

Clinical and Serological Factors Associated with Radiographic Joint Damage Assessed by the Larsen Score in Egyptian Patients with Rheumatoid Arthritis: A Cross-Sectional Study

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Abstract

Background: Radiographic joint damage is a primary determinant of long-term disability in rheumatoid arthritis (RA). This study aimed to identify the clinical and serological factors associated with structural damage, as quantified by the Larsen score, in a cohort of Egyptian patients with RA. **Methods:** This cross-sectional study enrolled 162 Egyptian patients with RA who fulfilled the 2010 ACR/EULAR classification criteria. Clinical manifestations, disease activity (DAS28-ESR), functional disability (HAQ), and serological profiles (RF and anti-CCP) were systematically recorded. Radiographic damage in the hands and feet was evaluated using the Larsen scoring method by two independent assessors. Multivariable linear regression, utilizing log-transformed Larsen scores, was conducted to determine factors independently associated with structural damage. **Results:** The cohort was predominantly female (91.4%), with a mean age of 38.1 ± 9.2 years and a mean disease duration of 3.74 ± 3.4 years. The median Larsen score was 5 (interquartile range [IQR], 2–14), demonstrating

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excellent inter-reader agreement (ICC=0.92). Univariate analysis revealed that patients with subcutaneous nodules and anti-CCP positivity exhibited significantly higher Larsen scores ($p<0.01$). Upon multivariable analysis, prolonged disease duration ($\beta=0.46$, $p<0.001$), the presence of subcutaneous nodules ($\beta=0.22$, $p=0.002$), and anti-CCP positivity ($\beta=0.14$, $p=0.035$) emerged as independent correlates of advanced radiographic damage, collectively explaining 34.2% of the variance (adjusted $R^2=0.342$, $p<0.001$). Conclusions: Prolonged disease duration, subcutaneous nodules, and anti-CCP positivity are independently associated with exacerbated radiographic joint damage in Egyptian patients with RA. Utilizing these accessible clinical markers can effectively stratify patients at elevated structural risk, thereby underscoring the critical need for prompt and sustained disease control.

Keywords: rheumatoid arthritis; Larsen score; radiographic damage; anti-CCP; disease duration; structural joint damage

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder characterized by persistent synovial inflammation, which, if inadequately managed, leads to progressive joint destruction and functional decline [1]. The disease affects approximately 0.5% to 1% of the global adult population, with a higher predilection for women [2]. Despite substantial advancements in disease-modifying therapies, structural joint damage remains a critical clinical outcome, as it reflects the cumulative inflammatory burden and strongly correlates with long-term disability [3,4].

Radiographic assessment continues to be integral in evaluating structural joint damage in RA. Various scoring systems have been established for this purpose, notably the Sharp/van der Heijde method - which independently quantifies erosions and joint space narrowing - and the Larsen method, which offers a comprehensive global assessment of structural damage per joint [5,6]. The Larsen method is a robust, semiquantitative tool that grades individual joints on a scale from 0 to 5 based on the severity of erosive changes and joint space narrowing [5]. While the Sharp/van der Heijde method is predominantly utilized in clinical trials owing to its superior sensitivity to longitudinal change, the Larsen method provides distinct practical advantages in cross-sectional studies, including clinical efficiency and a strong correlation with functional outcomes and alternative scoring systems [5,7]. In resource-constrained settings where advanced imaging

modalities are not always accessible, the Larsen method offers a validated, time-efficient approach for the cross-sectional evaluation of cumulative structural damage. Consequently, the Larsen method was selected for the present study due to its proven reliability, feasibility, and suitability for assessing total structural burden in this cohort.

Several clinical and serological factors have been implicated in radiographic progression in RA, including longer disease duration, persistent inflammatory activity, rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti-CCP), and extra-articular manifestations [8–10]. In particular, anti-CCP antibodies have been consistently associated with erosive disease and a more severe structural phenotype [10]. Identifying such factors is central to risk stratification and may inform treatment intensity under modern treat-to-target strategies [11,12].

