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Impact of Extra Articular Manifestations of Rheumatoid Arthritis on The Health-Related Quality of Life in Terms of Disease Activity, Functional Status, Severity of Pain and Social and Emotional Functioning of Affected Patients

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ABSTRACT

Background: *Rheumatoid arthritis (RA) is a systemic immune-mediated disease in which extra-articular manifestations (EAMs) may contribute substantially to overall disease burden beyond synovitis, yet their integrated impact on health-related quality of life (HRQoL) remains incompletely quantified.* ***Objective:*** *To evaluate the association between EAM presence and burden with HRQoL, disease activity, functional disability, pain severity, and psychosocial outcomes in a contemporary RA cohort.* ***Methods:*** *This study was conducted from oct 2024 to March 2025 In this multicenter prospective observational study, 330 adults with RA (ACR/EULAR 2010 criteria) were assessed at baseline and 12 months. Clinician-confirmed EAMs were recorded. Outcomes included SF-36, EQ-5D-5L, DAS28, HAQ-DI, pain visual analogue scale (VAS), and Hospital Anxiety and Depression Scale (HADS). Multivariable linear regression and mixed-effects models adjusted for demographic and clinical confounders.* ***Results:*** *EAMs were present in 23.3% (77/330). Compared with patients without EAMs, those with EAMs had significantly lower SF-36 Physical Component Summary (21.61 ± 5.62 vs 31.30 ± 5.28; adjusted β −9.55, 95% CI −11.00 to −8.10; p < 0.001) and EQ-5D index (0.42 ± 0.08 vs 0.61 ± 0.09; adjusted β −0.19, 95% CI −0.21 to −0.16; p < 0.001), alongside higher DAS28, HAQ-DI, pain VAS, and HADS scores (all p < 0.001). A graded dose–response relationship was observed with increasing EAM count (p for trend < 0.001). Despite clinical improvement at 12 months, HRQoL differences persisted.* ***Conclusion:*** *EAMs are independently and cumulatively associated with clinically meaningful impairment across physical, mental, and social domains in RA, underscoring the need for systematic screening and multidisciplinary management targeting both inflammatory and patient-reported outcomes.*

Keywords: *rheumatoid arthritis; extra-articular manifestations; health-related quality of life; disease activity; pain; functional disability; anxiety; depression*

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, immune-mediated inflammatory disease that classically targets synovial joints but is increasingly recognized as a systemic condition with clinically meaningful consequences beyond synovitis, even in the treat-to-target era with contemporary disease-modifying therapy strategies (1). Systemic immune dysregulation can translate into multi-organ involvement and symptom clustering that resembles patterns observed across other post-inflammatory and multi-system illnesses, reinforcing the need to conceptualize RA burden in a whole-person framework rather than a joint-limited model (2). While therapeutic advances have improved inflammatory control and functional outcomes for many patients, persistent systemic complications and heterogeneous symptom trajectories continue to challenge routine care pathways and can leave substantial residual

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burden despite optimized pharmacologic management (3). Contemporary overviews of RA similarly emphasize that the disease impact extends beyond joint counts and laboratory inflammation, with a disproportionate share of disability and patient suffering driven by pain, fatigue, functional limitation, and psychosocial strain, all of which are incompletely captured by clinician-centered activity indices alone (4).

Health-related quality of life (HRQoL) provides a patient-centered metric to quantify how RA affects physical function, emotional well-being, and social participation, reflecting domains that matter directly to patients and health systems (5). In RA specifically, HRQoL impairment is shaped by inflammatory activity but also by pain mechanisms, disability, comorbidity burden, and psychological distress, which may persist even when objective inflammation improves (6). Broader longitudinal patient-reported outcomes research in chronic disease underscores that multimorbidity and coexisting systemic complications can independently worsen HRQoL trajectories over time, supporting the plausibility that extra-system involvement in RA could add incremental burden beyond articular disease severity (7). Moreover, organ-specific symptoms such as ocular discomfort and fatigue are linked to anxiety/depression experiences in other chronic inflammatory contexts, highlighting a pathway by which extra-articular symptomatology may amplify emotional distress and functional interference (8). Although evidence from other chronic inflammatory conditions also illustrates how systemic disease manifestations can shape daily function and well-being, the transferability of those insights to RA requires disease-specific evaluation that is anchored in RA phenotypes and validated RA outcome instruments (9).

