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CAROTID INTIMA-MEDIA THICKNESS AS A SURROGATE MARKER OF SUBCLINICAL ATHEROSCLEROSIS IN RHEUMATOID ARTHRITIS: A CROSS-SECTIONAL ANALYSIS OF THE RELATIONSHIP WITH DISEASE SEVERITY

Karthik I*	Postgraduate Resident, Department of Medicine, Assam Medical College & Hospital, Dibrugarh, Assam- 786002, India *Corresponding Author
Prasanta Dihingia	Professor & Head, Department of Medicine, Assam Medical College & Hospital, Dibrugarh, Assam- 786002, India
Sreemanta Madhab Baruah	Professor, Department of Medicine, Assam Medical College & Hospital, Dibrugarh, Assam- 786002, India
Lipee Nath	Professor, Department of Radiodiagnosis, Assam Medical College & Hospital, Dibrugarh, Assam- 786002, India

ABSTRACT **Background:** Rheumatoid arthritis (RA) confers a substantially elevated cardiovascular risk through chronic immune-mediated endothelial injury and accelerated atherosclerosis. Carotid intima-media thickness (CIMT), measured by B-mode ultrasonography, serves as a validated, non-invasive surrogate for subclinical atherosclerosis and preclinical vascular change. **Objective:** To quantify the relationship between RA disease severity, as assessed by the Disease Activity Score in 28 joints using ESR (DAS28-ESR), and CIMT among patients attending a tertiary care centre in Upper Assam. **Methods:** This hospital-based cross-sectional analytical study enrolled 50 RA patients fulfilling the 2010 ACR/EULAR classification criteria at Assam Medical College and Hospital, Dibrugarh (October 2024–September 2025). Patients with type 2 diabetes, hypertension, dyslipidaemia, ischaemic heart disease, or cerebrovascular disease were excluded to minimise confounding. Bilateral CIMT was measured on the Samsung RS 80A Prestige using a 10–15 MHz linear-array transducer. Disease activity was categorised by DAS28-ESR score. Spearman correlation, Kruskal–Wallis test with post-hoc analysis, and multiple linear regression were used for statistical inference. **Results:** The mean age of participants was 46.46 ± 8.35 years with a marked female preponderance (96%). Median DAS28-ESR score was 5.00. Median mean CIMT was 0.92 mm, exceeding the subclinical atherosclerosis threshold of 0.9 mm. A strong positive correlation was documented between DAS28-ESR and mean CIMT (Spearman's $\rho = 0.887$, $p < 0.0001$). Median CIMT rose progressively across disease activity strata: 0.62 mm in remission to 1.11 mm in high disease activity ($p < 0.0001$). ESR independently correlated with CIMT ($\rho = 0.727$, $p < 0.0001$). On multiple linear regression, DAS28-ESR was the sole independent predictor of CIMT ($\beta = 0.835$, $p < 0.001$; $R^2 = 0.778$). Traditional cardiovascular risk markers — age, BMI, total cholesterol, and HbA1c — were not independent predictors in this cohort. **Conclusion:** RA disease activity is the principal driver of subclinical atherosclerosis in this cohort, independent of classical cardiovascular risk factors. These findings underscore the necessity of integrating cardiovascular risk surveillance into routine RA management, and highlight early, aggressive disease control as a strategy to mitigate vascular injury.

KEYWORDS : Rheumatoid Arthritis; Carotid Intima-Media Thickness; DAS28-ESR; Subclinical Atherosclerosis; Cardiovascular Risk; Endothelial Dysfunction

INTRODUCTION

Rheumatoid arthritis is a systemic autoimmune disorder characterised by persistent synovial inflammation, progressive articular destruction, and a broad spectrum of extra-articular manifestations[1]. Affecting approximately 0.5–1% of the global adult population, the disease shows a clear predilection for females and typically becomes clinically apparent between the fourth and sixth decades of life[2]. Beyond its well-recognised musculoskeletal burden, RA carries a substantially elevated risk of premature cardiovascular morbidity and mortality, accounting for roughly 30–50% of all deaths in affected individuals — a risk approximately 1.5- to 2-fold greater than that observed in the general population.

