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ORIGINAL RESEARCH

Assessment of the Prevalence of Extraarticular Manifestations in Rheumatoid Arthritis and Their Association with Serological Markers and Disease Severity

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ABSTRACT

Aim: To determine the prevalence of extraarticular manifestations (EAMs) in patients with rheumatoid arthritis (RA) and evaluate their relationship with serological status and disease severity.**Material and Methods:**This cross-sectional, observational study was conducted in the Department of General Medicine, enrolling 130 patients diagnosed with RA according to the 2010 ACR/EULAR classification criteria. Detailed demographic, clinical, serological, and radiographic assessments were performed. Disease severity was assessed using the DAS28 scoring system. The presence of EAMs such as rheumatoid nodules, Sjögren's syndrome features, interstitial lung disease, vasculitis, Felty's syndrome, ocular manifestations, and neurological involvement was recorded. Serological evaluation included rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody testing. Statistical analysis was performed using chi-square tests and independent t-tests, with a p-value < 0.05 considered statistically significant.**Results:**The mean age of the study population was 49.6 ± 11.2 years, with a female predominance (70.77%). The majority (80.00%) were seropositive. Disease activity assessment showed that 41.54% had moderate and 33.85% had high disease activity. Extraarticular manifestations were present in 60.00% of patients, with rheumatoid nodules (24.62%) and Sjögren's syndrome features (21.54%) being most common. A significant association was found between the presence of EAMs and seropositivity ($p = 0.002$) as well as higher disease activity ($p = 0.001$). Rheumatoid nodules were significantly more frequent among seropositive patients ($p = 0.013$).**Conclusion:**This study highlights a high prevalence of extraarticular manifestations in rheumatoid arthritis, particularly among seropositive patients and those with elevated disease activity. Early identification and aggressive management of disease activity are crucial to minimize systemic involvement and improve patient outcomes.

Keywords: Rheumatoid arthritis, Seropositive rheumatoid arthritis, Disease Activity Score (DAS28), Anti-CCP antibodies

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder that primarily affects the synovial joints, leading to progressive joint destruction, deformity, and significant functional impairment. However, it is now well recognized that RA extends beyond the joints, with systemic involvement that gives rise to a variety of extraarticular manifestations (EAMs). These manifestations can affect virtually every organ system, including the skin, eyes, lungs, heart, blood vessels, kidneys, and nervous system. Extraarticular features of RA are a major contributor to increased morbidity and mortality in affected patients, and their presence often indicates a more aggressive disease course and poorer prognosis.[1]

The prevalence of extraarticular manifestations among individuals with RA varies widely across different studies and populations, reflecting variations in genetic background, environmental exposures, disease duration, access to healthcare, and the use of disease-modifying therapies. Reported prevalence rates range from approximately 20% to 50% in different cohorts. EAMs may occur early in the disease course or may develop after many years of disease evolution. Some extraarticular features, such as subcutaneous rheumatoid nodules, are considered relatively specific to RA, whereas others, including pulmonary fibrosis or vasculitis, may present more subtly and be recognized only through careful clinical evaluation or advanced imaging modalities.[2]

A significant focus in the study of extraarticular manifestations relates to their association with serological markers of disease activity, particularly rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP). These autoantibodies are hallmarks of seropositive RA and are known to be predictive of more severe joint disease. Several clinical observations suggest that seropositive individuals are more prone to developing systemic manifestations compared to seronegative counterparts. This relationship may be explained by the heightened systemic inflammatory activity that characterizes seropositive RA, leading not only to synovial pathology but also to widespread vascular and organ-specific immune-mediated damage.[3]

The severity of RA, as measured by composite disease activity indices such as the Disease Activity Score-28 (DAS28), has also been linked to the occurrence of EAMs. Patients with persistently high disease activity are at greater risk for systemic involvement, potentially due to sustained exposure to pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1). These cytokines have systemic effects that contribute to the development of various extraarticular complications, including interstitial lung disease, pericarditis, scleritis, and amyloidosis. Consequently, timely recognition and control of systemic inflammation are critical not only for preserving joint function but also for preventing potentially life-threatening extraarticular involvement.[4]

