 versus 7.62±4.38 respectively with high significance p<0.001.<sup>2</sup> SJC did not differ between cases and controls (6.41±3.89 versus 5.94±3.72; p=0.48). This dichotomy reflects results from Pollard et al who reported a disproportionately high TJC in fibromyalgia RA patients compared to the presence of objective signs of inflammation.<sup>7</sup> As TJC is a reflection of pain experience and not synovial swelling, it becomes particularly exaggerated in conditions of central sensitization.<sup>6</sup> The above absence of significant difference in SJC support that Inflammatory burden is equal despite different pain reporting. Composite disease activity scores confirm this disparity even more starkly. DAS28 was significantly higher in RA coexisting with FM (5.23±1.11) than in RA without FM (3.89±1.08), p<0.001. CDAI (27.81±9.65 versus 16.42±8.34; p<0.001) and SDAI (30.94±10.12 versus 18.77±9.02; p<0.001) were also

significantly increased in the FM group. These findings are in line with reports showing that fibromyalgia syndrome inflates composite RA disease activity scores.<sup>9,10</sup> It is worth noting that DAS28 includes tender joint count and patient's global, and that CDAI, SDAI are also predominantly subjective.<sup>3,4</sup> Thus, increased scores in the FM group represent probably rather more sensitized pain than an increase of inflammatory activity. Laboratory findings provide crucial context. ESR levels were 40.81±17.92 mm/hour in RA with FM and 38.26±18.14 mm/hour in RA without FM (p=0.46). CRP levels were also comparable (12.39±6.71 mg/l versus 11.84±6.23 mg/l; p=0.63). These p values are not significant indicating that there was no meaningful difference in inflammatory burden between groups. A dissociation between subjective disease scores and inflammatory markers has been reported earlier.<sup>7,8</sup> Aletaha et al also pointed out that less weight is given to acute phase reactants in composite indices compared with joint counts and patient report.<sup>4</sup> Inflammatory markers did not correlate with the stark variance observed within composite scores in this sample. Psychological and symptom pertinent factors showed high correlations with fibromyalgia. Depression was found in 58.3% of RA with FM as opposed to 29.8% of RA without FM (p=0.003). Fatigue was described by 77.8% versus 43.0%, respectively (p<0.001). These results correspond to the concept of a multi-dimensional nature of fibromyalgia as proposed by Wolfe et al and Clauw where mood and fatigue disturbances play key roles.<sup>5</sup> Depression has also been correlated with heightened perception of disease activity in RA independently.<sup>11</sup> The greater proportion of FM-positive patients reporting depression and fatigue probably explains this observed increased reporting of symptoms. Patient's visual analog scale scores were significantly higher in RA (FM+) group with respect to FM-RAs (7.91±1.42 and 5.12±1.88, respectively, p<0.001). As patient VAS is included in the directly entering variables of DAS28, CDAI and SDAI, its elevation has a significant impact on disease activity categories. Coury et al found similar result and showed that fibromyalgic RA patient are likely to be categorized into higher levels of disease activity despite the comparable objective sign of inflammation.<sup>10</sup> These results are quite relevant from a clinical point of view. The treat-to-target approach focusses on remission, or at least low disease activity according to a composite index.<sup>1</sup> However, in the presence of co-morbid fibromyalgia, advanced scores may lead to inappropriate step-up immunosuppression. Pollard et al reported that fibromyalgic RA subjects are treated more aggressively, even though inflammatory profiles were similar.<sup>7</sup> Identifying fibromyalgia as an additional diagnosis can avoid over-medicalisation and promote a multidisciplinary treatment plan, also focusing on psychological and pain issues.

**CONCLUSION**

FM was detected in almost one out of four (24%) patients with rheumatoid arthritis, pointing that a clinically relevant

parallelism exists between the diseases. Patients with concurrent FM had significantly higher TJC, DAS28, CDAI and SDAI scores as well as worse psychological status (depression and fatigue) but similar levels of ESR and CRP. These findings indicate that high disease activity scores in this subset are substantially due to face-value subjective exaggeration rather than active inflammation. Close assessment for FM is important with RA patients to avoid overestimating disease activity and allow for a more holistic approach to treatment.

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