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Delayed referral, socioeconomic status, and disease characteristics as factors associated with disabilities in rheumatoid arthritis patients: a multicenter observational study

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Abstract

*Objective.*This study aims to identify factors associated with higher Rheumatoid Arthritis Articular Damage (RAAD) scores in rheumatoid arthritis (RA) patients and to evaluate correlations between disease duration, joint involvement, extra-articular manifestations, and functional outcomes with the severity of articular damage.
Methods. This multicenter, cross-sectional study was conducted across 8 tertiary care centers in India using the Indian Rheumatology Association database (2019-2022). Patients fulfilling the 2010 ACR/EULAR RA criteria were included. Demographic, clinical, socioeconomic, comorbidity, and disease-specific variables were collected. Articular damage was assessed using the RAAD score. Logistic regression was performed to identify predictors of damage.
Results. Of 4641 recruited patients, 4213 were analyzed (mean age 52.8 years; 87.6% female). Severe damage was observed in 9%, moderate in 9.2%, and absent in 81.9%. Patients with severe damage had longer disease duration (median 13 vs. 8 years; $p<0.001$), more frequent extra-articular (10.3%) and systemic features (7.9%), and greater functional disability (mean health assessment questionnaire 11.12 vs. 3.96; $p<0.001$). Logistic regression identified longer disease duration [odds ratio (OR) 1.008, $p<0.001$], higher visual analog scale pain (OR 1.054, $p=0.009$), physician (OR 1.134, $p=0.004$) and patient global assessments (OR 1.224, $p<0.001$), extra-articular features (OR 2.885, $p<0.001$), and systemic features (OR 4.935, $p<0.001$) as independent predictors of joint damage.
Conclusions. Severe joint damage is associated with delayed presentation, higher disease activity, and extra-articular/systemic features. Socioeconomic factors and comorbidities also influence outcomes. Early referral and comprehensive management are essential to reduce long-term disability in RA.

Key words: rheumatoid arthritis, DMARDs, disability, extra-articular, RAAD score, socioeconomic factors.

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Introduction

Rheumatoid arthritis (RA), a chronic systemic inflammatory autoimmune disorder primarily involving the joints, affects approximately 0.5-1% of the global population, with a prevalence of 0.75% in India (1, 2). RA significantly contributes to the global burden of musculoskeletal conditions, leading to progressive joint damage, functional impairment, and reduced quality of life if inadequately treated (3-5). Despite advances in treatment strategies, RA remains a major cause of long-term and preventable disability worldwide (6, 7).

The disease primarily impacts the joints, where articular damage is conventionally assessed using radiographic evaluation (8). As the disease progresses, extra-articular manifestations may develop, contributing to increased morbidity and mortality, often due to poorly controlled disease (9, 10). Early diagnosis and timely intervention are crucial to prevent damage and disability; however, barriers such as delayed referrals and limited access to care remain prevalent in resource-limited settings such as India (11).

The Rheumatoid Arthritis Articular Damage (RAAD) score, although not frequently used or widely reported in the literature, provides a structured assessment of long-term joint damage in RA patients. It clinically evaluates 16 large and small joints and correlates strongly with radiological damage scores and functional outcomes measured through the Health Assessment Questionnaire (HAQ) (2, 8, 12). This makes RAAD a potentially useful tool in low-resource settings, where access to advanced imaging may be limited, allowing clinicians to monitor irreversible joint damage and prioritize interventions effectively.

Multiple factors contribute to higher RAAD scores and greater disability in RA. Demographic characteristics such as older age and lower education levels, along with clinical factors like prolonged

disease activity, psychosocial aspects, and socioeconomic challenges, play significant roles. Effective management involves the appropriate and timely use of disease-modifying antirheumatic drugs (DMARDs) and ensuring patient adherence to treatment regimens. Persistent moderate to severe disease activity has been strongly linked to diminished quality of life and increased functional limitations (8, 13).

This study aims to identify factors associated with higher RAAD scores in RA patients and to evaluate the influence of disease duration, socioeconomic status, systemic features, and treatment patterns on disease severity. Understanding these factors can help clinicians develop targeted interventions and optimize disease management to prevent joint damage.

Materials and Methods

Registry/database design and study population

This independent, multicenter, cross-sectional study was conducted across eight tertiary care centers in India, using data collected from the database registry established by the Indian Rheumatology Association in April 2020, covering the period from 2019 to 2022. The centers were selected based on their geographical distribution, and the registry was used to collect data on six different autoimmune rheumatic diseases (AIRDs), namely RA, spondyloarthropathy, psoriatic arthritis, systemic lupus erythematosus, scleroderma, and primary Sjögren's syndrome. The current study focused exclusively on RA, including both newly diagnosed and follow-up patients who met the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA (14).