Among the most common extraarticular manifestations in RA are subcutaneous nodules, which typically occur in individuals with high-titer RF and long-standing disease. Other frequently encountered features include secondary Sjögren's syndrome, presenting with dryness of the eyes and mouth due to lymphocytic infiltration of exocrine glands; pulmonary complications such as pleural effusion and interstitial lung disease; and cardiovascular manifestations like pericarditis and accelerated atherosclerosis. Less commonly, patients may develop severe manifestations such as rheumatoid vasculitis, which involves small and medium-sized blood vessels, leading to skin ulcerations, peripheral neuropathy, and, in rare cases, life-threatening organ ischemia.[5]

The occurrence of EAMs poses significant challenges in the management of RA. These manifestations may be asymptomatic in early stages, requiring a high index of suspicion for diagnosis. Furthermore, the treatment of extraarticular disease often necessitates a more aggressive therapeutic approach, including the use of high-dose corticosteroids, biologic agents targeting specific cytokines, and, in some cases, immunosuppressive drugs such as cyclophosphamide. The presence of extraarticular disease frequently complicates the therapeutic decision-making process, as clinicians must balance the need for immunosuppression against the risks of adverse effects, particularly in patients with coexisting infections, organ dysfunction, or malignancies.[6]

Importantly, EAMs also have profound psychosocial implications for patients with RA. Organ system involvement can lead to additional physical disability, reduced quality of life, increased healthcare utilization, and substantial economic burden. Emotional distress, depression, and anxiety are commonly observed in RA

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patients, particularly those with systemic disease manifestations, emphasizing the need for holistic care that addresses both physical and psychological aspects of the disease.[7]

In recent years, advances in the understanding of RA pathogenesis and the introduction of targeted biologic therapies have led to improvements in disease control and a reduction in the incidence of some severe extraarticular complications. Early and aggressive treatment strategies aimed at achieving disease remission or low disease activity have been shown to decrease the risk of systemic involvement. Nonetheless, despite these therapeutic advances, extraarticular manifestations remain a significant concern, particularly in patients with longstanding or poorly controlled RA.

The relationship between serological status, disease severity, and the occurrence of extraarticular manifestations continues to be an area of active investigation. Identifying patients at higher risk for systemic involvement allows for closer monitoring, early diagnosis, and tailored treatment interventions aimed at improving long-term outcomes. Future research is needed to elucidate the precise mechanisms linking autoantibody production, systemic inflammation, and organ-specific damage in RA, as well as to develop predictive models that can guide clinical management.[8]

AIM AND OBJECTIVS

Aim

To evaluate the prevalence of extraarticular manifestations (EAMs) in patients with rheumatoid arthritis (RA) and to assess their association with serological status and disease severity.

Objectives

1. To determine the prevalence and pattern of extraarticular manifestations among patients with rheumatoid arthritis.
2. To evaluate the association between extraarticular manifestations and serological status (rheumatoid factor [RF] and anti-cyclic citrullinated peptide [anti-CCP] antibodies).
3. To assess the relationship between extraarticular manifestations and disease severity as measured by Disease Activity Score in 28 joints (DAS28).

MATERIALS AND METHODS

Study Design

This was a cross-sectional, observational study conducted to evaluate the prevalence of extraarticular manifestations (EAMs) in rheumatoid arthritis (RA) and their relationship with serological status and disease severity.

Study Population

A total of 130 patients diagnosed with RA according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria were consecutively enrolled from the outpatient and inpatient departments of a tertiary care teaching hospital.

Study Place

The study was conducted in the Department of General Medicine in collaboration with Department of orthopaedic and Department of Pathology, ShriRamkrishna Institute of Medical Sciences &Sanaka Hospitals, Durgapur, West Bengal, India.

Study Period

The study was carried out over a period one year, fromNovember 2023 to October 2024.

Ethical Considerations

Approval was obtained from the Institutional Ethics Committee before the commencement of the study. Written informed consent was obtained from all participants prior to their inclusion in the study, ensuring confidentiality and voluntary participation.

Inclusion Criteria

- Adults aged 18 years and above.
- Confirmed diagnosis of RA as per the 2010 ACR/EULAR classification criteria.
- Willingness to provide informed written consent and complies with study protocols.