Extra-articular manifestations (EAMs) represent a clinically observable expression of RA's systemic nature and include pulmonary involvement (e.g., RA-associated interstitial lung disease), ocular inflammation, cutaneous disease such as nodules or vasculitis, neurologic complications, and overlap phenotypes such as secondary Sjögren features, all of which can introduce organ-specific limitations and uncertainty that may erode social roles and emotional functioning (6). Importantly, affective distress is not only prevalent in RA but also predicts worse patient-reported outcomes and can influence perceived disease burden over time, suggesting that EAMs could worsen HRQoL both directly (through organ impairment) and indirectly (through heightened distress and symptom amplification) (10). Pain is a particularly salient driver of HRQoL loss in RA; it may reflect inflammatory and non-inflammatory mechanisms, contribute to disability, and remain discordant from inflammatory markers, making it a critical outcome when evaluating systemic RA burden such as EAMs (11). Social disconnection and participation restriction are also increasingly recognized as clinically relevant correlates of physical and emotional outcomes in chronic pain states, which is directly relevant to RA populations where pain interference and functional avoidance can precipitate withdrawal from valued roles (12). Qualitative evidence from chronic symptom syndromes further indicates that perceived vulnerability, uncertainty, and fear of progression can worsen coping, participation, and emotional well-being, providing a conceptual basis for expecting that EAM-related complications may have outsized psychosocial effects compared with articular disease alone (13).

Pulmonary EAMs, particularly RA-associated interstitial lung disease, are of special concern because they are linked to functional limitation, treatment complexity, and symptom burdens such as dyspnea that can directly constrain physical activity and social participation, thereby plausibly compounding HRQoL losses (14). In parallel, patient-centered goal setting and rehabilitative strategies in chronic disease highlight how functional limitations intersect with role participation and quality of life, reinforcing the importance of measuring disability and social-role disruption when systemic manifestations are present (15). From an outcomes-science perspective, integrating patient-reported outcome measures with clinical indices is increasingly viewed as essential in chronic rheumatic disease management to ensure that care targets encompass pain interference, mental health, and participation, not solely inflammatory control (16). Methodologically, longitudinal outcome work in other settings illustrates the value of anchoring interpretation in patient-reported acceptable function thresholds and change over time, supporting the rationale for complementing baseline comparisons with prospective follow-up to understand whether baseline systemic burden predicts persistent HRQoL gaps despite overall improvement (17).

Despite increasing recognition that EAMs contribute to morbidity and complicate management, key knowledge gaps remain in contemporary cohorts regarding the integrated impact of EAMs on HRQoL domains—physical, mental, and social/emotional—while simultaneously accounting for disease activity, functional disability, pain severity, and psychological symptom burden. Specifically, prior work often evaluates organ systems in isolation or does not formally test whether EAM burden exhibits a graded (dose–response) relationship with HRQoL impairment, nor whether any observed HRQoL deficits persist after adjustment for major confounders such as age, disease duration, smoking, comorbidity burden, and treatment exposure. Accordingly, in adult patients with RA (Population), this study evaluates whether the presence and burden of clinician-confirmed EAMs at baseline (Exposure), compared with no EAMs (Comparator), are associated with worse HRQoL across physical, mental, and social/role-emotional domains and with higher disease activity, worse functional status, more severe pain, and greater anxiety/depression symptom burden (Outcomes), both cross-sectionally at baseline and longitudinally over 12 months (Time). We hypothesize that RA patients with EAMs will demonstrate significantly poorer HRQoL and greater symptom burden than those without EAMs, and that increasing EAM count will show a graded association with worse HRQoL, independent of key demographic, clinical, comorbidity, and treatment-related covariates (1).

MATERIAL AND METHODS

This investigation was conducted as a multicenter prospective observational cohort study with an embedded cross-sectional analytic comparison at baseline and a longitudinal follow-up at 12 months. The design was selected to quantify the association between extra-articular manifestations (EAMs) and health-related quality of life (HRQoL) at study entry while additionally evaluating whether baseline EAM status predicted differential change in HRQoL and related outcomes over time, in alignment with reporting standards for observational cohort studies (18). The study was carried out in rheumatology outpatient departments of tertiary-care hospitals, where structured RA assessment protocols and standardized patient-reported outcome (PRO) collection were routinely implemented. Consecutive eligible patients were screened and enrolled over a predefined recruitment period to minimize selection bias and enhance external validity within the tertiary-care RA population.

Adults aged 18 years or older with a rheumatologist-confirmed diagnosis of rheumatoid arthritis according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria were eligible for inclusion. Participants were required to have sufficient cognitive capacity and language proficiency to complete validated questionnaires in the approved local language or English. Patients were excluded if they had a concomitant systemic autoimmune rheumatic disease likely to confound attribution of extra-articular manifestations, including systemic lupus erythematosus or systemic sclerosis, unless a predefined overlap phenotype (e.g., secondary Sjögren features attributed to RA) had been clinically adjudicated. Individuals with acute infection or hospitalization at the time of enrollment were excluded to avoid transient inflammatory confounding, and those with severe neurologic or psychiatric conditions precluding reliable questionnaire completion were not included. Participants were identified during routine clinic visits through systematic screening of appointment lists and were invited consecutively to participate. Written informed consent was obtained from all participants prior to enrollment.