The cardiovascular excess risk in RA is not fully explained by conventional risk factors such as hypertension, dyslipidaemia, or diabetes. A growing body of evidence implicates chronic systemic inflammation itself as an independent driver of accelerated atherogenesis[3]. Pro-inflammatory cytokines — particularly tumour necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) — promote endothelial dysfunction, oxidative stress, and lipid modification, thereby creating a pro-atherogenic milieu even in the absence of overt metabolic derangement.[4]

Carotid intima-media thickness (CIMT), measured using high-resolution B-mode ultrasonography, has emerged as a validated, non-invasive surrogate marker for generalised subclinical atherosclerosis. Quantifying the combined thickness of the intimal and medial layers of the common carotid artery, CIMT captures early vascular structural change before clinical cardiovascular events manifest. Studies conducted in diverse rheumatological populations have consistently demonstrated higher CIMT in RA patients compared with age- and sex-matched healthy controls, and several cohort analyses have linked elevated CIMT to subsequent cardiovascular events.[5]

Despite this evidence, structured cardiovascular surveillance using CIMT remains uncommon in routine rheumatology practice, particularly in resource-limited settings. Furthermore, data from Northeast India — a region with a distinct epidemiological and genetic background — are scarce. The present study was undertaken to evaluate the relationship between RA disease severity, quantified by the DAS28-ESR score, and CIMT among patients attending a tertiary care centre in Upper Assam, with the dual aim of characterising the local cardiovascular burden and identifying modifiable inflammatory predictors of subclinical vascular injury.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This was a hospital-based cross-sectional analytical study conducted in the Department of Medicine, Assam Medical College and Hospital (AMCH), Dibrugarh — a tertiary referral centre serving Upper Assam and parts of Arunachal Pradesh. The study period extended from 1 October 2024 to 30 September 2025.

2.2 Participants

Fifty patients with established RA, fulfilling the 2010 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria, were enrolled by consecutive sampling from the Rheumatology and General Medicine outpatient departments and inpatient wards. Eligible participants were aged 18–65 years and provided written informed consent. Sample size was derived from published CIMT data in RA populations (mean CIMT 0.68 ± 0.17 mm), yielding a minimum of 46 patients at a 95% confidence interval and 5% margin of error, rounded up to 50.

Patients with type 2 diabetes mellitus, hypertension, dyslipidaemia, ischaemic heart disease, cerebrovascular accident, active or former smoking, alcohol use disorder, pregnancy, age >65 years, or a history of statin or long-term corticosteroid use (≥6 months) were excluded to isolate RA-driven inflammatory contributions to CIMT.

2.3 Disease Activity Assessment

Disease activity was quantified using the DAS28-ESR score, which incorporates the tender joint count across 28 joints, swollen joint count across 28 joints, erythrocyte sedimentation rate (ESR), and patient's global health assessment on a visual analogue scale (0–100 mm). Participants were stratified into four disease activity categories: remission (DAS28 < 2.6), low activity (2.6–3.2), moderate activity (3.2–5.1), and high activity (>5.1).

2.4 CIMT Measurement

CIMT was measured bilaterally using a Samsung RS 80A Prestige ultrasound system equipped with a 10–15 MHz linear-array transducer. With the patient supine and the neck slightly extended and rotated 45°, a longitudinal image of the far wall of the common carotid artery was obtained 1 cm proximal to the carotid bifurcation. Measurements were acquired at end-diastole to minimise pulsation-related variability. The mean of three readings from each side was calculated, and the bilateral mean CIMT was used for analysis. All scans were performed by a single radiologist to ensure inter-session reproducibility.

2.5 Laboratory Investigations

Investigations included complete blood count, ESR (Westergren method), high-sensitivity C-reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies, fasting lipid profile, HbA1c, renal function tests, liver function tests, and thyroid-stimulating hormone. These were performed to characterise the inflammatory-metabolic parameters and to confirm exclusion of metabolic confounders.