Exclusion Criteria

- Patients diagnosed with other connective tissue diseases (e.g., systemic lupus erythematosus, mixed connective tissue disease).
- Patients with significant comorbidities likely to independently cause extraarticular manifestations (e.g., chronic infections, malignancy).
- Pregnant or lactating women.
- Patients with incomplete clinical or serological data.

Study Procedure

Following enrollment, detailed demographic and clinical data were collected using a structured proforma, including age, gender, disease duration, and treatment history. Comprehensive clinical examinations were performed to assess for the presence of EAMs, which included:

- Rheumatoid nodules

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- Features suggestive of Sjögren's syndrome (xerophthalmia, xerostomia)
- Interstitial lung disease (ILD)
- Vasculitis
- Felty's syndrome
- Ocular manifestations (scleritis, episcleritis)
- Neurological involvement (peripheral neuropathy)

Disease severity was assessed using the Disease Activity Score in 28 joints (DAS28), incorporating tender joint count, swollen joint count, erythrocyte sedimentation rate (ESR), and patient's global assessment. Disease activity was categorized as:

- Remission: DAS28 < 2.6
- Low disease activity: DAS28 2.6–3.2
- Moderate disease activity: DAS28 3.2–5.1
- High disease activity: DAS28 > 5.1
- For serological evaluation:
- Rheumatoid factor (RF) levels were measured using nephelometry (positive if >20 IU/mL).
- Anti-cyclic citrullinated peptide (anti-CCP) antibodies were measured by enzyme-linked immunosorbent assay (ELISA) (positive if >5 U/mL).
- Inflammatory markers, including ESR and C-reactive protein (CRP), were assessed.
- Patients were categorized as **seropositive** (positive for RF and/or anti-CCP) or **seronegative** (negative for both).
- Radiographic evaluation was performed via standard anteroposterior radiographs of the hands and feet to detect joint erosions and deformities.

The pathologist's role in this study involves:

- **Histopathological Evaluation**: Analyzing tissue samples to confirm and characterize extraarticular manifestations (e.g., rheumatoid nodules, vasculitis, interstitial lung disease).
- **Synovial Biopsy Analysis**: Assessing the degree of inflammation, cartilage degradation, and immune cell infiltration in joint tissues.
- **Collaboration**: Working with rheumatologists to correlate histological findings with clinical and serological data.
- **Diagnosis of Overlap Syndromes**: Identifying autoimmune or other pathologies that may mimic or complicate RA.
- **Support in Ocular and Neurological Manifestations**: Examining eye or nerve biopsies in cases of RA-related ocular or neurological issues.
- **Outcome Measures**
- Prevalence and pattern of extraarticular manifestations in patients with RA.
- Association between the presence of extraarticular manifestations and serological status (RF and anti-CCP).
- Association between extraarticular manifestations and disease severity (based on DAS28 scores).

Statistical Analysis

Data were compiled using Microsoft Excel and analyzed with SPSS version 26.0.

- Categorical variables were summarized as frequencies and percentages.
- Continuous variables were presented as mean ± standard deviation (SD).
- Associations between categorical variables were tested using the chi-square test or Fisher's exact test.
- For continuous variables, independent t-test or Mann-Whitney U test was used based on the distribution of data.
- A p-value < 0.05 was considered statistically significant.

RESULTS

The present study enrolled a total of 130 patients diagnosed with rheumatoid arthritis (RA).

Table 1: Demographic and Baseline Characteristics of Study Population (n = 130)

Parameter	Number (n)	Percentage (%)
Mean age (years)	49.6 ± 11.2	-
Gender		
Male	38	29.23%
Female	92	70.77%
Mean disease duration (years)	6.4 ± 3.1	-
Serological status		
Seropositive	104	80.00%
Seronegative	26	20.00%
Disease severity (DAS28)		

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Remission (<2.6)	12	9.23%
Low disease activity (2.6–3.2)	20	15.38%
Moderate disease activity (3.2–5.1)	54	41.54%
High disease activity (>5.1)	44	33.85%

As shown in **Table 1**, the mean age of the study population was 49.6 ± 11.2 years. A female predominance was noted, with 92 (70.77%) females compared to 38 (29.23%) males. The mean duration of disease among patients was 6.4 ± 3.1 years. Regarding serological status, the majority of the patients, 104 (80.00%), were seropositive for either rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) antibodies, while 26 (20.00%) were seronegative. In terms of disease activity assessed by the DAS28 score, 12 patients (9.23%) were in remission, 20 patients (15.38%) had low disease activity, 54 patients (41.54%) had moderate disease activity, and 44 patients (33.85%) had high disease activity.