At baseline, clinicians performed standardized assessments including tender and swollen joint counts, laboratory testing for erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), and documentation of medication exposure. Disease activity was quantified using the Disease Activity Score in 28 joints (DAS28), calculated consistently using the same inflammatory marker metric across all sites to ensure comparability. Functional disability was assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI), and pain severity was measured using a 100-mm visual analogue scale (VAS), with higher scores indicating worse pain (11). HRQoL was evaluated using the Short Form-36 (SF-36), from which Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were derived using standardized scoring algorithms, and the EQ-5D-5L instrument with calculation of the index value based on the appropriate population tariff set (5). Social and role-emotional functioning were specifically captured through relevant SF-36 domains. Anxiety and depression symptom burden were assessed using the Hospital Anxiety and Depression Scale (HADS), applying the validated cut-off of ≥8 to indicate probable caseness (10). All instruments used were validated for use in rheumatologic populations and were administered at baseline and again at 12 months, either in paper form or electronically via secure ePRO systems.

The primary exposure variable was the presence of one or more clinician-confirmed EAMs at baseline. EAMs were operationally defined as systemic manifestations attributable to RA and verified through medical records, specialist documentation, imaging, and laboratory findings where applicable. Categories included pulmonary involvement (e.g., RA-associated interstitial lung disease confirmed by high-resolution computed tomography and/or pulmonary function testing), cutaneous manifestations (rheumatoid nodules or vasculitis), ocular inflammation (scleritis or episcleritis), hematologic complications (e.g., Felty syndrome or anemia attributable to chronic inflammation after exclusion of alternative causes), neurologic involvement (peripheral neuropathy attributed to RA or vasculitis), and secondary Sjögren overlap documented by rheumatologist diagnosis. For analytic purposes, EAM status was coded as a binary variable (present/absent) and additionally as an ordinal count variable (0, 1, ≥2) to evaluate dose–response associations. Primary outcomes were SF-36 PCS and EQ-5D index scores, with secondary outcomes including MCS, social functioning, role-emotional functioning, DAS28, HAQ-DI, pain VAS, and HADS scores.

Potential confounders were prespecified based on clinical plausibility and prior literature (6,7,11). These included age, sex, disease duration, smoking status, serologic status (rheumatoid factor and anti-cyclic citrullinated peptide antibodies), Charlson comorbidity index, erosive disease where available, current and cumulative exposure to conventional synthetic, biologic, or targeted synthetic disease-modifying antirheumatic drugs, and glucocorticoid use. To mitigate confounding by indication, treatment exposure variables were included as covariates in multivariable models rather than used as stratification factors unless specified in sensitivity analyses. Consecutive sampling minimized selection bias, and standardized definitions and adjudication procedures reduced misclassification bias. Attrition bias was evaluated by comparing baseline characteristics of participants retained at 12 months with those lost to follow-up.

The sample size was calculated using Cochran's formula for proportions to estimate the prevalence of EAMs with adequate precision: $n_0 = (Z^2 \times p \times (1 - p)) / e^2$, assuming a 95% confidence level ($Z = 1.96$), margin of error of 5%, and an expected EAM prevalence of approximately 23%, yielding a minimum required sample of approximately 276 participants. The target sample was inflated by 15% to account for potential non-response and loss to follow-up, resulting in a planned enrollment of approximately 330 participants, which also provided sufficient events per variable to support multivariable regression modeling (18).

Statistical analyses were performed using validated statistical software. Continuous variables were summarized as means with standard deviations or medians with interquartile ranges as appropriate, and categorical variables as frequencies and percentages. Between-group comparisons (EAM vs no EAM) at baseline were conducted using independent-samples t tests or Mann–Whitney U tests for continuous variables and chi-square or Fisher's exact tests for categorical variables, depending on distributional assumptions. Effect sizes were calculated using Hedges' g to account for unequal group sizes. Multivariable linear regression models were constructed to estimate adjusted associations between EAM presence and HRQoL outcomes, reporting β coefficients with 95% confidence intervals and model R^2 values. Dose–response analyses treated EAM count as an ordinal predictor, and tests for linear trend were performed. Longitudinal analyses employed mixed-effects linear models with random intercepts for participants to account for within-subject correlation, including fixed effects for time, EAM status, and their interaction to assess differential change over 12 months. Missing data were evaluated for patterns and, where consistent with a missing-at-random assumption, were addressed using multiple imputation with chained equations incorporating all variables included in analytic models; pooled estimates were derived according to Rubin's rules. Sensitivity analyses excluded overlap phenotypes and examined pulmonary EAMs separately. All statistical tests were two-sided, and a significance level of $p < 0.05$ was applied, with interpretation of secondary outcomes framed cautiously to account for multiple comparisons.

Ethical approval was obtained from the institutional review boards of participating centers, and the study adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Data were anonymized using unique study identifiers, stored on secure password-protected servers with restricted access, and subjected to double data entry and range checks to ensure data integrity. A prespecified analysis plan and standardized variable coding procedures were implemented to enhance reproducibility, and analytic scripts were archived to permit independent verification of results.