Data were collected using two structured proformas: the first gathered information on demographics, socioeconomic status, functional impairment, obstetric history, and health-related parameters, while the second focused on disease-specific details. The data collection questions were developed by experts involved in deploying the database and underwent a trial phase before being finalized. Clinical research associates (CRAs) completed the responses based on patient feedback and the patients' charts available at the centers. To ensure consistency across all centers, both the principal investigators (PIs) and CRAs participated in online training sessions organized by the primary center. Any questions related to data collection were addressed by the PI at the primary center. All participating centers received approval from their respective institutional ethics committees, including IEC-CRICR-132/101/2020 (details of all other ethics committees are provided below).

Sample size calculation for registry

For the entire database registry, the minimum number of subjects with AIRDs required for comparison was calculated to achieve the primary objective of evaluating the clinical and laboratory profiles of six AIRDs. Based on prevalence data, the total number of patients to be recruited for the entire registry was estimated at 6500. The sample size for each individual disease was determined proportionally according to its prevalence. For RA, with an estimated prevalence of 0.6% to 1.2%, approximately 2000 patients were considered the minimum target (15).

Data collection and definition

Demographic data included age, gender, duration of RA at presentation (the time from the onset of initial symptoms or signs attributable to RA), and total disease duration at the time of recruitment (encompassing both RA at presentation and follow-up). The initial presentation was defined as the earliest symptom, sign, or joint affected within the first 6 weeks, as recalled by the patients. Based on the involved joints, these were categorized into upper limb, lower limb, or both (referred to as "all joints"). The initial manifestation attributable to RA was captured and defined as the first joint or joints involved within the first 6 months. Based on joint involvement, the presentation was classified as upper limb (*e.g.*, metacarpophalangeal joints of the hands and shoulders), lower limb (*e.g.*, knees, feet), or "other than joints" (*e.g.*, neck, back, non-joint areas). If pain occurred in multiple areas, such as both upper and lower limb joints, it was classified as a polyarticular presentation. Oligoarthritic involvement was defined separately. In terms of socioeconomic classification, the upper-lower and lower classes were combined into the lower class, the lower-middle class was considered the middle class, and the upper and upper-middle classes were grouped under the upper class. The modified scale was used for socioeconomic classification (16) (*Supplementary Table 1*).

The data on comorbidities were collected as per the definitions in the new International Classification of Diseases (ICD)-10 version of the Charlson Comorbidity Index (17). Confirmation of these conditions was based on documented information from patients' previous visits or treating physicians; no additional investigations were performed to actively screen for comorbidities. This approach was used to comply with international definitions and to standardize the assessment of comorbidities across all sites. The presence of any one of the comorbidities, as per the definitions, was considered as having a comorbidity. RAAD score was calculated as per the proforma at the point of recruitment. The score was assessed by the study coordinator and was supervised by the PIs, who is a rheumatologist (*Supplementary Table 2*). Extra-articular manifestations were included as per the definition (18). Fever, fatigue, and weight loss were considered systemic features. Sjögren's features referred to sicca symptoms, identified as either dry eyes on ophthalmic examination or dry mouth on routine clinical examination.

Statistical analysis

Descriptive statistics were used, with categorical variables expressed as percentages and continuous variables summarized as mean ± standard deviation. For categorical variables, Fisher's exact test and the chi-square test were utilized, while analysis of variance was applied to continuous variables. The RAAD score was coded as follows: score 0 = no damage, score 1-10 = moderate damage, and score above 10 = severe damage. The study considered only cardiac conditions, hypertension, and diabetes for comorbidity inclusion. The comorbidity variable was coded as "Yes" for the presence of any of the specified comorbidities and "No" for their absence. The analysis focused on patients with more than 5 years of disease to evaluate how RA duration affects deformities compared with shorter disease duration.

For the regression analysis, the RAAD score was categorized into two groups: damage score >0 and no damage (score = 0). Variables with a univariate p-value <0.10 were considered for inclusion in the multivariable logistic regression model. Although total disease duration was significantly associated with the RAAD score, it was highly correlated with the duration of RA at presentation to the rheumatology unit. To reduce multicollinearity, only the duration of RA at presentation was retained in the model. Other variables, including first RA-related symptom, joint

examination findings, and the Indian HAQ score, met the initial screening criterion but were excluded from the final model based on clinical judgment, as they were not considered independent predictors of the RAAD score.