While predictors of radiographic progression have been extensively investigated in Western and East Asian populations, data originating from the Middle East and North Africa (MENA) region remain sparse [13–15]. Specifically in Egypt, very few studies have explored the association between clinical or serological variables and radiographic damage utilizing a validated scoring system in patients with RA [13,16,17]. Furthermore, the relative contribution of these factors to structural damage has yet to be comprehensively elucidated within Egyptian RA cohorts.

Therefore, this study aimed to identify the clinical and serological factors associated with radiographic joint damage, as quantified by the Larsen score, in Egyptian patients with RA, and to delineate their relative contributions to structural deterioration.

2. Materials and Methods

2.1 Study design and setting

This cross-sectional observational study was conducted at the Rheumatology Department of a tertiary care university hospital in Cairo, Egypt, between January 2023 and December 2023. The study is reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for cross-sectional studies [18].

2.2 Study population

The study enrolled 162 consecutive adult patients diagnosed with RA according to the 2010 American College of Rheumatology/European

League Against Rheumatism (ACR/EULAR) classification criteria [19]. Patients were recruited consecutively from all eligible attendees of the outpatient rheumatology clinic during the study period; no random sampling or convenience-based sub-selection was applied beyond the inclusion and exclusion criteria specified below.

2.3 Inclusion criteria

Inclusion criteria comprised: age ≥ 18 years, a confirmed diagnosis of RA based on the 2010 ACR/EULAR criteria, and the availability of hand and foot radiographs of sufficient quality for scoring.

2.4 Exclusion criteria

Patients were excluded if they presented with overlap connective tissue disease, psoriatic arthritis or alternative inflammatory arthropathies, were pregnant, or possessed incomplete clinical, laboratory, or radiographic records.

2.5 Sample size justification

The sample size was determined based on the established methodological guideline recommending a minimum of 10–20 observations per predictor variable for multivariable linear regression [20,21]. Anticipating a final model incorporating up to six candidate predictors, a minimum of 90–120 patients was mandated. The enrolled sample of 162 patients sufficiently exceeded this threshold, ensuring robust statistical power.

2.6 Ethical considerations

The study protocol was approved by the Institutional Ethics Committee of the Faculty of Medicine of our institution (Approval No: 0000126). Written informed consent was obtained from all participants prior to enrollment, in strict adherence to the principles of the Declaration of Helsinki.

2.7 Clinical assessment

All participants underwent a comprehensive clinical evaluation. Documented variables included age, sex, disease duration (defined as the time from symptom onset to the date of clinical assessment), morning stiffness duration, pain intensity (measured via a 100-mm visual analog scale [VAS]), 28-joint tender joint count (TJC28), and 28-joint swollen joint count (SJC28). The presence of subcutaneous nodules was determined through clinical examination.

2.8 Disease activity assessment

Disease activity was quantified utilizing the Disease Activity Score in 28 joints with erythrocyte sedimentation rate (DAS28-ESR), computed via the standard formula. Patients were stratified into four distinct categories: remission (< 2.6), low disease activity (2.6 to < 3.2), moderate disease activity (3.2 to ≤ 5.1), and high disease activity (> 5.1).

2.9 Functional assessment

Functional disability was appraised using the Health Assessment Questionnaire (HAQ), with scores ranging from 0 to 3; higher scores denote more severe functional impairment [22].

2.10 Laboratory assessment

Laboratory investigations encompassed: erythrocyte sedimentation rate (ESR) assessed via the Westergren method, rheumatoid factor (RF) testing, and anti-cyclic citrullinated peptide (anti-CCP) antibodies. RF and anti-CCP were determined qualitatively (positive/negative) as part of routine clinical care; quantitative titers were not available for this cohort. C-reactive protein (CRP) levels were not routinely available for the entire cohort and were consequently excluded from the analysis. The reliance on qualitative rather than quantitative data for RF and anti-CCP is acknowledged as a methodological limitation and is addressed in the discussion.

