Disease Activity Indices In Patients Of Rheumatoid Arthritis With Concomitant Fibromyalgia

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KEYWORDS

Rheumatoid Arthritis, Fibromyalgia, Disease Activity Score 28 (DAS28), Clinical Disease Activity Index (CDAI), Inflammatory Markers, Anti-CCP, Disease Modifying Antirheumatic Drugs (DMARDs).

ABSTRACT:

Background: Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by joint inflammation and progressive damage. Fibromyalgia syndrome (FMS), a condition marked by widespread pain and fatigue, frequently coexists with RA, complicating disease assessment and management. This study aimed to evaluate the impact of fibromyalgia on disease activity in RA patients, focusing on the Disease Activity Score 28 (DAS28) and Clinical Disease Activity Index (CDAI). ***Methods:*** A total of 50 RA patients diagnosed according to the 2010 American College of Rheumatology (ACR) criteria were enrolled in this cross-sectional study. Patients were divided into two groups: Group I (RA with fibromyalgia) and Group II (RA without fibromyalgia). Socio-demographic, clinical, and disease activity data were collected. Disease activity was assessed using DAS28 and CDAI, while inflammatory markers (ESR, CRP) and serological tests (RF, anti-CCP) were also measured. ***Results:*** The mean age of participants was 48.04 ± 13.78 years. Fibromyalgia was present in 24% of RA patients. No significant differences were observed in inflammatory markers (ESR, CRP) or serological tests (RF, anti-CCP) between the two groups. However, disease activity indices were significantly higher in patients with fibromyalgia. All patients in Group I had high DAS28 scores (>5.1), with a mean of 7.22 ± 0.81, compared to 65.8% in Group II (mean DAS28 5.77 ± 1.32). CDAI scores were also significantly higher in Group I (43.5 ± 6.14) compared to Group II (25.79 ± 15.67). ***Conclusion:*** Our findings suggest that the presence of fibromyalgia significantly increases disease activity in RA patients, as reflected by higher DAS28 and CDAI scores. These results highlight the importance of considering fibromyalgia when assessing disease activity in RA, as it may lead to an overestimation of disease severity and impact treatment decisions.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation, pain, and joint destruction, primarily affecting peripheral joints. It causes significant disability, morbidity, and premature mortality, with a prevalence of 0.5% to 1% in the population, mostly in middle-aged individuals, especially women [1,2]. Key features of RA include persistent symmetric polyarthritis and extra-articular manifestations, complicating management. Optimal care requires an integrated approach with pharmacological therapies like DMARDs, NSAIDs, analgesics, and corticosteroids [3]. Fibromyalgia syndrome (FMS) commonly co-occurs with RA, characterized by widespread pain, fatigue, sleep issues, and cognitive dysfunction, affecting 2-8% of the general population [4]. In RA patients, FMS complicates disease management due to overlapping symptoms like pain, fatigue, and stiffness [5]. Diagnosing and managing RA with FMS is challenging as their symptoms often overlap, making it hard to differentiate between RA activity and FMS symptoms [6]. FMS is reported in 11-30% of RA patients, with evidence suggesting it may worsen disease activity and negatively affect outcomes [7,8].

The pathogenesis of fibromyalgia syndrome (FMS) in rheumatoid arthritis (RA) patients is not fully understood, but studies indicate a significant inflammatory component. Elevated inflammatory cytokines in plasma and cerebrospinal fluid support the role of neuroinflammation and systemic inflammation in FMS development [9,10]. Additionally, central sensitization, where the central nervous system becomes more sensitive to pain, is common in both RA and FMS, complicating disease activity differentiation [11].

Diagnosing Fibromyalgia Syndrome (FMS) in Rheumatoid Arthritis (RA) patients usually requires the American College of Rheumatology (ACR) criteria, evaluating tender points and symptom severity [12]. However, these criteria can pose challenges in clinical practice, prompting the creation of alternative diagnostic tools like the Fibromyalgia Rapid Screening Tool (FiRST), known for its high sensitivity and specificity [13].

