



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Research Article

Profile of Extra-Articular Manifestations in Patients with Rheumatoid Arthritis Attending a Tertiary Care Centre in Kashmir: A Hospital-Based Observational Study

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ARTICLE INFO

Published: 07 Oct 2026

Keywords:

Rheumatoid arthritis; extra-articular manifestations; Kashmir; interstitial lung disease; Sjögren syndrome; anaemia; pulmonary hypertension

DOI:

10.5281/zenodo.23212865

ABSTRACT

Background: Rheumatoid arthritis (RA) is a systemic autoimmune disease in which extra-articular manifestations (EAMs) contribute substantially to morbidity and may involve multiple organ systems. Data describing the spectrum of EAMs in patients with RA from Kashmir are limited. **Objective:** To describe the clinical profile and spectrum of extra-articular manifestations among patients with RA attending a tertiary care rheumatology service at Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar. **Methods:** This hospital-based observational study used both retrospective and prospective data collection. Patients diagnosed with RA according to the 2010 ACR/EULAR classification criteria who attended the Rheumatology Division of Internal Medicine or were admitted to SKIMS up to May 2024 were evaluated. Clinical records and prospective clinical assessments were used to identify extra-articular involvement. Investigations included chest radiography, high-resolution computed tomography when indicated, pulmonary assessment including DLCO, echocardiography, nerve-conduction studies, complete blood count, peripheral blood film and erythrocyte sedimentation rate. Data were analysed using SPSS version 25; $p < 0.05$ was considered statistically significant. **Results:** Two hundred patients were included. The cohort was predominantly female (151/200, 75.5%), and 136/200 (68.0%) were aged 50–69 years. The mean DAS28 score was 1.7 ± 0.8 . Conventional DMARDs were being used by 158 patients (79.0%). Among the recorded extra-articular manifestations, episcleritis was present in 32 patients (16.0%) and dry eye in 26 (13.0%). Pulmonary manifestations included interstitial lung disease in 15 patients (7.5%), pulmonary hypertension in 13 (6.5%), pulmonary nodules in 5 (2.5%), bronchiectasis in 2 (1.0%) and pleural effusion in 2 (1.0%). Anaemia was present in 54 patients (27.0%), neuropathy in 18 (9.0%), secondary Sjögren syndrome in 21 (10.5%), proteinuria in 10 (5.0%), chronic kidney disease in 9 (4.5%), renal amyloidosis in 2

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



(1.0%), and heart failure in 10 (5.0%). Rheumatoid nodules, ulcers and vasculitis were recorded in 3.5%, 2.0% and 1.0%, respectively. No statistically significant differences were observed between cDMARD and non-cDMARD groups for the individual manifestations reported. Conclusion: A broad spectrum of extra-articular involvement was documented among patients with RA attending this tertiary-care centre, with ocular, haematological, pulmonary, neurological, renal, oral and cardiovascular manifestations represented. Routine clinical surveillance with organ-specific assessment when indicated may facilitate recognition of clinically important extra-articular disease. Prospective studies using standardized definitions and systematic screening are needed to determine the true burden and predictors of EAMs in the Kashmiri population.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized primarily by inflammatory synovitis and progressive joint damage. Its effects are not confined to the musculoskeletal system; extra-articular manifestations (EAMs) may involve the skin, eyes, lungs, cardiovascular system, nervous system, kidneys, and haematological and exocrine systems. These manifestations contribute to morbidity and may be associated with more severe systemic disease.[1–7]

The frequency and pattern of EAMs vary substantially among studies because of differences in disease duration, disease activity, patient selection, treatment exposure, definitions and screening strategies. Previous cohorts have reported pulmonary, haematological, ocular, neurological, renal, cardiovascular and mucocutaneous involvement with widely varying frequencies.[9–15,21–34]

Indian studies have similarly demonstrated substantial heterogeneity in the spectrum of EAMs. Pulmonary abnormalities, mucocutaneous disease and secondary Sjögren syndrome have been reported in different patient populations, while larger multicentre cohorts have suggested

associations with disease duration, seropositivity and disease activity.[22,25–28,31–34]

Kashmir has a distinct population and healthcare setting, and local data on the spectrum of RA-associated extra-articular disease are limited. The present study was therefore undertaken to describe the profile of extra-articular manifestations among patients with RA attending SKIMS, a tertiary-care referral centre in Kashmir.