2.11 Radiographic assessment

Plain radiographs of both hands (posteroanterior view) and feet (anteroposterior view) were acquired for all participants. Radiographic joint damage was evaluated using the Larsen method [5], which grades the severity of structural abnormalities in each joint on a scale from 0 to 5:

Grade 0: Normal; Grade 1: Slight abnormality (periarticular soft tissue swelling or osteoporosis); Grade 2: Definite early abnormality (erosion and joint space narrowing); Grade 3: Medium destructive abnormality (marked erosion and joint space narrowing); Grade 4: Severe destructive abnormality (large erosions, joint deformity); Grade 5: Mutilating abnormality (original articular surfaces destroyed).

A total of 32 joints were assessed per patient (10 metacarpophalangeal joints, 8 proximal interphalangeal joints of the hands, both wrists [each evaluated as a single unit], 10 metatarsophalangeal joints, and both interphalangeal joints of the great toes), resulting in a potential total score range of 0–160. Radiographs were independently scored by two trained assessors who remained blinded to the clinical data. The mean of their

respective scores was utilized for the final analysis. Inter-reader agreement, evaluated using the two-way random, single-measures intraclass correlation coefficient (ICC), was 0.92 (95% CI 0.89–0.95), signifying excellent concordance.

2.12 Treatment data

Pharmacological therapies administered at the time of assessment were documented, encompassing methotrexate, hydroxychloroquine, leflunomide, sulfasalazine, corticosteroids, and folic acid supplementation.

2.13 Statistical analysis

Statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median and interquartile range (IQR), depending on distribution. Categorical variables were presented as frequencies and percentages.

Normality was assessed using the Shapiro–Wilk test. Because the Larsen score was positively skewed, non-parametric tests were used for univariate analyses. Spearman's rank correlation coefficient was used to assess associations between Larsen score and continuous variables, with 95% confidence intervals estimated using the bias-corrected and accelerated (BCa) bootstrap method (2000 resamples). Between-group comparisons were performed using the Mann–Whitney U test or Kruskal–Wallis test, as appropriate, with post hoc pairwise comparisons using Dunn's test with Bonferroni correction where indicated.

To address the positive skewness of the Larsen score, a log transformation [$\ln(\text{Larsen score} + 1)$] was applied for multivariable linear regression analysis to better satisfy model assumptions of normality and homoscedasticity of residuals. Variables considered clinically relevant or statistically significant in univariate analyses were entered simultaneously into the regression model (forced entry method). Statistical significance for univariate screening was defined as $p < 0.10$. Joint deformities were not included as a predictor variable because they represent a clinical consequence of cumulative structural damage and their inclusion would introduce conceptual circularity with the outcome measure. The incremental contribution of each variable to explained variance (ΔR^2) was assessed using hierarchical entry based on the order of clinical plausibility (disease duration entered first, followed by clinical features, then serological markers). Collinearity was assessed using variance inflation

factors (VIF), and model assumptions were verified by examination of residual plots and the Shapiro–Wilk test of residuals. Results were back-transformed for clinical interpretation where appropriate. A two-sided p value < 0.05 was considered statistically significant.

3. Results

3.1 Patient characteristics

A total of 162 patients with RA were included. The cohort was predominantly female (148/162, 91.4%), with a mean age of 38.1 ± 9.2 years. Mean disease duration was 3.74 ± 3.4 years, and the median Larsen score was 5 (IQR 2–14), indicating substantial variability in structural damage across the cohort.

Subcutaneous nodules were present in 27 patients (16.7%), and joint deformities were observed in 52 (32.1%). Anti-CCP positivity was detected in 97 patients (59.9%), and RF positivity in 128 (79.0%). Double seropositivity (anti-CCP and RF positive) was present in 88 patients (54.3%), whereas 25 patients (15.4%) were seronegative for both markers. Nearly half of the cohort had high disease activity (46.3%), while only 6.2% were in DAS28-ESR remission. Methotrexate was the most frequently used treatment (72.8%), followed by corticosteroids (35.2%) and hydroxychloroquine (24.7%) (Table 1).