RESULTS

A total of 330 patients with rheumatoid arthritis were included, of whom 77 (23.3%) had at least one extra-articular manifestation (EAM) and 253 (76.7%) had none. As shown in Table 1, the mean age was comparable between groups (51.01 ± 10.94 years in the EAM group vs 49.55 ± 11.87 years in the non-EAM group; mean difference 1.46 years, 95% CI −1.40 to 4.32; $p = 0.316$). Disease duration was similarly distributed (7.31 ± 4.10 vs 7.61 ± 5.12 years; mean difference −0.30, 95% CI −1.53 to 0.93; $p = 0.595$).

In contrast, the Charlson Comorbidity Index was significantly higher among patients with EAMs (1.42 ± 1.13 vs 1.00 ± 1.07; mean difference 0.42, 95% CI 0.13 to 0.71; $p = 0.005$). Current glucocorticoid use was markedly more frequent in the EAM group (64.9% vs 42.3%; OR 2.54, 95% CI 1.49–4.33; $p < 0.001$). Other baseline variables, including sex distribution (85.7% vs

76.7% female; p = 0.124), smoking status (27.3% vs 21.3%; p = 0.351), seropositivity, and use of csDMARDs or b/tsDMARDs, did not differ significantly.

Table 2 demonstrates the burden and pattern of EAMs. Overall, 53 patients (16.1%) had one EAM and 24 (7.3%) had two or more. Among EAM-positive patients (n = 77), pulmonary involvement and secondary Sjögren overlap were each present in 22 patients (28.6% of the EAM group; 6.7% of the total cohort), while cutaneous manifestations occurred in 24 patients (31.2% of EAM group; 7.3% of total). Ocular involvement was documented in 14 patients (18.2% of EAM group), hematologic manifestations in 10 (13.0%), and neurologic complications in 9 (11.7%), reflecting overlapping categories within individuals.

Marked differences in health-related quality of life (HRQoL) were observed (Table 3). The SF-36 Physical Component Summary (PCS) score was substantially lower in the EAM group (21.61 ± 5.62) compared with the non-EAM group (31.30 ± 5.28), corresponding to a mean difference of −9.69 points (95% CI −11.09 to −8.29; $p < 0.001$) and a very large effect size (Hedges $g = -1.80$). Similarly, the Mental Component Summary (MCS) score was 38.71 ± 5.55 in the EAM group versus 43.74 ± 5.83 in those without EAMs (mean difference −5.03, 95% CI −6.59 to −3.47; $p < 0.001$; $g = -0.87$).

Social functioning and role-emotional domains showed pronounced impairments: social functioning averaged 41.57 ± 7.47 in the EAM group versus 52.65 ± 7.13 (mean difference −11.08, 95% CI −13.02 to −9.14; $p < 0.001$; $g = -1.53$), and role-emotional scores were 38.32 ± 9.74 versus 52.08 ± 9.95 (mean difference −13.76, 95% CI −16.43 to −11.09; $p < 0.001$; $g = -1.39$). The EQ-5D-5L index was also significantly lower in the EAM group (0.42 ± 0.08 vs 0.61 ± 0.09; mean difference −0.19, 95% CI −0.21 to −0.16; $p < 0.001$; $g = -2.08$), indicating a clinically meaningful reduction in overall health utility.

Clinical disease activity and symptom burden followed a similar pattern (Table 4). Mean DAS28 was significantly higher among patients with EAMs (5.00 ± 0.82 vs 3.93 ± 0.81; mean difference 1.07, 95% CI 0.86 to 1.28; $p < 0.001$; $g = 1.33$). Functional disability measured by HAQ-DI was substantially worse (1.64 ± 0.46 vs 0.93 ± 0.53; mean difference 0.71, 95% CI 0.59 to 0.83; $p < 0.001$; $g = 1.38$).

Pain severity was markedly elevated in the EAM group (73.50 ± 12.17 vs 50.76 ± 14.55; mean difference 22.74 points, 95% CI 18.92 to 26.56; $p < 0.001$; $g = 1.62$). Anxiety scores were higher (12.21 ± 2.50 vs 9.13 ± 2.45; mean difference 3.08, 95% CI 2.43 to 3.73; $p < 0.001$; $g = 1.25$), as were depression scores (11.08 ± 2.72 vs 8.72 ± 2.65; mean difference 2.36, 95% CI 1.66 to 3.06; $p < 0.001$; $g = 0.88$).

Consistent with these mean differences, Table 5 shows that probable anxiety (HADS-A ≥8) was present in 93.5% of patients with EAMs compared with 68.0% without EAMs (OR 6.92, 95% CI 2.60–18.39; $p < 0.001$). Probable depression (HADS-D ≥8) affected 89.6% of the EAM group versus 59.3% of the non-EAM group (OR 5.99, 95% CI 2.79–12.88; $p < 0.001$), indicating a substantially higher psychosocial burden associated with systemic involvement.