Binary logistic regression was performed using SPSS with the RAAD score as the dependent variable and covariates including age, duration of RA at presentation, socioeconomic class, extra-articular features, visual analog scale (VAS) pain score, VAS physician's global assessment, VAS patient's global assessment, systemic features, and comorbidities. Categorical covariates were defined with reference categories: "lower class" for socioeconomic status and "No" for extra-articular features, systemic features, and comorbidities. The model used stepwise entry and removal (p-values set at 0.05 and 0.10, respectively), with the classification cutoff set at 0.5 and a maximum of 20 iterations. Tables were created using Microsoft® Excel® 2019 MSO (Version 2409 Build 16.0.18025.20030) 64-bit. Statistical analyses were performed using SPSS version 29.0.2.0.

Data on drug usage, including DMARDs, steroids, and targeted therapies, were collected from RA patients across severity groups and analyzed using chi-square or Fisher's exact tests ($p<0.05$). Drug usage patterns were also compared across multiple centers to assess heterogeneity in prescribing practices.

Results

Overall cohort

After excluding 374 patients with missing RAAD scores, 28 with incomplete RA duration data, 24 with missing socioeconomic class data, and 2 with implausible records, 4213 of 4641 subjects were included in the study. The cohort had a mean age of 52.8 years (range 16-97) and a strong female predominance (3693 females *vs*. 520 males). The median total probable duration of RA was 8.08 years (range 0.08-50), while the median duration of RA at presentation to a rheumatology center was 7 years (range 0-50).

Categorization based on the severity of damage

Categorization of patients based on the severity of damage revealed that those with severe joint damage were slightly older (54.20±12.12 years) compared to patients with moderate (52.40±11.55 years) or no damage (52.71±12.17 years) (p=0.059). Female predominance was consistent across all groups, with no significant difference in gender distribution (p=0.547). Both the total probable duration of RA and the duration at presentation to rheumatology were significantly longer in patients with more severe damage, with medians of 13 and 10 years in the severe group

Table 1. Clinical and functional characteristics of rheumatoid arthritis patients categorized by severity of joint damage.

Variables	Severe damage (n=378)	Moderate damage (n=387)	No damage (n=3448)	p
Age	54.20±12.12 (20-87)	52.40±11.55 (22-82)	52.71±12.17 (16-97)	0.059#
Gender, female (male)	331 (47)	346 (41)	3016 (432)	0.547*
Total probable duration of illness (years)	13 (0.17-50)	10 (0.17-49)	8 (0.08-48.17)	<0.001#
Duration of rheumatoid arthritis at presentation to rheumatology (years)	10 (0.17-50)	8 (0.08-35)	6 (0-44.5)	<0.001#
Socioeconomic class, n (%)				
Lower class	82 (21.69)	77 (19.9)	568 (16.47)	0.002*
Middle class	121 (32.01)	124 (32.04)	1357 (39.36)	
Upper class	175 (46.3)	186 (48.06)	1523 (44.17)	
First rheumatoid arthritis-related symptom, n (%)				
Upper limb joints	95 (25.13)	123 (31.78)	599 (17.37)	<0.001*
Lower limb joints	67 (17.72)	98 (25.32)	457 (13.25)	
Polyarticular presentation	62 (16.4)	76 (19.64)	283 (8.21)	
Other than joints	7 (1.85)	2 (0.52)	19 (0.55)	
Unknown	147 (38.89)	88 (22.74)	2090 (60.61)	
Extra-articular features	39 (10.32)	29 (7.49)	57 (1.65)	<0.001*
Systemic features	30 (7.94)	11 (2.84)	16 (0.46)	<0.001*
Indian health assessment questionnaire	11.12±8.22 (0-36)	8.49±6.63 (0-35)	3.96±5.35 (0-36)	<0.001#
Total duration of rheumatoid arthritis, n (%)				
<2 years	17 (4.5)	29 (7.49)	336 (9.74)	<0.001*
2 to 5 years	36 (9.52)	42 (10.85)	718 (20.82)	
5 to 10 years	83 (21.96)	106 (27.39)	1003 (29.09)	
>10 years	242 (64.02)	210 (54.26)	1391 (40.34)	
Duration of rheumatoid arthritis (at presentation to rheumatology) (n=4212), n (%)				
<6 months	7 (1.85)	4 (1.03)	79 (2.29)	<0.001*
6 to 24 months	26 (6.88)	47 (12.14)	552 (16.01)	
25 to 60 months	63 (16.67)	69 (17.83)	862 (25)	
> 60 months	282 (74.6)	267 (68.99)	1954 (56.67)	
Comorbidity	88 (23.28)	110 (28.42)	1038 (30.1)	0.020*