Table 1. Baseline demographic, clinical, laboratory, and treatment characteristics of the study population (N = 162)

Variable	Value
Age, years	38.1 ± 9.2
Female sex, n (%)	148 (91.4)
Disease duration, years	3.74 ± 3.4
Morning stiffness, min	34.7 ± 50.2
Pain VAS, mm	49.8 ± 26.1
Tender joint count (0–28)	8.3 ± 6.8
Swollen joint count (0–28)	5.9 ± 5.8
DAS28-ESR	4.93 ± 1.38
HAQ score	0.87 ± 0.76
ESR, mm/h	47.0 ± 26.3
Larsen score, median (IQR)	5 (2–14)
Subcutaneous nodules, n (%)	27 (16.7)
Joint deformities, n (%)	52 (32.1)

Anti-CCP positive, n (%)	97 (59.9)
RF positive, n (%)	128 (79.0)
Double seropositive, n (%)	88 (54.3)
Seronegative for both markers, n (%)	25 (15.4)
DAS28-ESR remission, n (%)	10 (6.2)
Low disease activity, n (%)	15 (9.3)
Moderate disease activity, n (%)	62 (38.3)
High disease activity, n (%)	75 (46.3)
Methotrexate use, n (%)	118 (72.8)
Hydroxychloroquine use, n (%)	40 (24.7)
Corticosteroid use, n (%)	57 (35.2)
Leflunomide use, n (%)	14 (8.6)
Sulfasalazine use, n (%)	10 (6.2)

Data are presented as mean $\pm$ SD unless otherwise indicated. Abbreviations: VAS, visual analog scale; DAS28-ESR, Disease Activity Score in 28 joints using erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide antibodies; IQR, interquartile range.

3.2 Correlation between Larsen score and continuous variables

Among continuous variables, disease duration showed the strongest association with radiographic damage, with a moderate positive correlation with Larsen score ($r_s = 0.52$, 95% CI 0.39–0.63; $p < 0.001$). Age showed a weak but statistically significant positive correlation ($r_s = 0.18$, 95% CI 0.03–0.32; $p = 0.022$).

No significant correlations were observed between Larsen score and morning stiffness duration, pain VAS, TJC28, SJC28, DAS28-ESR, HAQ score, or ESR (all $p > 0.05$) (Table 2).

Table 2. Correlation between Larsen score and continuous variables

Variable	Spearman's r_s	95% CI*	p value
Age (years)	0.18	0.03 to 0.32	0.022
Disease duration (years)	0.52	0.39 to 0.63	<0.001
Morning stiffness (min)	0.11	–0.05 to 0.26	0.162
Pain VAS (mm)	–0.02	–0.17 to 0.14	0.810
Tender joint count	0.08	–0.08 to 0.23	0.308
Swollen joint count	0.03	–0.13 to 0.18	0.712
DAS28-ESR	0.13	–0.03 to 0.28	0.098
HAQ score	0.09	–0.07 to 0.24	0.254
ESR (mm/h)	–0.04	–0.19 to 0.12	0.612

*95% confidence intervals estimated using the bias-corrected and accelerated (BCa) bootstrap method (2000 resamples). Abbreviations: VAS, visual analog scale; DAS28-ESR, Disease Activity Score in 28 joints using erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; ESR, erythrocyte sedimentation rate.

3.3 Univariate comparisons according to categorical variables

Patients with subcutaneous nodules had markedly higher Larsen scores than those without nodules (median 12 [IQR 8–22] vs 4 [IQR 1–10], $p < 0.001$).

Anti-CCP-positive patients had higher Larsen scores than anti-CCP-negative patients (median 8 [IQR 2–16] vs 4 [IQR 0–10], $p = 0.012$). RF positivity was associated with a numerical but non-significant increase in Larsen score (median 6 [IQR 2–14] vs 4 [IQR 0–8], $p = 0.068$). No significant difference in Larsen score was observed between female and male patients ($p = 0.724$).