Table 2: Prevalence of Extraarticular Manifestations (EAMs) among Patients

Extraarticular Manifestation	Number (n)	Percentage (%)
Rheumatoid nodules	32	24.62%
Sjögren's syndrome features	28	21.54%
Interstitial lung disease (ILD)	18	13.85%
Vasculitis	12	9.23%
Felty's syndrome	5	3.85%
Ocular manifestations	14	10.77%
Neurological involvement	9	6.92%
Any EAM (at least one)	**78**	**60.00%**

The prevalence of extraarticular manifestations (EAMs) among the study participants is detailed in **Table 2**. Among the patients, 78 (60.00%) had at least one form of EAM. The most common manifestation was rheumatoid nodules, present in 32 patients (24.62%), followed by Sjögren's syndrome features such as xerophthalmia and xerostomia, found in 28 patients (21.54%). Interstitial lung disease (ILD) was detected in 18 patients (13.85%), vasculitis was seen in 12 patients (9.23%), and ocular manifestations such as scleritis and episcleritis were noted in 14 patients (10.77%). Felty's syndrome and neurological involvement were less frequently observed, reported in 5 (3.85%) and 9 (6.92%) patients, respectively.

Table 3: Distribution of Serological Status among Patients with and without EAMs

Serological Status	EAM Present (n=78)	EAM Absent (n=52)	p-value
Seropositive	70 (89.74%)	34 (65.38%)	0.002
Seronegative	8 (10.26%)	18 (34.62%)	

The distribution of serological status among patients with and without extraarticular manifestations is shown in **Table 3**. A significant association was observed between serological status and the presence of EAMs ($p = 0.002$). Among patients who exhibited EAMs, 70 (89.74%) were seropositive, compared to 34 (65.38%) seropositive patients among those without EAMs. Conversely, seronegativity was more common among patients without EAMs (34.62%) than among those with EAMs (10.26%), indicating a strong link between seropositivity and the development of extraarticular manifestations.

Table 4: Association between Extraarticular Manifestations and Disease Severity (DAS28 categories)

Disease Severity	EAM Present (n=78)	EAM Absent (n=52)	p-value
Remission (DAS28 <2.6)	3 (3.85%)	9 (17.31%)	0.001
Low activity (2.6–3.2)	6 (7.69%)	14 (26.92%)	
Moderate activity (3.2–5.1)	32 (41.03%)	22 (42.31%)	
High activity (>5.1)	37 (47.44%)	7 (13.46%)	

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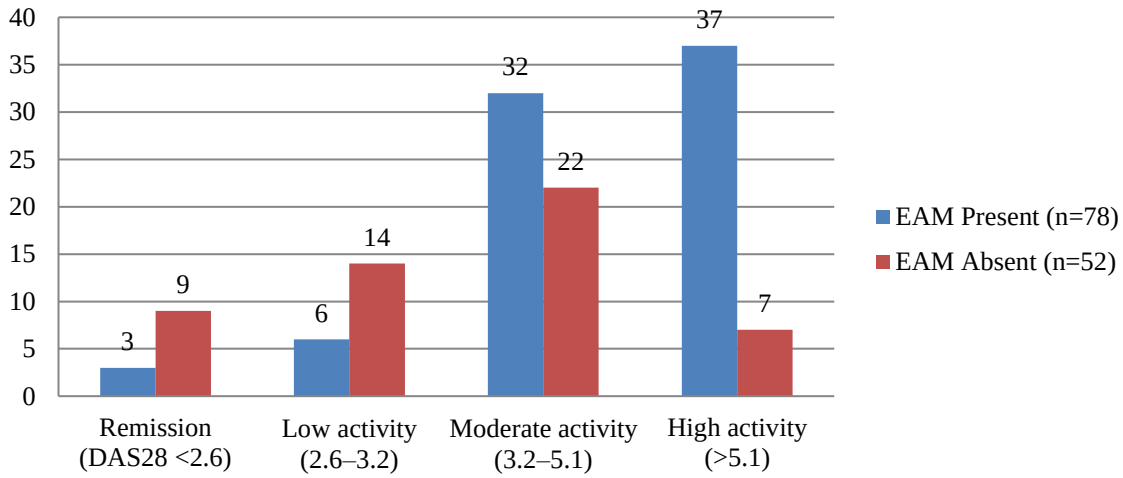
Figure I: Association between extraarticulation manifestation and diease severity