*Chi-square; #analysis of variance; NA, the variables were not treated as continuous due to their significant skewness and were instead considered categorical. Similarly, the Rheumatoid Arthritis Articular Damage score, which was significantly right-skewed, was also treated as a categorical variable.

compared to 8 and 6 years in the no-damage group (p<0.001). Distribution by disease duration further emphasized this trend. A total of 64.02% of patients with severe damage had RA for more than 10 years, compared with 40.34% in the no-damage group (p≤0.001). At presentation, 74.6% of severe damage patients had already experienced RA for over 60 months, compared with 56.67% of those without damage (p<0.001). A higher proportion of patients with severe damage belonged to the lower socioeconomic class (21.69%) compared with those without damage (16.47%) (p=0.002).

First RA-related symptoms varied significantly, with severe damage more frequently associated with upper limb involvement compared to lower limb involvement (25.13% *vs.* 17.72%) or a polyarticular presentation (16.4%), while patients without damage most commonly reported unknown onset (60.61%) (p<0.001). Functional disability increased with joint damage severity, with mean Indian HAQ scores of 11.12 in severe, 8.49 in moderate, and 3.96 in no-damage patients (p<0.001). Comorbidities were slightly less frequent among severe cases (23.28%) than in moderate (28.42%) and no-damage patients (30.1%) (p=0.020), whereas extra-articular features (10.32%) and systemic manifestations (7.94%) were more prevalent in severe cases (p<0.001) (Table 1).

Rheumatoid nodules occurred in 5% of severe, 3.6% of moderate, and 0.6% of no-damage patients (p<0.001). Sjögren's features were present in 4.8%, 3.9%, and 0.8% of patients, Raynaud's phenomenon in 0.8%, 0.3%, and 0.06%, dermatitis in 0.5% of severe cases, and vasculitis in 0.3%, 0.5%, and 0.06% of severe, moderate, and no-damage patients, respectively (p-values of 0.001, 0.005, 0.008, and 0.045). Pulmonary manifestations were rare and not significantly different (p=1.000) (*Supplementary Table 3*). Disease activity scores were higher in patients with damage, with a mean VAS pain of 4.28±2.31, 4.02±2.14, and 3.22±2.44 in severe, moderate, and no-damage groups (p<0.001). Physician global assessment was 2.79±2.43, 3.12±2.12, and 1.25±1.91, and patient global assessment was 3.02±2.70, 3.14±2.24, and 1.23±1.96 in severe, moderate, and no-damage groups, respectively (p<0.001) (*Supplementary Table 3*).

Categorization based on the total probable duration of rheumatoid arthritis

The analysis of patients stratified by total probable duration of RA revealed that longer disease duration was associated with older age, with patients having RA for more than 10 years showing a mean age of 56.15±11.25 years compared to 48.71±12.65 years in those with disease duration less than 2 years (p<0.001). Female predominance was observed across all groups (p=0.011). The median duration of RA at presentation to rheumatology increased progressively across the groups, ranging from 0.76 years in patients with total RA duration under 2 years to 12.74 years in those with over 10 years of disease (p<0.001). Socioeconomic distribution showed modest variation (p=0.002) (Table 2).

Patterns of first RA-related symptoms varied with disease duration, with upper limb involvement most common in the 2-5 years group and unknown onset most frequent in the <2 years and >10 years groups (p<0.001). Extra-articular features increased modestly with longer duration (1.31% in <2 years to 3.74% in >10 years; p=0.029), while systemic features did not differ significantly (p=0.212). Functional disability assessed by the Indian HAQ rose with disease duration, reaching 5.74±6.54 in the >10 years group (p<0.001). Rheumatoid nodules increased from 0.52% in <2 years to 1.84% in >10 years (p=0.043). Other extra-articular features, including pulmonary, cutaneous, vasculitic, Raynaud's, dermatitis, and Sjögren's features, remained rare and unchanged (p>0.05). Disease activity by VAS pain, physician, and patient global assessment also increased with longer duration (p<0.001, 0.022, and 0.013, respectively) (*Supplementary Table 4*). RAAD score analysis showed that severe joint damage increased with RA duration,

Table 2. Demographic and clinical characteristics of patients stratified by total probable duration of rheumatoid arthritis.