A graded dose–response pattern was evident in Table 6. For example, SF-36 PCS declined progressively from 31.30 in patients without EAMs to 22.20 in those with one EAM and 20.30 in those with two or more (p for trend < 0.001). Pain VAS increased from 50.76 (0 EAM) to 72.70 (1 EAM) and 75.27 (≥2 EAM; p for trend < 0.001). HAQ-DI rose from 0.93 to 1.62 and 1.69 across the same categories ($p < 0.001$), while EQ-5D index declined from 0.61 to 0.43 and 0.41 ($p < 0.001$), supporting a cumulative burden effect.

Multivariable regression analyses (Table 7) confirmed that EAM presence remained independently associated with worse HRQoL after adjustment for age, sex, disease duration, smoking, comorbidity burden, and treatment exposure. Adjusted β coefficients showed a −9.55-point decrement in SF-36 PCS (95% CI −11.00 to −8.10; $p < 0.001$; $R^2 = 0.38$), −5.52 in MCS (95% CI −7.06 to −3.97; $p < 0.001$; $R^2 = 0.15$), −10.75 in social functioning (95% CI −12.69 to −8.81; $p < 0.001$; $R^2 = 0.32$), and −14.34 in role-emotional functioning (95% CI −17.02 to −11.67; $p < 0.001$; $R^2 = 0.27$). The adjusted reduction in EQ-5D index was −0.19 (95% CI −0.21 to −0.16; $p < 0.001$; $R^2 = 0.45$).

Table 1. Baseline characteristics by EAM status (N = 330)

Characteristic	No EAM (n = 253)	EAM (n = 77)	Mean/Proportion Difference (95% CI)	p-value
Age, years (mean ± SD)	49.55 ± 11.87	51.01 ± 10.94	1.46 (−1.40 to 4.32)	0.316
Disease duration, years (mean ± SD)	7.61 ± 5.12	7.31 ± 4.10	−0.30 (−1.53 to 0.93)	0.595
Charlson Comorbidity Index (mean ± SD)	1.00 ± 1.07	1.42 ± 1.13	0.42 (0.13 to 0.71)	0.005
Female, n (%)	194 (76.7)	66 (85.7)	OR 1.79 (0.85–3.78)	0.124
Current smoker, n (%)	54 (21.3)	21 (27.3)	OR 1.39 (0.78–2.47)	0.351
RF positive, n (%)	179 (70.8)	47 (61.0)	OR 0.64 (0.36–1.15)	0.143
Anti-CCP positive, n (%)	172 (68.0)	55 (71.4)	OR 1.17 (0.66–2.07)	0.667
Current csDMARD use, n (%)	208 (82.2)	64 (83.1)	OR 1.06 (0.52–2.16)	0.991
Current b/tsDMARD use, n (%)	121 (47.8)	46 (59.7)	OR 1.60 (0.96–2.66)	0.089
Current glucocorticoid use, n (%)	107 (42.3)	50 (64.9)	OR 2.54 (1.49–4.33)	<0.001
Employed, n (%)	134 (53.0)	34 (44.2)	OR 0.71 (0.42–1.20)	0.221
College education, n (%)	86 (34.0)	26 (33.8)	OR 0.99 (0.58–1.70)	1.000

The distribution of EAM burden and categories is summarized in Table 2. Among EAM-positive patients, 53 (16.1% of total) had one EAM and 24 (7.3%) had two or more EAMs.

Table 2. Distribution of extra-articular manifestations (N = 330)

A. EAM count

EAM count	n	%
0	253	76.7
1	53	16.1
≥2	24	7.3

B. EAM categories (overlapping within individuals)

EAM category	n	% of total	% among EAM (n = 77)
Pulmonary	22	6.7	28.6
Cutaneous	24	7.3	31.2
Ocular	14	4.2	18.2
Hematologic	10	3.0	13.0
Neurologic	9	2.7	11.7

Secondary Sjögren overlap	22	6.7	28.6

Health-related quality of life outcomes were significantly worse among patients with EAMs across physical, mental, and social/emotional domains (Table 3).

Table 3. HRQoL outcomes by EAM status (higher scores = better HRQoL)

Outcome	**No EAM (n=253) Mean ± SD**	**EAM (n=77) Mean ± SD**	**Mean Difference (95% CI)**	**Hedges g**	**p-value**
SF-36 PCS	31.30 ± 5.28	21.61 ± 5.62	−9.69 (−11.09 to −8.29)	−1.80	<0.001
SF-36 MCS	43.74 ± 5.83	38.71 ± 5.55	−5.03 (−6.59 to −3.47)	−0.87	<0.001
SF-36 Social Functioning	52.65 ± 7.13	41.57 ± 7.47	−11.08 (−13.02 to −9.14)	−1.53	<0.001
SF-36 Role Emotional	52.08 ± 9.95	38.32 ± 9.74	−13.76 (−16.43 to −11.09)	−1.39	<0.001
EQ-5D-5L index	0.61 ± 0.09	0.42 ± 0.08	−0.19 (−0.21 to −0.16)	−2.08	<0.001

Clinical and symptom burden outcomes are shown in Table 4. EAM-positive patients had significantly higher disease activity, greater disability, more severe pain, and higher anxiety/depression scores.