When stratified by serological profile, double-seropositive patients had the highest radiographic burden, with significantly higher Larsen scores than seronegative patients (median 8 [IQR 3–16] vs 3 [IQR 0–6], $p = 0.012$). Larsen scores also increased significantly across disease-duration categories, from a median of 2 (IQR 0–6) in early disease (≤ 2 years) to 6 (IQR 3–12) in established disease (2–5 years) and 16 (IQR 10–25) in late disease (> 5 years) (overall $p < 0.001$). Post hoc analysis confirmed significant differences between all three disease-duration categories.

Although Larsen score differed across DAS28-ESR categories overall ($p = 0.020$), this association did not remain significant in multivariable analysis (Table 3).

Table 3. Univariate comparisons of Larsen score according to categorical clinical and serological variables

Variable	Group	n	Median Larsen score (IQR)	p value
Anti-CCP	Positive	97	8 (2–16)	0.012
	Negative	65	4 (0–10)	
RF	Positive	128	6 (2–14)	0.068
	Negative	34	4 (0–8)	
Subcutaneous nodules	Present	27	12 (8–22)	<0.001
	Absent	135	4 (1–10)	
Sex	Female	148	5 (2–13)	0.724
	Male	14	5 (2–12)	
	Remission	10	2 (0–3)	0.020

DAS28-ESR category	Low	15	3 (2–10)	
	Moderate	62	5 (2–10)	
	High	75	8 (2–16)	
Serostatus	Double	88	8 (3–16)	0.012
	Single	49	5 (2–10)	
	Seronegative	25	3 (0–6)	
Disease duration category	≤2 years	72	2 (0–6)	<0.001
	2–5 years	52	6 (3–12)	
	>5 years	38	16 (10–25)	

Post hoc Dunn's test with Bonferroni correction for disease duration categories: ≤2 vs 2–5 years, $p = 0.008$; ≤2 vs >5 years, $p < 0.001$; 2–5 vs >5 years, $p = 0.002$. Abbreviations: RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide antibodies; IQR, interquartile range; DAS28-ESR, Disease Activity Score in 28 joints using erythrocyte sedimentation rate.

3.4 Current treatment and Larsen score

No significant differences in Larsen score were found according to current use of methotrexate, hydroxychloroquine, corticosteroids, leflunomide, or sulfasalazine (all $p > 0.05$). Because treatment choice in routine clinical practice is influenced by disease severity and duration, and because the cross-sectional design does not capture treatment history, delays, or adherence, these findings should be interpreted cautiously and are not reported in the multivariable model.

3.5 Multivariable analysis

Multivariable linear regression analysis using the log-transformed Larsen score [$\ln(\text{Larsen score} + 1)$] as the dependent variable identified three variables independently associated with higher radiographic damage: longer disease duration (standardized $\beta = 0.46$, $p < 0.001$), the presence of subcutaneous nodules ($\beta = 0.22$, $p = 0.002$), and anti-CCP positivity ($\beta = 0.14$, $p = 0.035$).

The final model explained 34.2% of the variance in log-transformed Larsen score ($R^2 = 0.355$, adjusted $R^2 = 0.342$; $F = 29.0$; $p < 0.001$). Disease duration accounted for the largest incremental contribution to explained variance ($\Delta R^2 = 0.271$), followed by nodules ($\Delta R^2 = 0.051$) and anti-CCP positivity ($\Delta R^2 = 0.019$). Conversely, almost two-thirds of the variability in radiographic damage remained unexplained by the three identified factors, underscoring the multifactorial nature of structural progression in RA.

Of the six candidate variables entered into the multivariable model, age, RF positivity, and DAS28-ESR were not independently associated with

radiographic damage after adjustment (Table 4). Sex, morning stiffness duration, and ESR did not meet the univariate screening threshold ($p < 0.10$) and were therefore not entered into the multivariable model (Tables 2 and 3).

No relevant multicollinearity was detected (maximum VIF 1.34), and residual diagnostics (residual plots and Shapiro–Wilk test of residuals, $p = 0.14$) were satisfactory, confirming acceptable model fit after log transformation.