Several studies have explored the effects of fibromyalgia (FMS) on disease activity in rheumatoid arthritis (RA) patients. One study showed that FMS significantly impacted the Disease Activity Score in 28 joints (DAS28) and Clinical Disease Activity Index (CDAI), leading to higher scores in RA patients with FMS [14]. Another analysis found that FMS was an independent predictor of elevated DAS28 scores in RA patients, even after adjusting for other markers [7]. Additionally, RA patients with fibromyalgia had notably worse functional outcomes and higher disease activity scores, regardless of traditional RA markers [15].

Considering the significant impact of fibromyalgia syndrome (FMS) on rheumatoid arthritis (RA), it is imperative to further investigate the relationship between these conditions. This study seeks to examine the extent to which the presence of FMS affects RA disease activity, focusing on clinical outcomes and disease evaluation using the Disease Activity Score 28 (DAS28) and Clinical Disease Activity Index (CDAI) scores. The findings will provide crucial insights for managing RA patients with fibromyalgia, emphasising the need to consider fibromyalgia in RA assessments.

MATERIALS AND METHODS

Study settings and population: This hospital-based observational study assessed the prevalence of fibromyalgia among rheumatoid arthritis (RA) patients and examined associated clinical and socio-demographic characteristics. Conducted at Chittagong Medical College Hospital (CMCH) in Chittagong, participants included those admitted or visiting the outpatient department (OPD) and Rheumatology Clinic. Valuable data was collected over 10 months, from February to November 2018, enhancing our understanding of this crucial issue. The sample size calculation was based on an estimated fibromyalgia prevalence of 17% to 20% among rheumatoid arthritis (RA) patients. Using the formula $n = (z^2 \cdot p \cdot q)/e^2$, the required sample size was approximately 154 participants. However, due to time and resource constraints, a convenience sample of 50 RA patients was selected. Additionally,

purposive sampling identified the study participants. The study population includes all patients admitted to or visiting the Outpatient Department (OPD) or Rheumatology Clinic who met the American College of Rheumatology (ACR) 2010 diagnostic criteria for rheumatoid arthritis. Inclusion criteria included patients diagnosed with rheumatoid arthritis (RA) according to the ACR 2010 criteria. Exclusion criteria involved patients with other rheumatological disorders, such as systemic lupus erythematosus (SLE), systemic sclerosis (SSC), mixed connective tissue disease (MCTD), and those who did not provide written informed consent to participate in the study. **Study Procedure:** Patients were divided into two groups: Group I (RA with fibromyalgia) and Group II (RA without fibromyalgia). Fibromyalgia was diagnosed per the 2016 revision of the fibromyalgia diagnostic criteria. Depression and cognition were assessed using the Patient Health Questionnaire (PHQ-9) and the Mini-Mental State Examination (MMSE), respectively. A PHQ-9 score above 5 classified patients as depressed; an MMSE score below 24 indicated mild cognitive impairment. The Disease Activity Score (DAS28) and Clinical Disease Activity Index (CDAI) scores were compared between the groups. Socio-demographic and clinical characteristics were analyzed to identify predictive factors for fibromyalgia in RA patients through multivariate analysis. **Data Analysis:** Data were analyzed using SPSS version 26. Descriptive statistics analysed qualitative variables like age group, gender, and occupation through percentages and proportions. Quantitative variables, such as age, were analyzed for mean and standard deviation. T-tests and chi-square tests compared groups, with p-values < 0.05 considered significant. **Data Processing and Interpretation:** Following data collection, information was reviewed, verified, and coded. All data were entered into a structured digital form. Each patient had a unique entry form with personal, examination, and investigation details, saved as distinct files. After reaching the target sample size, statistical analysis was conducted using SPSS-26 software. Qualitative variables like sex and occupation were analyzed by percentage, while quantitative variables, such as age, were assessed using mean values. Chi-square tests examined the relationship between RA disease activity and fibromyalgia presence, with a p-value below 0.05 considered statistically significant. **Ethical Considerations:** Ethical approval for this study was obtained from the Institutional Review Board of Chittagong Medical College Hospital (Approval No. [insert approval number]). Informed written consent was secured from all participants after providing a clear explanation of the study's purpose. Participants were informed of their right to withdraw at any stage without penalty. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki to ensure the rights, safety, privacy, and confidentiality of all participants. Interviews were conducted at times and locations convenient to the participants to maintain comfort and discretion during data collection.