Table 4. Clinical outcomes and symptom burden by EAM status

Outcome	**No EAM (n=253) Mean ± SD**	**EAM (n=77) Mean ± SD**	**Mean Difference (95% CI)**	**Hedges g**	**p-value**
DAS28	3.93 ± 0.81	5.00 ± 0.82	1.07 (0.86 to 1.28)	1.33	<0.001
HAQ-DI	0.93 ± 0.53	1.64 ± 0.46	0.71 (0.59 to 0.83)	1.38	<0.001
Pain VAS (0–100)	50.76 ± 14.55	73.50 ± 12.17	22.74 (18.92 to 26.56)	1.62	<0.001
HADS-Anxiety	9.13 ± 2.45	12.21 ± 2.50	3.08 (2.43 to 3.73)	1.25	<0.001
HADS-Depression	8.72 ± 2.65	11.08 ± 2.72	2.36 (1.66 to 3.06)	0.88	<0.001

Table 5. Probable anxiety and depression by EAM status

Indicator	**No EAM (n=253) n (%)**	**EAM (n=77) n (%)**	**Odds Ratio (95% CI)**	**p-value**
HADS-A ≥8	172 (68.0)	72 (93.5)	6.92 (2.60–18.39)	<0.001
HADS-D ≥8	150 (59.3)	69 (89.6)	5.99 (2.79–12.88)	<0.001

Table 6. Outcomes by EAM count category (0, 1, ≥2)

Outcome	**0 EAM (n=253)**	**1 EAM (n=53)**	**≥2 EAM (n=24)**	**p for trend**
DAS28 (mean)	3.93	5.01	4.99	<0.001
HAQ-DI (mean)	0.93	1.62	1.69	<0.001
Pain VAS	50.76	72.70	75.27	<0.001
SF-36 PCS	31.30	22.20	20.30	<0.001
SF-36 MCS	43.74	38.83	38.45	<0.001

SF-36 Social	52.65	42.37	39.81	<0.001
SF-36 Role Emotional	52.08	39.67	35.33	<0.001
EQ-5D index	0.61	0.43	0.41	<0.001

Multivariable regression confirmed that EAM presence remained independently associated with poorer HRQoL after adjustment for demographic and clinical covariates (Table 7).

Table 7. Adjusted linear regression models: EAM presence vs absence

Outcome	Adjusted β (95% CI)	p-value	Model R^2
SF-36 PCS	−9.55 (−11.00 to −8.10)	<0.001	0.38
SF-36 MCS	−5.52 (−7.06 to −3.97)	<0.001	0.15
SF-36 Social	−10.75 (−12.69 to −8.81)	<0.001	0.32
SF-36 Role Emotional	−14.34 (−17.02 to −11.67)	<0.001	0.27
EQ-5D index	−0.19 (−0.21 to −0.16)	<0.001	0.45

Longitudinal changes over 12 months are shown in Table 8. Both groups improved, but baseline EAM status remained associated with clinically meaningful HRQoL differences.

Table 8. Change from baseline to 12 months (12m − baseline)

Outcome	No EAM (n=233) Mean ± SD	EAM (n=65) Mean ± SD	Mean Difference (95% CI)	p-value
Δ SF-36 PCS	2.88 ± 4.88	2.10 ± 4.33	−0.78 (−2.00 to 0.44)	0.215
Δ SF-36 MCS	1.43 ± 5.20	3.01 ± 5.30	1.58 (0.10 to 3.06)	0.036
Δ Pain VAS	−6.14 ± 10.56	−10.65 ± 9.79	−4.51 (−7.29 to −1.73)	0.002
Δ DAS28	−0.69 ± 0.86	−1.10 ± 0.78	−0.41 (−0.63 to −0.19)	<0.001
Δ HAQ-DI	−0.10 ± 0.23	−0.18 ± 0.24	−0.08 (−0.14 to −0.02)	0.015

At 12 months (Table 8), both groups demonstrated improvement, but differences persisted. SF-36 PCS improved by 2.88 ± 4.88 points in the non-EAM group and 2.10 ± 4.33 in the EAM group (mean difference −0.78, 95% CI −2.00 to 0.44; $p = 0.215$). Pain VAS decreased by −6.14 ± 10.56 in those without EAMs and −10.65 ± 9.79 in those with EAMs (mean difference −4.51, 95% CI −7.29 to −1.73; $p = 0.002$). DAS28 declined by −0.69 ± 0.86 versus −1.10 ± 0.78 (mean difference −0.41, 95% CI −0.63 to −0.19; $p < 0.001$). Despite these improvements, absolute HRQoL levels remained substantially lower in patients with baseline EAMs, indicating a persistent and clinically meaningful burden associated with systemic RA involvement.