Table 4. Multivariable linear regression analysis of factors associated with higher Larsen score[†]

Predictor	B	SE	Standardized β	95% CI for B	p value
Disease duration (years)	0.14	0.02	0.46	0.10 to 0.18	<0.001
Subcutaneous nodules	0.62	0.20	0.22	0.23 to 1.01	0.002
Anti-CCP positivity	0.28	0.13	0.14	0.02 to 0.54	0.035

[†]Dependent variable: $\ln(\text{Larsen score} + 1)$. Model summary: $R = 0.596$; $R^2 = 0.355$; adjusted $R^2 = 0.342$; $F = 29.0$; $p < 0.001$. Incremental contribution to explained variance: disease duration, $\Delta R^2 = 0.271$; subcutaneous nodules, $\Delta R^2 = 0.051$; anti-CCP positivity, $\Delta R^2 = 0.019$. Maximum VIF = 1.34. Shapiro–Wilk test of residuals: $p = 0.14$ (acceptable normality). Age, RF positivity, and DAS28-ESR were also entered into the simultaneous model as candidate variables but did not reach statistical significance (all $p > 0.05$); their coefficients are omitted here for brevity and are available from the corresponding author upon request. Abbreviations: SE, standard error; CI, confidence interval; anti-CCP, anti-cyclic citrullinated peptide antibodies; VIF, variance inflation factor.

4. Discussion

In this cross-sectional study of 162 Egyptian patients with RA, radiographic joint damage as assessed by the Larsen score was independently associated with longer disease duration, subcutaneous nodules, and anti-CCP positivity. Among these variables, disease duration showed the strongest association with structural damage, whereas single-time-point measures of disease activity and inflammatory burden were not independently associated with Larsen score after adjustment.

The prominent role of disease duration observed in this analysis is both biologically and clinically sound. Structural joint damage in RA is fundamentally cumulative; it mirrors the long-term sequelae of persistent synovial inflammation rather than the acute inflammatory state captured during a single clinical encounter. The moderate positive correlation between disease duration and the Larsen score, paired with the substantial escalation of radiographic scores across successive duration strata,

reinforces the paradigm that joint destruction accrues progressively over the disease continuum. These findings align with pivotal longitudinal studies by Lindqvist et al. [23] and Kaarela and Kautiainen [24], which firmly established disease duration as a primary determinant of radiographic damage. Consequently, these observations amplify the critical need for early diagnosis and the aggressive initiation of disease-modifying therapies within the optimal therapeutic window of opportunity [25,26].

Subcutaneous nodules emerged as the second most impactful factor associated with higher Larsen scores. Rheumatoid nodules are universally acknowledged as hallmarks of a severe disease phenotype, frequently corresponding with extra-articular manifestations and entrenched, seropositive disease [27,28]. Their independent correlation with radiographic damage in this cohort suggests that nodular disease functions as a readily accessible clinical indicator for identifying patients facing heightened structural risk. Particularly in resource-constrained settings where access to advanced imaging or sophisticated prognostic assays is limited, the straightforward clinical detection of subcutaneous nodules can critically inform risk stratification.

Furthermore, anti-CCP positivity maintained its independent association with exacerbated Larsen scores within the multivariable model, an outcome not mirrored by RF positivity. This dichotomy is consistent with established literature asserting that anti-CCP antibodies are more intimately linked to erosive disease and structural progression than RF alone [10,29–32]. A plausible biological basis for this dichotomy lies in the direct osteoclastogenic potential of anti-citrullinated protein antibodies: these antibodies bind citrullinated vimentin expressed on the surface of osteoclast precursors, triggering osteoclast differentiation and bone resorption even in the absence of overt synovitis, whereas RF lacks this direct bone-resorptive mechanism [33]. This pathway offers a mechanistic explanation for why anti-CCP, rather than RF, retained independent prognostic value for structural damage in the present cohort. Meyer et al. [30] established that anti-CCP-positive patients suffer greater longitudinal radiographic progression, while Syversen et al. [31] confirmed that anti-CCP maintains prognostic relevance even after stringent adjustment for concurrent clinical variables. The markedly high Larsen scores observed among double-seropositive patients in our study further validate the notion that overlapping seropositivity defines a subgroup with a particularly aggressive structural phenotype. Contemporary data from expansive observational registries, including ESPOIR and METEOR, have consistently