Variables	<2 years (n=382)	2 to 5 years (n=796)	5 to 10 years (n=1192)	>10 years (n=1843)	p
Age	48.71±12.65 (18-87)	49.51±12.47 (16-82)	51.19±11.65 (18-97)	56.15±11.25 (20-96)	<0.001#
Gender, female (male)	320 (62)	683 (113)	1050 (142)	1640 (203)	0.011*
Duration of rheumatoid arthritis at presentation to rheumatology (years)	0.76 (0.08-1.92)	2.61 (0.42-4.83)	5.81 (1-9.92)	12.74 (0.75-50)	<0.001#
Socioeconomic class, n (%)					
Lower class	83 (21.73)	156 (19.6)	178 (14.93)	310 (16.82)	0.002*
Middle class	147 (38.48)	263 (33.04)	472 (39.6)	720 (39.07)	
Upper class	152 (39.79)	377 (47.36)	542 (45.47)	813 (44.11)	
First rheumatoid arthritis-related symptom, n (%)					
Upper limb joints	70 (18.32)	203 (25.5)	249 (20.89)	295 (16.01)	<0.001^
Lower limb joints	47 (12.3)	118 (14.82)	200 (16.78)	257 (13.94)	
Polyarticular presentation	43 (11.26)	87 (10.93)	118 (9.9)	173 (9.39)	
Other than joints	0 (0)	2 (0.25)	13 (1.09)	13 (0.71)	
Unknown	222 (58.12)	386 (48.49)	612 (51.34)	1105 (59.96)	
Extra-articular features	5 (1.31)	18 (2.26)	33 (2.77)	69 (3.74)	0.029*
Systemic features	7 (1.83)	16 (2.01)	14 (1.17)	20 (1.09)	0.212*
Indian health assessment questionnaire	4.60±6.53 (0-33)	4.25±5.58 (0-36)	4.54±5.93 (0-35)	5.74±6.54 (0-36)	<0.001#
Rheumatoid Arthritis Articular Damage score, n (%)					
No damage	336 (87.96)	718 (90.2)	1003 (84.14)	1391 (75.47)	<0.001*
Moderate damage	29 (7.59)	42 (5.28)	106 (8.89)	210 (11.39)	
Severe damage	17 (4.45)	36 (4.52)	83 (6.96)	242 (13.13)	
Comorbidity	88 (23.04)	185 (23.24)	306 (25.67)	657 (35.65)	<0.001*

*Chi-square; #analysis of variance; ^Fisher exact test; NA, the variables were not treated as continuous due to their significant skewness and were instead considered categorical. Similarly, the Rheumatoid Arthritis Articular Damage score, which was significantly right-skewed, was also treated as a categorical variable

observed in 13.13% of patients with >10 years *vs.* 4.45% in <2 years (p<0.001), while patients without damage decreased. Upper and lower limb involvement rose markedly with duration, from 9.95% to 22.46% (p<0.001) and 5.24% to 14.32% (p<0.001), respectively, whereas neck and other joints showed no difference (p=0.417). Comorbidities also increased with longer duration, from 23.04% in <2 years to 35.65% in >10 years (p<0.001). Disease activity and functional disability worsened with longer RA duration, with mean VAS pain (p<0.001), physician global assessment (p=0.004), patient global assessment (p<0.001), and Indian HAQ scores (p<0.001) all increasing significantly. Severe joint damage also rose with disease duration, from 7.78% in <6 months to 11.27% in >60 months (p<0.001), while patients without damage decreased. Comorbidities became more frequent over time, increasing from 22.22% to 33.72% across the same duration groups (p<0.001).

Findings of logistic regression analysis

Logistic regression analysis revealed that longer duration of RA at presentation [odds ratio (OR): 1.008, p<0.001], higher VAS pain scale (OR: 1.054, p=0.009), VAS physician's global scale (OR: 1.134, p=0.004), and VAS patient global assessment scale (OR: 1.224, p<0.001) were associated with increased damage. Patients with the presence of extra-articular features were 2.8 times more likely to experience deformities (OR: 2.885, p<0.001), while systemic features increased the likelihood by nearly fivefold (OR: 4.935, p<0.001). The middle socioeconomic class showed reduced odds of damage compared to the lower class (OR: 0.716, p=0.008), while the higher class showed no significant difference. Comorbidities were associated with reduced odds of damage (OR: 0.688, p<0.001). Age was not significant (p=0.271) (Table 3 and Figure 1).