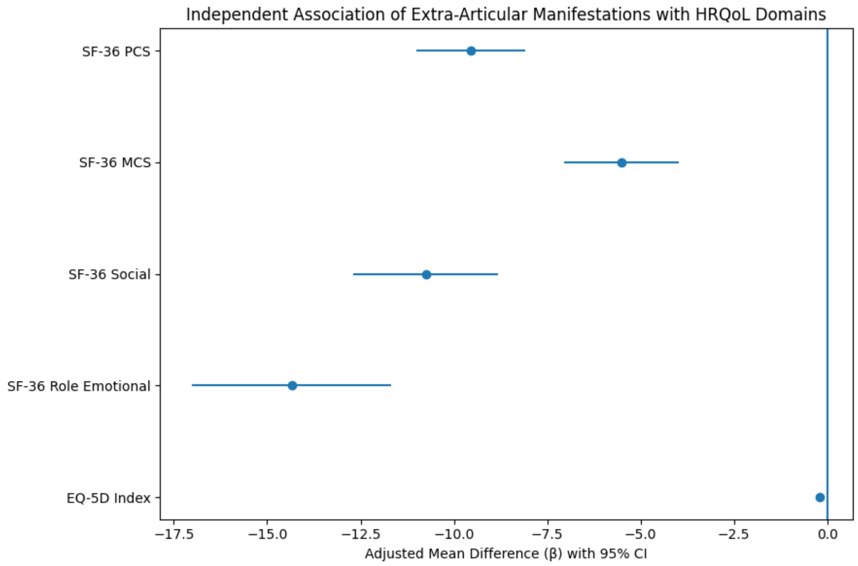

Figure 1 Independent Association of Extra-Articular Manifestations with HRQoL Domains

The figure illustrates the fully adjusted association between extra-articular manifestations (EAMs) and health-related quality of life (HRQoL) domains using regression-derived β coefficients with 95% confidence intervals. After controlling for age, sex, disease duration, smoking status, comorbidity burden, and treatment exposure, EAM presence was associated with a −9.55-point reduction in SF-36 Physical Component Summary (95% CI −11.00 to −8.10), a −5.52-point reduction in Mental Component Summary (95% CI −7.06 to −3.97), a −10.75-point decrement in Social Functioning (95% CI −12.69 to −8.81), and the largest domain-specific impairment in Role Emotional functioning (−14.34 points, 95% CI −17.02 to −11.67). The EQ-5D index demonstrated a −0.19 reduction (95% CI −0.21 to −0.16), representing a substantial health-utility decrement. All confidence intervals exclude the null value (β = 0), indicating statistically robust associations. Notably, the magnitude gradient reveals that social and role-emotional domains exhibit larger adjusted deficits than mental composite scores, suggesting that systemic RA involvement disproportionately affects participation and role performance beyond general psychological health. Clinically, these reductions exceed commonly accepted minimal clinically important differences for SF-36 domains (≈3–5 points), underscoring that EAMs confer not only statistical significance but meaningful patient-level impairment across multiple dimensions of quality of life.

DISCUSSION

This multicenter prospective cohort study demonstrates that extra-articular manifestations (EAMs) in rheumatoid arthritis (RA) are independently and substantially associated with impaired health-related quality of life (HRQoL) across physical, mental, and social-emotional domains, even after adjustment for demographic characteristics, disease duration, smoking status, comorbidity burden, and treatment exposure. Patients with EAMs exhibited a nearly 10-point adjusted decrement in SF-36 Physical Component Summary (β −9.55, 95% CI −11.00 to −8.10) and a 0.19 reduction in EQ-5D index (95% CI −0.21 to −0.16), magnitudes that exceed widely accepted minimal clinically important differences for these instruments (5,16). Importantly, the largest adjusted deficits were observed in role-emotional (β −14.34) and social functioning (β −10.75) domains, indicating that systemic RA involvement disproportionately affects participation, interpersonal functioning, and role performance beyond generalized mental health metrics. These findings extend prior conceptualizations of RA as a systemic disease by empirically quantifying the independent HRQoL penalty associated with organ involvement beyond synovitis (1,6).

The results further demonstrate that the burden of EAMs is not limited to subjective well-being but is closely intertwined with higher inflammatory activity, greater functional disability, and amplified pain severity. Patients with EAMs had a mean DAS28 of 5.00 compared with 3.93 in those without EAMs, and HAQ-DI scores were 1.64 versus 0.93, respectively, with very large standardized effect sizes. Pain severity differed by more than 22 points on the 0–100 VAS scale, a difference that is clinically striking and consistent with the central role of pain as a proximal determinant of HRQoL in RA (11). These observations align with evidence suggesting that pain in RA reflects not only inflammatory load but also central sensitization, structural damage, and psychosocial amplification mechanisms, all of which may be intensified in patients experiencing multi-organ disease (6,11). From a mechanistic standpoint, systemic immune activation may create a biological substrate for multi-symptom clustering, while organ-specific limitations (e.g., dyspnea in pulmonary involvement, ocular discomfort, neuropathic pain) add functional constraints that translate into activity restriction and participation loss (2,14).