RESULTS

The mean age of participants was 48.04 ± 13.78 years. Fibromyalgia was present in 24% of RA patients. No significant differences were observed in inflammatory markers (ESR, CRP) or serological tests (RF, anti-CCP) between the two groups. However, disease activity indices were significantly higher in patients with fibromyalgia. All patients in Group I had high DAS28 scores (>5.1), with a mean of 7.22 ± 0.81, compared to 65.8% in Group II (mean DAS28 5.77 ± 1.32). CDAI scores were also significantly higher in Group I (43.5 ± 6.14) compared to Group II (25.79 ± 15.67).

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Table 1: Distribution of the study patients by socio-demographic variable (n=50)

Socio-demographic variable	Number of patients	Percentage
Age (Years)		
15-35	9	18.0
36-55	25	50.0
56-72	16	32.0
Mean±SD	48.04±13.78	
Range (min-max)	15-72	
Gender		
Male	10	20.0
Female	40	80.0
Locality		

Rural	29	58.0
Urban	21	42.0
Religion		
Islam	40	80.0
Hindu	10	20.0
Monthly Expenditure		
Low	33	66.0
Medium	17	34.0
Educational Status		
Illiterate	7	14.0
Primary	22	44.0
SSC	14	28.0
HSC	5	10.0
Graduation	2	4.0
Marital Status		
Married	47	94.0
Unmarried	3	6.0
Ethnicity		
Bengali	50	100.0
Smoking		
Non smoke	47	94.0
Smoker	3	6.0
Alcohol		
NA	50	100.0

Table 1 shows the socio-demographic characteristics of 50 patients. Most patients were female (80%) with a mean age of 48.04 years (SD±13.78), primarily in the 36-55 age group (50%). A significant number lived in rural areas (58%), and Islam was the main religion (80%). In terms of education, 44% completed primary school, while 14% were illiterate. Most reported low monthly expenditures (66%), and the vast majority were married (94%). All patients were Bengali. Smoking was common in only 6% of the sample, and no one reported alcohol consumption.

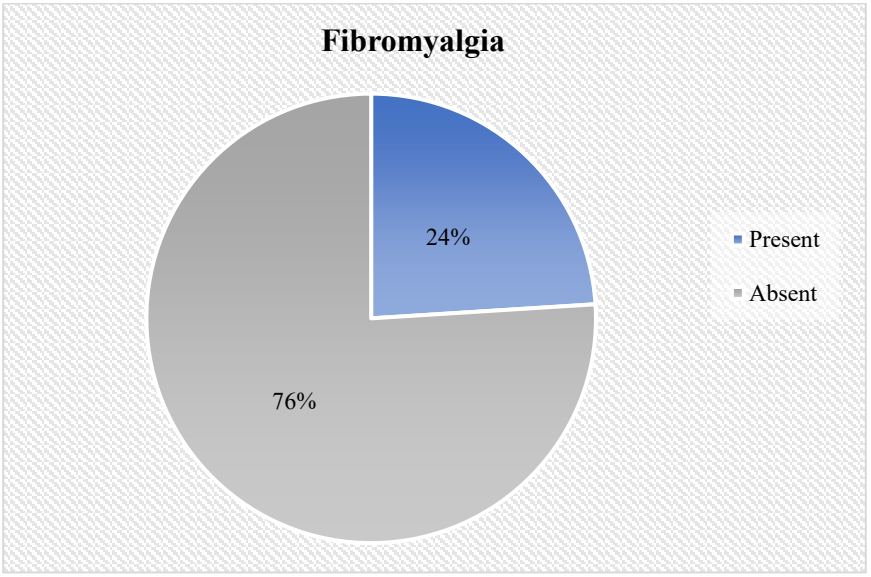

Figure 1: Distribution of Fibromyalgia Presence in Study Patients (n=50)

Figure 1 displays the prevalence of fibromyalgia among the study participants. According to the pie chart, 24% of the patients indicated a diagnosis of fibromyalgia, whereas the remaining 76% did not demonstrate the condition.