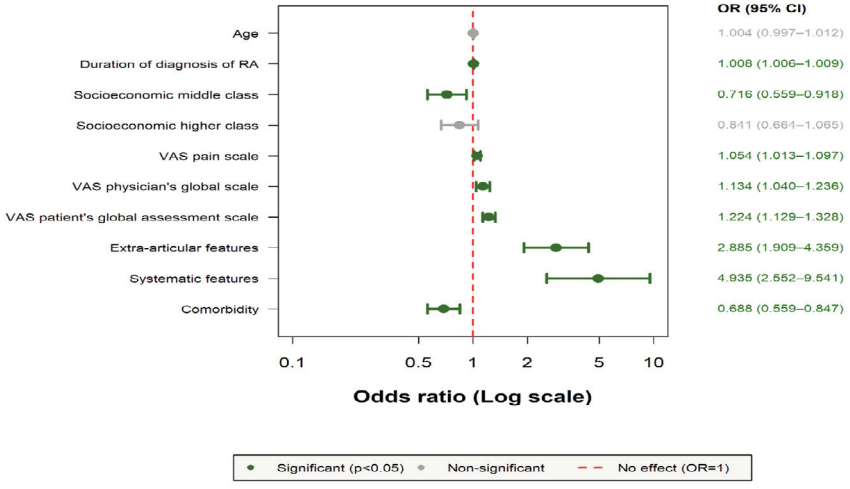

Figure 1. Forest plot depicting odds ratios and 95% confidence intervals for factors associated with the presence of articular damage (Rheumatoid Arthritis Articular Damage score >0) in rheumatoid arthritis patients. VAS, visual analog scale; CI, confidence interval; OR, odds ratio.

Table 3. Logistic regression analysis for predicting rheumatoid arthritis damage.

Variables	B	SE	Wald	df	p	Exp(B)	95% CI for EXP(B)	
							Lower	Upper
Age	0.004	0.004	1.214	1	0.271	1.004	0.997	1.012
Duration of rheumatoid arthritis (at presentation)	0.008	0.001	154.229	1	<0.001	1.008	1.006	1.009
Socioeconomic lower class	-	-	7.14	2	0.028	-	-	-
Socioeconomic middle class	-0.334	0.127	6.943	1	0.008	0.716	0.559	0.918
Socioeconomic higher class	-0.174	0.121	2.073	1	0.15	0.841	0.664	1.065
VAS pain scale	0.053	0.02	6.735	1	0.009	1.054	1.013	1.097
VAS physician's global scale	0.126	0.044	8.127	1	0.004	1.134	1.04	1.236
VAS patient global assessment scale	0.202	0.041	23.889	1	<0.001	1.224	1.129	1.328
Extra-articular features	1.059	0.211	25.285	1	<0.001	2.885	1.909	4.359
Systemyc features	1.596	0.336	22.52	1	<0.001	4.935	2.552	9.541
Comorbidity	-0.374	0.106	12.474	1	<0.001	0.688	0.559	0.847
Constant	-3.15	0.244	167.115	1	<0.001	0.043	-	-

VAS, visual analog scale; B, regression coefficient; SE, standard error; Wald, Wald chi-square statistic; df, degrees of freedom; Exp(B), exponentiated regression coefficient (odds ratio); CI, confidence interval; VAS, visual analog scale.

Analyses of the drug usage patterns

Notable differences were observed in drug usage across groups with varying degrees of disease damage. Hydroxychloroquine (HCQ) use was significantly higher among patients without damage (59.36%) compared to those with severe (52.65%) and moderate damage (47.55%) ($p<0.001$). In contrast, sulfasalazine (13.49% in severe, 16.02% in moderate, and 11.66% in no damage; $p=0.033$) and leflunomide (34.13%, 30.23%, and 27.03%, respectively; $p=0.008$) were significantly more frequently used in patients with moderate-to-severe damage. Similarly, tofacitinib use was higher in patients with severe damage (3.17%) compared to moderate (2.33%) and no damage (0.98%) ($p<0.001$). A significant difference was also observed in the use of other DMARDs (1.06%, 2.32%, and 0.93%; $p=0.040$), while methotrexate and steroid use did not differ significantly across groups ($p=0.053$ and $p=0.097$, respectively) (*Supplementary Table 5*). Across multiple centers, drug usage for managing active disease and varying severity showed notable heterogeneity. HCQ, steroids, methotrexate, sulfasalazine, and leflunomide varied significantly across centers ($p<0.001$ for all). Similarly, the use of other DMARDs, tofacitinib, rituximab, iguratimod, and tacrolimus differed significantly between centers ($p<0.05$ for all). In contrast, azathioprine, mycophenolate mofetil, and cyclophosphamide were used infrequently and did not show statistically significant differences across centers (*Supplementary Table 6*).