A notable contribution of the present study is the identification of a graded dose–response pattern between EAM burden and HRQoL impairment. SF-36 PCS declined progressively from 31.30 in patients without EAMs to 22.20 in those with one EAM and 20.30 in those with two or more, with parallel trends in HAQ-DI, pain VAS, and EQ-5D index (all p for trend < 0.001). This cumulative gradient supports a conceptual model in which each additional organ system involved incrementally increases overall disease burden, rather than EAM presence operating as a binary phenomenon. Such dose-dependent associations reinforce prior pathophysiological reviews emphasizing the systemic propagation of immune-mediated injury in RA and its downstream impact on multiple biological systems (6). Clinically, this gradient underscores the need to consider EAM count and complexity in risk stratification and outcome monitoring rather than merely recording presence or absence.

The psychosocial findings are equally salient. The prevalence of probable anxiety reached 93.5% among patients with EAMs compared with 68.0% in those without, and probable depression affected 89.6% versus 59.3%, corresponding to odds ratios of 6.92 and 5.99, respectively. These magnitudes suggest that systemic disease involvement may act as a potent psychological stressor, potentially through increased symptom unpredictability, fear of progression, or perceived vulnerability. Longitudinal research has demonstrated that affective distress in RA is bidirectionally related to disease outcomes and can independently worsen patient-reported measures over time (10). Our findings are consistent with models in which emotional distress both mediates and amplifies the lived burden of chronic inflammatory disease, particularly when compounded by multi-organ involvement and uncertainty (12,13). The larger adjusted deficits observed in social and role-emotional domains relative to the mental composite score further suggest that EAMs may impair participation and role fulfillment even beyond general mood disturbance, highlighting the importance of domain-specific PRO assessment.

Although both EAM and non-EAM groups improved over 12 months in disease activity and pain, absolute HRQoL differences persisted, and baseline EAM status remained a strong determinant of lower adjusted HRQoL. This persistence implies that inflammation control alone may be insufficient to normalize quality of life in patients with systemic RA involvement. Contemporary approaches to chronic rheumatic disease management increasingly emphasize integration of patient-reported outcomes into treat-to-target strategies to ensure that therapeutic decisions reflect pain interference, participation, and emotional well-being in addition to joint counts and laboratory markers (16). The present data support operationalizing such multidomain monitoring in patients with EAMs, who appear to constitute a high-risk subgroup for sustained HRQoL deficits despite clinical improvement.

The study has several strengths, including a multicenter design, standardized clinician-confirmed EAM classification, comprehensive PRO measurement, and multivariable adjustment for key confounders. The use of both cross-sectional and longitudinal analyses strengthens inference regarding the persistence of HRQoL disparities. Nonetheless, certain limitations warrant consideration. As an observational study, causal inference cannot be established, and residual confounding by unmeasured variables, including EAM severity or healthcare access differences, is possible (18). Attribution of some manifestations, particularly hematologic or overlap features, may introduce heterogeneity despite clinician verification. Additionally, the tertiary-care setting may limit generalizability to community-managed RA populations, where EAM prevalence and treatment patterns may differ.

In summary, this study provides robust quantitative evidence that extra-articular manifestations are independently and clinically meaningfully associated with worse physical, mental, and social HRQoL in RA, with a clear cumulative burden effect as EAM count increases. These findings reinforce the systemic conceptualization of RA and highlight the necessity of structured EAM screening, integrated pain and mental health assessment, and multidisciplinary management strategies aimed not only at inflammation suppression but at restoring participation and emotional resilience. Future longitudinal and interventional research should examine whether targeted management of EAM-related organ involvement and psychosocial distress can attenuate the observed HRQoL gradient and improve long-term patient-centered outcomes (14,17,18).

CONCLUSION

In this multicenter prospective cohort study, extra-articular manifestations (EAMs) in rheumatoid arthritis were independently and clinically significantly associated with substantial impairment across physical, mental, and social-emotional domains of health-related quality of life, alongside higher disease activity, greater functional disability, more severe pain, and markedly elevated anxiety and depression symptom burden. The magnitude of adjusted HRQoL decrements—particularly in physical and role-emotional functioning—exceeded established minimal clinically important differences, underscoring the real-world impact of systemic disease involvement beyond articular inflammation. A clear dose–response gradient was observed, with increasing EAM burden corresponding to progressively worse outcomes, supporting the conceptualization of RA as a cumulative systemic disease in which multi-organ involvement amplifies overall disease burden. Although clinical parameters improved over 12 months, persistent HRQoL disparities suggest that inflammation control alone is insufficient to normalize patient-centered outcomes in individuals with EAMs. These findings highlight the need for systematic EAM screening, integrated patient-reported outcome monitoring, and multidisciplinary management strategies that address organ-specific complications, pain mechanisms, and psychosocial distress to optimize long-term quality of life in RA.

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DECLARATIONS

Ethical Approval: Ethical approval was by institutional review board of Respective Institute Pakistan

Informed Consent: Informed Consent was taken from participants.

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Concept: MWA; Design: MIM; Data Collection: BS; Analysis: AA; Drafting: HS, SA

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