MATERIALS AND METHODS

Study design and setting

This was a hospital-based observational study conducted at Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar. The study incorporated retrospective review and prospective assessment of patients attending the Rheumatology Division of the Department of Internal Medicine.

Study population

Patients diagnosed with RA according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria who attended the outpatient service or were admitted to SKIMS up to May 2024 were considered. Patients of all ages and both sexes were eligible. The thesis protocol additionally specified inclusion of patients with documented or newly identified extra-articular manifestations and exclusion of patients with comorbid conditions considered capable of confounding identification of RA-related extra-articular manifestations.

Sampling and sample size

Patients fulfilling the study criteria during the study period were recruited. The thesis estimated approximately 120 eligible patients over 12



months and an estimated study-period sample of 180, which was rounded to 200. The final analysed sample comprised 200 patients.

Data collection and assessment of extra-articular manifestations

Retrospective data were obtained from medical records, including demographic characteristics, clinical history, previous investigations and documented extra-articular disease. Patients assessed prospectively underwent detailed history and clinical examination. Investigations used to identify or confirm organ involvement included chest radiography and high-resolution computed tomography of the chest, pulmonary assessment including diffusion capacity for carbon monoxide (DLCO), echocardiography, nerve-conduction velocity studies, complete blood count, peripheral blood film and erythrocyte sedimentation rate.

The study assessed skin manifestations (rheumatoid nodules, ulcers and vasculitis); ocular manifestations (dry eye, episcleritis and scleritis); pulmonary manifestations (pulmonary hypertension, interstitial lung disease, bronchiectasis, pulmonary nodules and pleural effusion); cardiovascular manifestations (pericarditis, myocarditis and heart failure); haematological manifestations (anaemia, bicytopenia, pancytopenia and thrombocytosis); neurological manifestations (neuropathy, carpal tunnel syndrome and myelopathy); renal manifestations (proteinuria, amyloidosis and chronic kidney disease); and oral manifestations (secondary Sjögren syndrome and salivary gland swelling).

Statistical analysis

Data were entered into Microsoft Excel and analysed using SPSS version 25. Categorical variables were summarized as frequencies and

percentages. Associations between treatment groups and individual manifestations were assessed using appropriate statistical tests as recorded in the thesis. A two-sided p value <0.05 was considered statistically significant.

Ethical considerations

The thesis states that the study protocol was submitted to the scientific and ethics committee of the institution and that ethical approval was obtained before recruitment. Written informed consent was obtained from participants, and study information was maintained in a confidential, password-protected database. Ethics committee approval number/date should be inserted in the final submission: [INSERT IEC/IRB APPROVAL NUMBER AND DATE].

RESULTS

A total of 200 patients were included. The age distribution was <50 years in 51 (25.5%), 50–59 years in 73 (36.5%), 60–69 years in 63 (31.5%), and ≥ 70 years in 13 (6.5%). Thus, 136 patients (68.0%) were aged 50–69 years. There were 151 females (75.5%) and 49 males (24.5%).

The mean DAS28 score was 1.7 ± 0.8 . Conventional DMARDs were being used by 158 patients (79.0%), while 42 (21.0%) were receiving non-cDMARD treatment.

The distribution of recorded extra-articular manifestations is summarized in Table 1. Among skin manifestations, rheumatoid nodules were present in 7 patients (3.5%), ulcers in 4 (2.0%) and vasculitis in 2 (1.0%). Ocular manifestations included episcleritis in 32 patients (16.0%) and dry eye in 26 (13.0%); no cases of scleritis were recorded.

Pulmonary manifestations included interstitial lung disease in 15 patients (7.5%), pulmonary



hypertension in 13 (6.5%), pulmonary nodules in 5 (2.5%), bronchiectasis in 2 (1.0%) and pleural effusion in 2 (1.0%). Cardiovascular involvement comprised heart failure in 10 patients (5.0%); no pericarditis or myocarditis was reported.

Haematological manifestations included anaemia in 54 patients (27.0%), bicytopenia in 20 (10.0%), pancytopenia in 5 (2.5%) and thrombocytosis in 2 (1.0%). Neurological manifestations included neuropathy in 18 patients (9.0%), carpal tunnel syndrome in 4 (2.0%) and myelopathy in 3 (1.5%). Renal manifestations included proteinuria in 10

patients (5.0%), chronic kidney disease in 9 (4.5%) and amyloidosis in 2 (1.0%). Oral manifestations included secondary Sjögren syndrome in 21 patients (10.5%) and salivary gland swelling in 8 (4.0%).