Discussion

The present study found that delayed presentation to rheumatology, longer disease duration, and higher disease activity were strongly associated with severe joint damage and disability in RA. The presence of extra-articular and systemic features further increased the risk. The lower socioeconomic class was linked to more severe joint damage. Comorbidities were linked to a modestly reduced risk, and neither age nor gender showed a significant impact on outcomes. These findings underscore the importance of early referral and comprehensive disease management in preventing long-term disability. Conducted across multiple tertiary care centers known for advanced RA management, the study shows that patients with severe or moderate damage were more likely to receive multiple or advanced disease-modifying therapies. The use of HCQ in combination with other DMARDs was more frequently observed in patients with less structural damage, which may suggest a beneficial role in reducing erosive progression. This observation is consistent with previous evidence indicating that HCQ may help slow disease progression and enhance treatment outcomes in patients with RA. In line with the current finding, a systematic review of 16 articles by Nazir *et al.* reported that HCQ is effective in slowing disease progression in RA patients and also enhances the therapeutic effects of methotrexate. Additionally, evidence indicates that HCQ therapy is strongly associated with a reduced risk of RA-related cardiovascular and renal complications (19). The present study also reported that sulfasalazine, leflunomide, tofacitinib, and other DMARDs were more commonly used in patients with moderate-to-severe joint damage, likely reflecting therapy escalation in response to disease severity rather than a failure to prevent damage. Methotrexate and steroid usage remained consistent across groups, indicating their role as anchor drugs irrespective of disease severity. International guidelines, including the 2019 EULAR recommendations and the 2016 ACR guidelines, emphasize the use of combination therapy or biologics in patients with high disease activity or poor prognostic factors (20, 21). Treat-to-target strategies further support intensifying therapy in patients with severe disease to achieve optimal outcomes. A systematic review by Hughes *et al.* found that intensive treatment more than doubles remission rates in both early and established RA compared to non-intensive therapy (22). In the present study, female predominance was consistent across groups, but gender did not significantly influence outcomes ($p=0.547$). This finding aligns with a study by Voulgari *et al.* in Greece, which analyzed early RA patients and reported that gender did not significantly affect the clinical expression of the disease (23). However, contrasting results were reported by Intriago *et al.* in Ecuador, suggesting that women with RA may experience higher disease activity and poorer quality of life compared to men. These differing findings indicate that gender-related disparities in RA outcomes may vary across populations (24). Female predominance in RA is well established, with the disease occurring approximately 2-3 times more frequently in women than men, particularly during the childbearing years (25, 26). Lower socioeconomic class was associated with higher rates of severe damage (21.69% *vs*. 16.47%, $p=0.002$), likely reflecting disparities in healthcare access and treatment adherence. These findings highlight the need for public health and policy interventions to address financial and systemic barriers to timely RA care, particularly in resource-limited settings in India. In line with these observations, a systematic review by Dey *et al*. reported an association between low socioeconomic status and higher disease activity, emphasizing the importance of a holistic approach to patient care (27). A US-based study by Molina *et al*. similarly found that lower socioeconomic status in RA patients was associated with longer delays in initiating DMARD therapy, which correlated with worse disease activity, joint damage, and functional disability (28). A previous study by the current authors showed that referral delays, influenced by primary care reluctance and socioeconomic factors, were not uniform across populations (29). The impact of socioeconomic status on RA outcomes is likely multifactorial, involving not only access to healthcare but also patient adherence. These delays, which can average several weeks, emphasize the need for targeted interventions to reduce patient reluctance in seeking early medical care, thereby improving disease outcomes (30).

Patients with longer total RA duration and delayed referral to rheumatology exhibited higher rates of severe joint damage and functional disability. The median disease duration at presentation was significantly longer in the severe damage group (10 years) compared to the no-damage group (6 years). The prevalence of severe joint damage increased with longer RA duration, observed in 13.13% of patients with disease >10 years compared to 4.45% in those with <2 years ($p<0.001$), while the proportion of patients without damage decreased correspondingly. Although deformities can appear as early as 2 years after disease onset, they are more commonly observed after 5 years. The optimal treatment window is within 6 months of symptom onset; however, even referral within 2 years can reduce the risk of severe deformities (31-34). Nell *et al.* reported a 3-month window of opportunity for treatment success, emphasizing the importance of early referral in controlling disease progression and optimizing prognosis (31). Aletaha *et al.* showed that longer disease duration (>10 years *vs*. <1 year) is associated with worse outcomes, such as smaller improvements in disease activity scores and lower response rates to therapy (35). Similarly, Anderson *et al*. found that longer disease duration in RA patients correlates with a lower treatment response, with a 53% response in patients with ≤1 year of disease *vs*. 35% for those with >10 years (36). These findings align with the present study, which observed

that longer disease duration is associated with higher RAAD scores, worse functional status (higher HAQ scores), and increased joint damage, including a higher prevalence of extra-articular features in patients with >10 years of disease duration.