2.6 Statistical Analysis

Data were entered into Microsoft Excel and analysed using IBM SPSS Statistics, Version 25.0. Continuous variables are expressed as mean ± standard deviation or median with interquartile range (IQR), depending on data distribution. Categorical variables are presented as frequency and percentage. Non-parametric Spearman rank correlation was used to assess associations between DAS28-ESR and CIMT, and between ESR and CIMT. Between-group CIMT comparisons across DAS28 categories were made using the Kruskal–Wallis test, with Dunn's post-hoc pairwise analysis for multiple comparisons. Independent predictors of CIMT were identified using multiple linear regression with backward elimination. A two-tailed p-value of <0.05 was considered statistically significant.

Ethical clearance was obtained from the Institutional Human Ethics Committee (H), AMCH, prior to study initiation (Ref. No AMC/EC/2026/112)

3. RESULTS

3.1 Demographic and Anthropometric Profile

The mean age of the 50 study participants was 46.46 ± 8.35 years (Table 1). The 51–60-year age group constituted the largest proportion (36%), followed by the 41–50-year group (32%). A striking female predominance was noted, with 48 of 50 participants (96%) being female (Table 2). Mean BMI was 21.10 ± 1.43 kg/m², placing the cohort in the normal weight category.

Table 1: Age Group Distribution of Study Participants (n = 50)

Age Group (Years)	Number of Patients	Percentage (%)
≤ 35	5	10.0
36 – 40	11	22.0
41 – 50	16	32.0
51 – 60	18	36.0
Total	50	100.0

The sex distribution and disease activity categories are illustrated below. The marked female predominance (96%) reflects established epidemiological trends in autoimmune rheumatic diseases across South Asian tertiary care populations.

Table 2: Sex Distribution (n = 50)

Sex	n	%
Female	48	96.0
Male	2	4.0
Total	50	100.0

3.2 Laboratory and Serological Parameters

Biochemical investigations confirmed adequate metabolic control across the cohort. Mean HbA1c was 5.58 ± 0.40%, mean serum creatinine 0.94 ± 0.17 mg/dL, and mean ALT 35 ± 12 U/L, all within normal reference ranges. Median CRP was 9.50 mg/L (IQR 5–16 mg/L), indicating active low-grade systemic inflammation. The lipid profile was unremarkable — median total cholesterol 170 mg/dL, LDL 76 mg/dL, HDL 56 mg/dL, and triglycerides 104 mg/dL — consistent with the exclusion of dyslipidaemia. Seropositivity was prevalent: median RF was 69 IU/mL (IQR 37–98) and median anti-CCP 78.25 U/mL (IQR 35–124), implying a predominantly seropositive cohort (Table 3).

Table 3: Selected Laboratory Parameters (n = 50) — Median (IQR)

Parameter	25th Percentile	Median	75th Percentile
ESR (mm/hr)	9	16	27
CRP (mg/L)	5	9.5	16
RF (IU/mL)	37	69	98
Anti-CCP (U/mL)	35	78.25	124
Total Cholesterol (mg/dL)	156	170	180
LDL (mg/dL)	69	76	85
HDL (mg/dL)	46	56	61
Triglycerides (mg/dL)	91	104	123

3.3 Disease Activity Distribution

On categorisation by DAS28-ESR, 44% of participants had moderate disease activity and 28% had high disease activity; only 8% were in remission (Table 4). The median DAS28-ESR raw score across the cohort was 5.00 (IQR 3.00–6.00), confirming a predominantly active inflammatory state in the study population.

Table 4: Distribution of Disease Activity Categories by DAS28-ESR (n = 50)

DAS28-ESR Category	n	Percentage (%)
Remission (< 2.6)	4	8.0
Low Activity (2.6–3.2)	10	20.0
Moderate Activity (3.2–5.1)	22	44.0
High Activity (> 5.1)	14	28.0
Total	50	100.0

3.4 CIMT Measurements

Bilateral CIMT measurements demonstrated subclinical atherosclerosis in a substantial proportion of participants. The median mean CIMT was 0.92 mm (IQR 0.75–1.01 mm), exceeding the conventionally accepted threshold of 0.9 mm for subclinical atherosclerosis. Mean left CIMT was 0.89 ± 0.20 mm and median right CIMT was 0.92 mm (IQR 0.72–1.01 mm) (Table 5).