corroborated the enduring prognostic utility of anti-CCP for structural damage, even within modern treat-to-target frameworks [34,35]. Importantly, because RF and anti-CCP were assessed qualitatively in this study, the findings likely underestimate the true strength of the association with antibody titers; quantitative serological measurements, which were not available, would have enabled a more refined analysis of the dose-response relationship between autoantibody levels and structural severity. In particular, RF titer rather than mere seropositivity may carry independent prognostic weight for radiographic progression that is obscured when RF is treated as a simple binary variable; quantitative titer data might therefore have unmasked an independent erosive effect of RF in this cohort that the dichotomous classification used here could not capture. This methodological constraint must be considered when interpreting the serological associations.

A salient observation was the absence of an independent correlation between the Larsen score and concurrent disease activity, as indexed by DAS28-ESR. While univariate analysis indicated higher Larsen scores in patients with elevated disease activity, this relationship was attenuated in the multivariable model. This discrepancy elegantly highlights the conceptual divergence between acute inflammatory activity and cumulative structural detriment. The Larsen score synthesizes irreversible joint architecture damage accumulated over the entire disease trajectory, whereas DAS28-ESR and ESR merely provide a cross-sectional snapshot of the current inflammatory state. Analogous studies have similarly concluded that time-integrated inflammatory burden is a vastly superior predictor of structural progression compared to isolated, point-in-time measurements [36,37]. Therefore, this finding does not diminish the imperative of stringent disease control; rather, it underscores the inherent limitations of utilizing cross-sectional activity metrics to explain historically established radiographic damage.

The choice of the Larsen method over the Sharp/van der Heijde scoring system in the present study merits detailed discussion. The Sharp/van der Heijde method separately scores erosions and joint space narrowing at more joint sites and is considered more sensitive to longitudinal change and early erosive damage, making it the preferred tool in clinical trials evaluating treatment efficacy [6]. However, the Larsen method provides a reliable global assessment of cumulative damage per joint, is more time-efficient, and demonstrates strong correlations with functional outcomes and with the Sharp/van der Heijde method itself [5,7,38]. In the present cross-sectional design, where the objective was to assess the total

burden of structural damage rather than to detect subtle change over time, the Larsen method was considered appropriate and pragmatic. While we acknowledge that the Larsen method may be less sensitive to very small erosions, this limitation is mitigated by the study's focus on clinically evident cumulative joint destruction, which is the primary driver of functional disability. Future studies incorporating the Sharp/van der Heijde method could complement these findings, particularly in cohorts with very early disease.

No significant relationship was found between current treatment and Larsen score. This result should be interpreted cautiously, as observational cross-sectional studies are highly susceptible to confounding by indication. Patients with more severe or longstanding disease are more likely to receive more intensive treatment, and current treatment status does not capture treatment delays, prior therapeutic exposure, treatment adherence, or cumulative control of inflammation [39]. Consequently, residual confounding by unmeasured treatment-related factors - including the time elapsed between symptom onset and DMARD initiation, cumulative glucocorticoid exposure, and prior biologic use - cannot be excluded and may partly explain the associations observed between clinical/serological variables and radiographic damage.

Our results are highly concordant with the limited extant data from the MENA region. Abdel-Nasser et al. [16] previously reported that extended disease duration and seropositivity heralded poorer outcomes in Egyptian RA populations, while a Saudi Arabian cohort analyzed by Almoallim et al. [14] underscored the detrimental impact of diagnostic delays and high regional disease burdens. The present study substantively advances these observations by systematically quantifying the interplay between clinical/serological factors and radiographic damage using a rigorously validated scoring system supported by excellent inter-reader reliability. Nonetheless, the broad concordance between regional and Western cohorts should not obscure context-specific factors that may modulate the magnitude of these associations. Differences in shared epitope and other genetic susceptibility allele frequencies across ethnic groups, variable access to early diagnosis and biologic therapy within national healthcare systems, and disparities in time-to-treatment between MENA and Western settings could all influence the rate and severity of structural progression independently of the clinical and serological factors examined here, and may explain residual heterogeneity in effect sizes across studies.