The presence of extra-articular features (OR: 2.885, p<0.001) and systemic manifestations (OR: 4.935, p<0.001) significantly increased the risk of joint deformities. Systemic features such as weight loss and fever were also associated with an increased incidence of severe deformity. However, these manifestations are not specific to RA alone. They may indicate poorly controlled, long-standing systemic inflammation in inadequately managed RA, but alternative causes such as chronic infections, drug-related adverse effects, or underlying malignancies should also be considered, particularly in populations with limited healthcare access and delayed follow-up. A study from Karnataka reported extra-articular manifestations in 56% of RA patients, with a higher incidence in males, aligning with the current finding that these features are more common in patients with longer disease duration and severe RA (37). Similarly, a study from Tamil Nadu observed extra-articular manifestations in 27% of patients, most commonly interstitial lung disease (38). Data from Sweden indicate that patients with longer disease duration are at higher risk of irreversible joint deformities and extra-articular manifestations, with those affected showing a threefold increase in mortality (39). A Spanish study by Paloma Vela reported that extra-articular manifestations occur in 17.8% to 40.9% of patients with RA. Rheumatoid nodules were the most common extra-articular manifestation and were associated with severe complications such as vasculitis, rheumatoid lung disease, pericarditis, and pleuritis, particularly in patients who developed these manifestations within two years of RA diagnosis (40). Similarly, the present study observed rheumatoid nodules, Sjögren's features, Raynaud's phenomenon, vasculitis, and dermatitis as more common in patients with severe joint damage (p<0.05). A study by Galloway and Cope discussed systemic features such as fever in various rheumatic diseases, noting that while fever is less commonly reported in RA compared to other rheumatic conditions, its presence may indicate a more aggressive disease course (41). Sparks *et al*. examined the impact of weight changes during the early RA period on subsequent mortality risk, showing that severe weight loss (>30 lbs) around the time of diagnosis was associated with increased mortality, suggesting a link between significant weight loss and more severe disease progression (42). In the present study, 4.8% of patients with severe joint damage exhibited Sjögren's features, compared to 0.8% of those without damage (p<0.001). A study from northern India by Mehra *et al*. reported a prevalence of 26.58% for Sjögren's syndrome among RA patients (43). Similarly, a US registry-based study by the Consortium of Rheumatology Researchers of North America (CORRONA) conducted by Harrold *et al*. found that 30% of RA patients had secondary Sjögren's syndrome, with prevalence increasing with longer disease duration (44). A Korean study reported a prevalence of 8.7% among RA patients, as diagnosed by rheumatologists, and noted that the presence of Sjögren's syndrome did not influence RA treatment patterns (45). Moreover, an unusual observation in the present study was that the presence of comorbidities was associated with a modestly reduced risk, which may be attributed to patients with comorbidities being more vigilant about their health and adhering more closely to medical advice and treatment regimens. The study involved eight centers across India, providing a diverse sample that enhances the generalizability of the findings across different regions. All centers were tertiary care facilities, ensuring accessibility and broad representation of the population. The large sample size enabled robust statistical analysis for evaluating factors influencing RA outcome. Additionally, the use of the ICD-10 version of the Charlson Comorbidity Index provided a standardized framework for defining and categorizing comorbidities. However, the study also has some limitations. Although participants were drawn from multiple regions of India, a larger proportion were from South India, which warrants cautious generalization of the results. The study included patients presenting for the first time to rheumatology, which allowed evaluation of delays in treatment initiation. While this strengthens the clinical relevance of the findings, it also introduces the possibility of recall bias regarding symptom onset and early disease course. Furthermore, data on compliance and continuation of therapy, rheumatoid factor positivity, and detailed measures of treatment adherence were not included. Inclusion of these data could have provided additional insights.

Conclusions

Longer RA duration, delayed referral, and lower socioeconomic status are strongly associated with severe joint damage and disability. Extra-articular and systemic features significantly increase the risk of deformities, reflecting the burden of uncontrolled disease. These findings emphasize the importance of early referral, timely initiation of therapy, and socioeconomic support to reduce long-term disability in RA.

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Online supplementary material
Supplementary Table 1. Definitions used in the study.
Supplementary Table 2. The Rheumatoid Arthritis Articular Damage score: definition for scoring damage in individual joints.
Supplementary Table 3. Clinical characteristics, extra-articular features, and disease activity measures of rheumatoid arthritis patients categorized by severity of joint damage.
Supplementary Table 4. Clinical and demographic characteristics of rheumatoid arthritis patients stratified by total probable duration of illness.
Supplementary Table 5. Distribution of drug usage among rheumatoid arthritis patients according to severity of joint damage (n=4213).
Supplementary Table 6. Distribution of drug usage across multiple centers.

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