Table 2: Distribution of clinical variables between patients with and without concomitant fibromyalgia (n=50)

Clinical Variables	Group I (Fibromyalgia Present) (n=12)		Group II (Fibromyalgia Absent) (n=38)		P-value
	n	%	n	%	
Rheumatoid Arthritis (RA)					
Positive	10	83.3	32	84.2	0.942 ns
Negative	2	16.7	6	15.8	
Anti-cyclic Citrullinated Peptide (Anti CCP)					
Positive	6	50.0	27	71.1	0.179 ns
Negative	6	50.0	11	28.9	
Disease Duration (Years)					
≤10	9	75.0	33	86.7	
>10	3	24.9	5	13.0	
Mean±SD	5.99±6.78		5.28±5.04		b 0.685 ns
Range (min-max)	0.41-20		0.33-18		

ns= not significant, a p value reached from Chi square test, b p value reached from unpaired t-test

Table 2 outlines the distribution of study patients by clinical variables based on fibromyalgia presence. Among patients with fibromyalgia (Group I), 83.3% (n=10) tested positive for rheumatoid arthritis (RA), compared to 84.2% (n=32) in the fibromyalgia absent group (Group II), with no significant difference (p=0.942). For anti-cyclic citrullinated peptide (anti-CCP) positivity, 50.0% (n=6) of Group I and 71.1% (n=27) of Group II were positive, but the difference was not statistically significant (p=0.179). Disease duration was comparable across both groups, with 75.0% (n=9) of Group I and 86.7% (n=33) of Group II having a duration of 10 years or less. The mean duration for Group I was 5.99±6.78 years, and for Group II, it was 5.28±5.04 years, with no significant difference (p=0.685).

Table 3: Comparison of treatment parameters between patients with and without concomitant fibromyalgia (n=50)

Parameter	Group I (Fibromyalgia Present) (n=12)		Group II (Fibromyalgia Absent) (n=38)		P-value
	n	**%**	**n**	**%**	
Duration of Treatment (Years)					
≤1	8	66.6	22	57.9	
>1	4	33.3	16	42.2	
Mean±SD	2.51±4.98		2.86±4.55		a 0.821 ns
Range (min-max)	0.16-18		0-18		
Receiving Steroid					
Yes	6	50.0	11	28.9	b 0.179 ns
No	6	50.0	27	71.1	
Duration of receiving steroid (Year)					
0-0.5	3	25.0	5	13.2	
>0.5	4	33.3	5	13.2	
Mean±SD	0.55±0.67		0.71±1.06		0.626 ns
Range (min-max)	0-2		0.08-3		
No of Disease-Modifying Antirheumatic Drugs (DMARDs)					

0	1	8.3	7	18.4	
1	7	58.3	21	55.3	
2	3	25.0	8	21.1	[b] 0.347 [ns]
3	0	0.0	2	5.3	
8	1	8.3	0	0.0	

Table 3 summarizes patient distribution by treatment parameters. Regarding treatment duration, 66.6% (n=8) of Group I and 57.9% (n=22) of Group II were treated for one year or less, with no significant difference (p=0.821). For steroid use, 50.0% (n=6) of Group I and 28.9% (n=11) of Group II received steroids, showing no statistical significance (p=0.179). In terms of steroid use duration, 25.0% (n=3) of Group I and 13.2% (n=5) of Group II used steroids for 0-0.5 years, with no significant difference (p=0.626). The number of disease-modifying antirheumatic drugs (DMARDs) varied across groups, with no significant differences in 0, 1, 2, or 3 DMARDs (p=0.347).

Table 4: Comparison of inflammatory markers between patients with and without concomitant fibromyalgia (n=50)

Parameter	Group I (Fibromyalgia Present) (n=12)		Group II (Fibromyalgia Absent) (n=38)		P-value
	n	%	n	%	
Erythrocyte Sedimentation Rate (ESR) (mm/hr)					
<50	6	49.8	22	57.9	
50-100	5	41.6	12	31.5	
>100	1	8.3	4	10.4	
Mean±SD	66.08±37.72		51.74±27.17		0.154 [ns]
Range (min-max)	27-150		15-130		
C-reactive protein (CRP) (mg/L)					
<50	4	50.0	20	80.0	
>50	4	50.0	5	20.0	
Mean±SD	94.38±137.88		33.45±47.44		0.053 [ns]
Range (min-max)	0-412		0-200		