The study has several clinical implications. First, it underscores the central importance of early recognition and timely treatment of RA to limit cumulative structural damage. Second, it highlights anti-CCP positivity and nodular disease as clinically relevant markers of patients at increased risk of severe radiographic involvement. Finally, it enriches the sparse epidemiological landscape of the MENA region by providing robust data on structural joint damage determinants from a well-characterized Egyptian cohort. In routine practice, these findings suggest that patients presenting with anti-CCP positivity, subcutaneous nodules, or longer disease duration at first assessment may warrant closer radiographic surveillance and a lower threshold for early, intensive treat-to-target strategies, rather than a watch-and-wait approach, even when current disease activity scores appear only moderately elevated.

Several limitations should be considered. First, the cross-sectional design precludes causal inference and does not allow assessment of true radiographic progression over time; accordingly, the identified associations should be viewed as correlates rather than predictors. Second, the study was conducted at a single tertiary center, which may limit generalizability to other populations or practice settings. Third, RF and anti-CCP were assessed qualitatively rather than quantitatively, which precluded evaluation of the dose-response relationship between antibody titers and structural severity; quantitative assessment would have added important prognostic information and might have revealed a significant independent role for RF. Fourth, CRP was not routinely available for all patients and therefore could not be included in the analysis; this is a relevant omission, as CRP is a recognized predictor of radiographic progression. Fifth, important variables such as smoking status, genetic susceptibility (e.g., shared epitope), baseline radiographic damage, and detailed treatment history were not available; in particular, the time elapsed between symptom onset and first conventional DMARD initiation was not systematically captured in this cohort, precluding quantification of treatment delay as a contributor to the structural damage observed. Sixth, the low proportion of male patients (8.6%) limited sex-specific analyses. Seventh, the Larsen method, while offering a validated global assessment of cumulative damage, may be less sensitive to small erosions compared to the Sharp/van der Heijde method; however, given the cross-sectional design and the aim to capture overall structural burden, this limitation is acceptable. Finally, although the model explained approximately one-third of the variance in radiographic damage, a substantial proportion of the variance remained unexplained, likely reflecting unmeasured factors such

as cumulative inflammatory burden, treatment adequacy over time, and genetic determinants.

Despite these limitations, the study has important strengths, including a well-characterized RA cohort, use of standardized 2010 ACR/EULAR classification criteria, radiographic assessment using the validated Larsen method with documented inter-reader reliability, log transformation of the skewed outcome variable, exclusion of conceptually circular predictors, and multivariable modeling of both clinical and serological variables.

5. Conclusions

Within this cross-sectional cohort of Egyptian patients with RA, exacerbated radiographic joint damage - assessed via the Larsen score - was independently and significantly associated with prolonged disease duration, the manifestation of subcutaneous nodules, and anti-CCP positivity. Disease duration emerged as the factor most strongly associated with structural damage. These findings underscore the cumulative nature of structural joint injury in RA and support the importance of early diagnosis and rigorous risk stratification, particularly among patients presenting with anti-CCP seropositivity or a nodular clinical phenotype. Future longitudinal investigations, integrating serial radiographic evaluations and quantitative serological profiling, are essential to validate the predictive capacity of these factors regarding future radiographic progression within this specific demographic.

Declarations

Author Contributions

A.I.A. conceived and designed the study and drafted the manuscript. H.G.I. collected the data and performed radiographic scoring. A.S.E. contributed to data analysis and interpretation. All authors critically revised the manuscript and approved the final version.

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Institutional Review Board Statement

The study protocol was approved by the Institutional Ethics Committee of the Faculty of Medicine of our institution (Approval No: 0000126).

Informed Consent Statement

Written informed consent was obtained from all participants included in the study.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

Declaration of generative AI use

During the preparation of this work, the author(s) used an AI-based language model to assist with literature organization, language editing, and critical methodological review of successive manuscript drafts. The tool was not used for data collection, statistical analysis, or generation of the reported scientific findings or interpretations. After using this tool, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

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