For the individual manifestations reported in the thesis, none showed a statistically significant difference between the cDMARD and non-cDMARD groups. The lowest reported p value was 0.068 for dry eye, followed by 0.092 for neuropathy; both remained above the prespecified threshold of 0.05.

Table 1. Spectrum of recorded extra-articular manifestations in the study population (n=200)

Organ system	Manifestation	n (%)
Skin	Rheumatoid nodules	7 (3.5)
Skin	Ulcers	4 (2.0)
Skin	Vasculitis	2 (1.0)
Ocular	Episcleritis	32 (16.0)
Ocular	Dry eye	26 (13.0)
Ocular	Scleritis	0 (0)
Pulmonary	Interstitial lung disease	15 (7.5)
Pulmonary	Pulmonary hypertension	13 (6.5)
Pulmonary	Pulmonary nodules	5 (2.5)
Pulmonary	Bronchiectasis	2 (1.0)
Pulmonary	Pleural effusion	2 (1.0)
Cardiovascular	Heart failure	10 (5.0)
Cardiovascular	Pericarditis	0 (0)
Cardiovascular	Myocarditis	0 (0)
Haematological	Anaemia	54 (27.0)
Haematological	Bicytopenia	20 (10.0)
Haematological	Pancytopenia	5 (2.5)
Haematological	Thrombocytosis	2 (1.0)
Neurological	Neuropathy	18 (9.0)
Neurological	Carpal tunnel syndrome	4 (2.0)
Neurological	Myelopathy	3 (1.5)
Renal	Proteinuria	10 (5.0)
Renal	Chronic kidney disease	9 (4.5)
Renal	Amyloidosis	2 (1.0)
Oral	Secondary Sjögren syndrome	21 (10.5)
Oral	Salivary gland swelling	8 (4.0)

Table 2. Selected comparisons between cDMARD and non-cDMARD groups

Manifestation	cDMARDs n (%)	Non-cDMARDs n (%)	p value
Rheumatoid nodules	6 (3.8)	1 (2.4)	0.657
Dry eye	17 (10.8)	9 (21.4)	0.068
Episcleritis	28 (17.8)	4 (9.5)	0.193



Pulmonary hypertension	10 (6.3)	3 (7.1)	0.849
Interstitial lung disease	13 (8.2)	2 (4.8)	0.448
Heart failure	9 (5.7)	1 (2.4)	0.391
Anaemia	46 (29.1)	8 (19.0)	0.192
Neuropathy	17 (10.8)	1 (2.4)	0.092
Proteinuria	10 (6.3)	0 (0)	0.094
Chronic kidney disease	7 (4.4)	2 (4.8)	0.927
Secondary Sjögren syndrome	18 (11.4)	3 (7.1)	0.425

Only selected comparisons are shown. Complete treatment-group tables are available in the underlying thesis. No comparison shown reached $p < 0.05$.

DISCUSSION

The present hospital-based study describes a broad spectrum of extra-articular involvement among 200 patients with RA attending a tertiary-care centre in Kashmir. The cohort was predominantly female (75.5%), and more than two-thirds of patients were aged 50–69 years. This demographic pattern is broadly consistent with previous RA cohorts, including the KRAC study, which reported a marked female predominance, and the Egyptian cohort of El-Baz et al., in which 88% of participants were female.[23,25]

The mean DAS28 score in the present cohort was 1.7 ± 0.8 , indicating low disease activity by conventional DAS28 interpretation. This is relevant because previous studies have reported associations between disease activity and extra-articular involvement. El-Baz et al. reported a relationship between disease activity and EAMs, while ElSherbiny et al. identified disease duration and DAS28 as predictors of EAMs.[23,9] Because the present study is observational and the available data do not establish temporal relationships, the low disease activity observed here should be interpreted as a characteristic of the cohort rather than evidence that disease control caused a lower frequency of EAMs.

Ocular manifestations were prominent in this cohort, particularly episcleritis (16.0%) and dry eye (13.0%). The observed frequency of ocular involvement falls within the broad range reported in previous studies, although direct comparison is limited by differences in definitions and screening methods. ElSherbiny et al. reported ocular involvement in 23% of patients, whereas Zafar et al. reported lower overall neurological and cardiac involvement and a different distribution of EAMs.[9,31] The absence of recorded scleritis in the present cohort may reflect its relative rarity and/or the clinical characteristics of the study population.