ns= not significant, p value reached from unpaired t-test

Table 4 illustrates the patient distribution by erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. In Group I, 49.8% (n=6) and in Group II, 57.9% (n=22) had ESR values less than 50 mm/hr. For ESR values between 50-100 mm/hr, 41.6% (n=5) of Group I and 31.5% (n=12) of Group II were noted. The mean ESR was 66.08±37.72 mm/hr for Group I and 51.74±27.17 mm/hr for Group II, with no significant difference (p=0.154). For CRP levels, 50.0% (n=4) of Group I and 80.0% (n=20) of Group II had values less than 50 mg/L, while the same percentage in Group I and 20.0% (n=5) in Group II had levels above 50 mg/L. The mean CRP was 94.38±137.88 mg/L for Group I and 33.45±47.44 mg/L for Group II, with no significant difference observed (p=0.053).

Table 5: Comparison of disease activity indices between patients with and without concomitant fibromyalgia (n=50)

Parameter	Group I (Fibromyalgia Present) (n=12)		Group II (Fibromyalgia Absent) (n=38)		P-value
	n	%	n	%	
Patient Health Questionnaire (PHQ-9)					
<5	0	0.0	11	28.9	
5-10	2	16.7	10	26.3	
11-15	2	16.7	8	21.1	
16-20	5	41.7	7	18.4	

>20	3	25.0	2	5.3	
Mean±SD	17.58±6.3		10.55±6.42		0.053 ns
Range (min-max)	6-27		2-24		
Disease Activity Score (DAS 28)					
<2.6 Remission	0	0.0	0	0.0	
2.6-<3.2 Low diseases activity	0	0.0	0	0.0	
3.2-5.1 Moderate diseases activity	0	0.0	13	34.2	
> 5.1 High diseases activity	12	100.0	25	65.8	
Mean±SD	7.22±0.81		5.77±1.32		0.001 s
Range (min-max)	5.63-8.4		3.38-8.62		
Clinical Disease Activity Index (CDAI 25 page)					
0.0-2.8 Remission	0	0.0	1	2.6	
2.9-10.0 Low Activity	0	0.0	6	15.8	
10.1-22.0 Moderate diseases activity	0	0.0	7	18.4	
22.1-76.0 High diseases activity	12	100.0	24	63.2	
Mean±SD	43.5±6.14		25.79±15.67		0.004 s
Range (min-max)	33-53		2.5-68		

s= significant, ns= not significant, p value reached from unpaired t-test

Table 5 presents the distribution of patients by disease activity parameters, including the Patient Health Questionnaire (PHQ-9), Disease Activity Score (DAS 28), and Clinical Disease Activity Index (CDAI 25). In terms of PHQ-9 scores, 25.0% (n=3) of Group I (fibromyalgia present) had scores above 20, while 28.9% (n=11) of Group II (fibromyalgia absent) scored below 5. The mean PHQ-9 score was significantly higher for Group I (17.58±6.3) than Group II (10.55±6.42) with a p-value of 0.053. For DAS 28, 100% (n=12) of Group I had high disease activity (score >5.1) compared to 65.8% (n=25) of Group II, showing a significant difference (p=0.001). For CDAI 25, 100% (n=12) of Group I exhibited high disease activity (score >22.1), while 63.2% (n=24) of Group II did. The mean CDAI score was significantly higher in Group I (43.5±6.14) than in Group II (25.79±15.67) (p=0.004).

DISCUSSION

This study explored fibromyalgia (FM) prevalence in rheumatoid arthritis (RA) patients and its impact on Disease Activity Score 28 (DAS28) and Clinical Disease Activity Index (CDAI). We assessed the characteristics of RA patients with and without fibromyalgia. Our findings highlight the significant effect of fibromyalgia on RA activity, confirming its importance as a co-morbidity in disease progression assessments.

The study enrolled 50 patients with rheumatoid arthritis (RA) diagnosed per the 2010 ACR criteria. Participants had a mean age of 48.04 ± 13.78 years, with 50% in the 36-55 age range. This aligns with prior findings of a mean age of 45.3 ± 11.5 years among RA patients [14]. Variations in age across cohorts may arise from geographical, ethnic, and genetic factors highlighted in earlier research, which noted a higher mean age[16].