The table 4 and figure I, presents **the** association between extraarticular manifestations **(EAMs)** and **disease severity**, categorized by **DAS28 scores** in patients with rheumatoid arthritis (RA).Among the 130 RA patients studied, 78 patients had extraarticular manifestations (EAM Present group), and 52 patients did not (EAM Absent group).In the Remission group (DAS28 < 2.6),only 3 patients (3.85%) with EAMs were in remission compared to 9 patients (17.31%) without EAMs. This suggests that patients without EAMs were more likely to achieve remission.In the Low disease activity group (DAS28 2.6–3.2), 6 patients (7.69%) with EAMs had low disease activity compared to 14 patients (26.92%) without EAMs, again indicating better disease control among patients without EAMs.Inthe Moderate disease activity group (DAS28 3.2–5.1), the proportions were relatively similar: 32 patients (41.03%) with EAMs versus 22 patients (42.31%) without EAMs.However, in the High disease activity group (DAS28 >5.1), a striking difference was observed: 37 patients (47.44%) with EAMs had high disease activity compared to only 7 patients (13.46%) without EAMs. This shows that high disease activity was significantly more common among patients with extraarticular manifestations. The p-value is 0.001, indicating a highly statistically significant association between the presence of EAMs and higher disease severity.In simple terms, patients with extraarticular manifestations tend to have more severe disease activity compared to those without EAMs.

Table 5: Distribution of Specific EAMs according to Serological Status

Manifestation	Seropositive (n=104)	Seronegative (n=26)	p-value
Rheumatoid nodules	30 (28.85%)	2 (7.69%)	0.013
Sjögren's syndrome features	25 (24.04%)	3 (11.54%)	0.145
Interstitial lung disease	16 (15.38%)	2 (7.69%)	0.353
Vasculitis	11 (10.58%)	1 (3.85%)	0.296
Felty's syndrome	5 (4.81%)	0 (0.00%)	0.341
Ocular manifestations	13 (12.50%)	1 (3.85%)	0.197
Neurological involvement	8 (7.69%)	1 (3.85%)	0.464

The distribution of specific extraarticular manifestations according to serological status is summarized in **Table 5**. Rheumatoid nodules were significantly more frequent among seropositive patients (28.85%) than seronegative patients (7.69%) ($p = 0.013$). Although the prevalence of other EAMs such as Sjögren'ssyndrome features, ILD, vasculitis, ocular manifestations, and neurological involvement was higher in seropositive patients compared to seronegative patients, these differences did not reach statistical significance ($p > 0.05$ for each). Notably, Felty's syndrome was only observed among seropositive patients

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(4.81%) and was absent in the seronegative group; however, this difference was not statistically significant (p = 0.341).

DISCUSSION

In the present study, the mean age of patients was 49.6 ± 11.2 years, with a clear female predominance (70.77%), which is consistent with global epidemiological patterns showing higher RA prevalence among females, as reported by **Intriago et al 2019**. The average disease duration in our cohort was 6.4 ± 3.1 years, reflecting a relatively established disease course at the time of evaluation.[9] A high seropositivity rate of 80.00% was observed, comparable to findings by **Aletaha et al 2010**, who emphasized the role of seropositivity, particularly rheumatoid factor (RF) and anti-CCP antibodies, in defining the classic immunopathologic features of RA.[10] Disease activity, as assessed by DAS28, revealed that only 9.23% of patients were in remission, whereas 41.54% had moderate disease activity and 33.85% exhibited high disease activity, suggesting that despite ongoing treatment, many patients continued to have active disease. This pattern is similar to observations made by **Salaffi et al 2014**, who reported persistent moderate-to-severe disease activity in real-world RA cohorts.[11]