Pulmonary disease represented an important component of the observed EAM profile. Interstitial lung disease was documented in 7.5% and pulmonary hypertension in 6.5% of patients. Previous Indian studies have reported substantial pulmonary abnormalities in RA, including HRCT and pulmonary-function abnormalities, and the KRAC study identified a lower overall frequency of EAMs in a large multicentre cohort.[22,25,28] Differences in prevalence between studies may arise from whether systematic HRCT, pulmonary-function testing and echocardiography were performed in all participants or selectively in symptomatic patients.

Anaemia was the most frequent haematological manifestation in the present study, occurring in 27% of patients. This is consistent with the prominence of anaemia in several RA cohorts,



although the frequency was lower than the 43% reported by ElSherbiny et al.[9] Bicytopenia and pancytopenia were less common. These abnormalities may have multiple causes in patients with RA, including chronic inflammation, nutritional deficiency, renal disease, medication effects and marrow disorders; therefore, they should not automatically be attributed to RA itself.

Neurological manifestations included neuropathy (9.0%), carpal tunnel syndrome (2.0%) and myelopathy (1.5%). The neuropathy frequency was lower than that reported in the seropositive subgroup of Kumar et al., but the carpal tunnel frequency was similar to that reported by Zafar et al.[30,31] Differences may reflect variation in disease duration, ascertainment and use of nerve-conduction studies.

Renal involvement included proteinuria, chronic kidney disease and amyloidosis. Renal amyloidosis was present in 1% of the cohort, lower than the 6% reported in the hospital-based Saudi Arabian study by Al-Ghamdi et al.[21] Because renal disease in RA may also result from comorbid hypertension, diabetes, medications or other kidney diseases, attribution requires appropriate clinical and laboratory evaluation.

Secondary Sjögren syndrome was recorded in 10.5% of the present cohort. Santosh et al. reported 5.5% secondary Sjögren syndrome in northern Indian patients with RA, whereas Ksir et al. reported 22.1% in a Moroccan cohort.[27,29] Such differences may reflect differences in patient selection, disease duration and diagnostic criteria. The present findings support attention to sicca symptoms and appropriate evaluation when clinically indicated.

No statistically significant differences were identified between cDMARD and non-cDMARD groups for the individual manifestations analysed.

These comparisons should not be interpreted as evidence that treatment has no effect on EAMs because treatment allocation was not randomized, the groups were unequal in size, and confounding by disease severity and duration is likely. Larger prospective studies with multivariable adjustment are needed to examine treatment-related associations.

STRENGTHS AND LIMITATIONS

Strengths include inclusion of 200 patients from a tertiary rheumatology service, assessment across multiple organ systems, and use of clinical, laboratory, radiological, pulmonary, cardiac and neurological investigations where indicated.

Several limitations should be considered. First, this was a single-centre hospital-based observational study, limiting generalizability to the wider Kashmiri or Indian RA population. Second, retrospective and prospective data were combined, which may introduce information and ascertainment bias. Third, the thesis does not provide a complete standardized definition or systematic screening protocol for every EAM, and the frequency of a manifestation may therefore reflect the clinical investigations performed. Fourth, the available results do not permit determination of the proportion of patients with at least one EAM because individual manifestations may overlap within patients. Fifth, potentially important predictors such as RA disease duration, rheumatoid factor titre, anti-CCP status, smoking, radiographic joint damage and detailed medication exposure were not analysed comprehensively in the presented results. Finally, the treatment-group comparisons are observational and should not be interpreted causally.



CONCLUSION

Patients with rheumatoid arthritis attending this tertiary-care centre demonstrated a diverse spectrum of extra-articular involvement, with anaemia, episcleritis, dry eye, interstitial lung disease, pulmonary hypertension, neuropathy and secondary Sjögren syndrome among the more frequently recorded manifestations. The findings emphasize the multisystem nature of RA and the importance of clinical surveillance for organ involvement. Future multicentre prospective studies using standardized definitions and systematic screening should better quantify the burden of EAMs and identify independent demographic, serological, disease-related and treatment-related predictors in the Kashmiri population.

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HOW TO CITE: Dr. Parveez Ahmad Khan, Dr. Mushtaq Ahmad Dangroo, Dr. Muzaffar Bindroo, Profile of Extra-Articular Manifestations in Patients with Rheumatoid Arthritis Attending a Tertiary Care Centre in Kashmir: A Hospital-Based Observational Study, *Int. J. of Pharm. Sci.*, 2026, Vol 4, Issue 10, 1114-1121. <https://doi.org/10.5281/zenodo.23212865>