One of the interesting discoveries from our study is that females are predominantly affected by rheumatoid arthritis (RA), making up a remarkable 80% of our cohort. This aligns well with the female-to-male ratio of 4:1 that previous studies have highlighted [16,17]. We believe that this documented gender difference may be influenced by hormonal and genetic factors, as mentioned in other research [18]. Moreover, our findings are supported by evidence showing that fibromyalgia tends to occur more often in females, especially among those facing chronic inflammatory conditions like RA [8].

The prevalence of fibromyalgia among patients diagnosed with rheumatoid arthritis (RA) within our cohort was observed to be 24%, which corresponds with the findings of earlier studies that reported a prevalence of 23% [19]. This statistic is also comparable to that of another investigation, which identified that 20.8% of their RA cohort presented with concomitant fibromyalgia. In contrast, a

significantly higher prevalence of 51.4% was documented in another study, a disparity that may be ascribed to variations in diagnostic criteria, geographic location, and patient selection [18,20]. These discrepancies underscore the complexity inherent in diagnosing fibromyalgia in individuals with RA and emphasise the urgent necessity for more standardized criteria within clinical practice.

Our study showed that fibromyalgia did not significantly impact rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-CCP) positivity, with 83.3% of fibromyalgia patients (Group I) and 84.2% of non-fibromyalgia patients (Group II) testing positive for RF. Similarly, 50% of fibromyalgia patients and 71.1% of those without fibromyalgia tested positive for anti-CCP, with no statistically significant differences. This aligns with earlier findings of similar RF positivity rates [17]. Thus, fibromyalgia appears not to affect serological markers used for assessing disease activity in RA. There were no significant differences in disease duration between fibromyalgia and non-fibromyalgia groups, as seen in previous studies [8]. This indicates fibromyalgia does not impact RA duration or onset timing. Treatment strategies, like steroids and Dmards, were similar for both groups, reinforcing that fibromyalgia does not change RA management. However, the presence of fibromyalgia complicates disease activity assessments, which is critical for clinicians.

Inflammatory markers like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) showed no significant differences between fibromyalgia and non-fibromyalgia groups. This aligns with previous research that found no differences in ESR and CRP levels between RA patients with and without fibromyalgia [21]. It suggests fibromyalgia does not influence systemic inflammation like RA, as its pathophysiology involves distinct mechanisms from those driving inflammation in RA [5,7].

Notwithstanding the absence of significant differences in inflammatory markers, the disease activity scores, specifically the DAS28 and CDAI, were markedly elevated in patients diagnosed with fibromyalgia. These findings are consistent with prior research that indicated poorer disease activity and health outcomes in rheumatoid arthritis (RA) patients afflicted with fibromyalgia [5,15]. The elevated disease activity scores may reflect the additional burden of chronic pain and fatigue experienced by patients with fibromyalgia, which can skew subjective evaluations of disease activity, such as tender joint count and patient global assessments. This underscores the necessity of accounting for the presence of fibromyalgia when assessing disease activity indices in RA patients.

The Patient Health Questionnaire (PHQ-9) scores were significantly higher in the fibromyalgia group, indicating a greater impact on mental health. This aligns with previous studies showing an association between fibromyalgia and increased depression severity in RA patients [22]. The co-occurrence of RA and fibromyalgia exacerbates mental health issues, worsening disease activity and reducing quality of life.

Our study confirms that fibromyalgia significantly impacts RA patients, emphasising the need for comprehensive management when both conditions coexist. While RA treatment remains unchanged, clinicians must consider fibromyalgia's added burden, leading to higher disease activity scores, increased depression, and worse outcomes. Future research should target improved diagnostic tools for fibromyalgia in RA and tailored treatment strategies to enhance patient outcomes.

CONCLUSION

This study evaluated disease activity indices in rheumatoid arthritis (RA) patients with fibromyalgia. Most participants were females aged 35-55 from rural areas with low socio-economic status and limited education. Fibromyalgia was found in about one-fourth of RA patients. Clinical variables like anti-CCP positivity, disease duration, treatment duration, steroid use, number of DMARDs, ESR, CRP, and PHQ-9 scores were similar in both groups. However, DAS28 and CDAI scores were significantly higher in those with fibromyalgia. These findings suggest fibromyalgia affects disease activity assessments in RA, emphasising the need to consider this comorbidity in evaluating RA status and treatment strategies.

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