Regarding extraarticular manifestations (EAMs), our study found that 78 out of 130 patients (60.00%) had at least one EAM. The most common manifestations included rheumatoid nodules (24.62%), features of secondary Sjögren's syndrome (21.54%), interstitial lung disease (13.85%), ocular involvement (10.77%), vasculitis (9.23%), Felty's syndrome (3.85%), and neurological involvement (6.92%). These findings align with the work of **Young et al 2007**, who described rheumatoid nodules and pulmonary involvement as among the most common EAMs.[12] The relatively high prevalence of ILD in our patients corresponds with the findings of **Hochberg et al 2008**, who reported respiratory system involvement among major causes of morbidity in RA patients.[13]

When analyzing the association between serological status and the presence of EAMs, a significant relationship was observed (p = 0.002). Among those with EAMs, 89.74% were seropositive, compared to only 65.38% of those without EAMs. Conversely, seronegativity was more common in patients without EAMs (34.62%) compared to those with EAMs (10.26%). This strong link between seropositivity and systemic involvement is well supported by **Turesson et al 2007**, who found that RF and anti-CCP positivity were major predictors of severe extraarticular disease.[14] Similarly, **Sahatçiu-Meka et al 2010** reported a lower frequency of systemic involvement among seronegative RA patients, underscoring the immunological mechanisms driving EAMs.[15]

A significant association was also found between the presence of EAMs and disease severity (p = 0.001). Among patients with EAMs, 47.44% had high disease activity (DAS28 >5.1), compared to only 13.46% in those without EAMs. Conversely, remission was less common in patients with EAMs (3.85%) than those without (17.31%). Patients without EAMs more frequently had low disease activity (26.92%) compared to those with EAMs (7.69%). These findings are consistent with the study by **Turesson et al 2002**, which demonstrated that patients with higher inflammatory burden are at greater risk of developing systemic complications.[16] Our study further supports the notion that controlling disease activity is crucial not only for joint outcomes but also for reducing systemic disease manifestations.

When examining specific EAMs in relation to serological status, rheumatoid nodules were significantly more frequent among seropositive patients (28.85%) compared to seronegative patients (7.69%) (p = 0.013). This finding is in agreement with **Shankar et al 2006**, who reported a strong association between seropositivity and nodular disease. Other manifestations such as Sjögren's syndrome features (24.04% vs. 11.54%), ILD (15.38% vs. 7.69%), vasculitis (10.58% vs. 3.85%), ocular involvement (12.50% vs. 3.85%), and neurological involvement (7.69% vs. 3.85%) were more common among seropositive patients, although the differences were not statistically significant (p > 0.05 for each).[17] These trends mirror the findings of **El Sawi et al 2011**, who suggested that seropositive RA patients are more prone to systemic disease, though variations in manifestation types might not always reach significance.[18]

Pulmonary involvement in the form of ILD was noted in 18 patients (13.85%), with a trend toward higher occurrence in seropositive patients. This is consistent with the findings of **Corcoran et al 2014**, who stressed that ILD remains a serious extraarticular complication predominantly affecting seropositive individuals.[19]Felty's syndrome was reported exclusively among seropositive patients in our

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study (4.81%), echoing the observations made by **Al-Dalaan et al 1998**, who documented Felty's syndrome primarily in long-standing seropositive RA cases.[20]

LIMITATIONS OF THE STUDY

- The study was conducted at a single tertiary care centre, which may limit the generalizability of the findings to the broader RA population.
- The cross-sectional design precludes establishing a causal relationship between serological status, disease severity, and the development of EAMs.
- The sample size may not be large enough to detect less common extraarticular manifestations.
- Potential recall bias and incomplete patient histories may have influenced the accuracy of reported extraarticular features.
- Lack of long-term follow-up prevents assessment of the progression or resolution of EAMs over time.

CONCLUSION

In current study, extraarticular manifestations (EAMs) were found to be common among patients with rheumatoid arthritis (RA). The presence of EAMs showed a significant association with seropositivity for rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies, as well as with higher disease activity scores (DAS28). These findings highlight the importance of early detection and management of EAMs in RA patients to prevent disease progression, reduce complications, and improve quality of life. Regular clinical evaluation for EAMs should be incorporated into the routine assessment of RA patients, especially in those with high disease activity and positive serology.

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