Table 5: Carotid Intima-Media Thickness — Summary Statistics (n = 50)

Parameter	25th Percentile	Median / Mean ± SD	75th Percentile
Right CIMT (mm)	0.72	0.92	1.01
Left CIMT (mm) [Mean ± SD]	—	0.89 ± 0.20	—
Mean CIMT (mm)	0.75	0.92	1.01

3.5 Correlation Between DAS28-ESR and CIMT

Spearman rank correlation revealed a strong, highly significant positive association between DAS28-ESR raw score and mean CIMT ($\rho = 0.887$, $p < 0.0001$) (Table 6). This indicates that as disease activity intensifies, a corresponding and proportionate increase in carotid intimal thickening occurs, reflecting greater cumulative vascular injury from systemic inflammation.

Table 6: Spearman Correlation between DAS28-ESR Raw Score and Mean CIMT (n = 50)

Variable Pair	Spearman's ρ	p-value
Mean CIMT vs DAS28-ESR (raw score)	0.887	< 0.0001
Mean CIMT vs ESR (mm/hr)	0.727	< 0.0001

3.6 CIMT across DAS28-ESR Disease Activity Strata

CIMT values increased progressively across DAS28-ESR strata (Kruskal–Wallis $p < 0.0001$) (Table 7). Participants in remission had a median CIMT of 0.62 mm; those with high disease activity had a median CIMT of 1.11 mm — a near doubling across the disease activity spectrum. Post-hoc pairwise analysis confirmed statistically significant differences between remission and both moderate and high activity groups, between low and moderate activity groups, and between all groups compared to high activity (Table 8).

Table 7: Median CIMT across DAS28-ESR Disease Activity Categories (n = 50)

DAS28 Category	25th Pctile (mm)	Median CIMT (mm)	75th Pctile (mm)	p-value

Remission	0.58	0.62	0.65	< 0.0001
Low Activity	0.56	0.64	0.75	
Moderate Activity	0.87	0.92	0.98	
High Activity	1.02	1.11	1.15	

Table 8: Post-hoc Pairwise Comparisons of CIMT across DAS28-ESR Categories

Comparison	Adjusted p-value	Significance
Remission vs Low Activity	> 0.05	Not significant
Remission vs Moderate Activity	< 0.05	Significant
Remission vs High Activity	< 0.05	Significant
Low vs Moderate Activity	< 0.05	Significant
Low vs High Activity	< 0.05	Significant
Moderate vs High Activity	< 0.05	Significant

3.7 CIMT and Individual Inflammatory Markers

Individual serological markers — CRP, RF, and anti-CCP — showed no statistically significant correlation with mean CIMT in isolation (CRP: $\rho = 0.149$, $p = 0.303$; RF: $\rho = -0.015$, $p = 0.917$; anti-CCP: $\rho = -0.045$, $p = 0.755$) (Table 9). This underscores the superiority of the composite DAS28-ESR score, which integrates clinical and laboratory parameters, over individual biomarkers as a predictor of vascular burden.

Table 9: Correlation between Individual Inflammatory Markers and Mean CIMT

Marker	Spearman's ρ	p-value
CRP (mg/L)	0.149	0.303
RF (IU/mL)	−0.015	0.917
Anti-CCP (U/mL)	−0.045	0.755

3.8 Multiple Linear Regression — Independent Predictors of CIMT

Multiple linear regression with mean CIMT as the dependent variable and DAS28-ESR raw score, age, BMI, total cholesterol, and HbA1c as independent variables yielded a highly significant overall model ($F = 30.833$, $p < 0.001$; $R^2 = 0.778$; adjusted $R^2 = 0.753$) (Table 10). DAS28-ESR was the sole statistically significant independent predictor (standardised $\beta = 0.835$, $p < 0.001$). Neither age, BMI, total cholesterol, nor HbA1c reached significance, confirming that inflammation — as captured by the composite disease activity score — rather than metabolic or demographic variables, primarily determines vascular thickening in this cohort.

Table 10: Multiple Linear Regression — Predictors of Mean CIMT

Predictor	Unstand. B	Std Error	Stand. β	t	p-value
Constant	0.993	0.314	—	3.157	0.003
DAS28-ESR	0.105	0.009	0.835	11.291	< 0.001
Age (years)	−0.002	0.002	−0.070	−0.934	0.355
BMI (kg/m²)	−0.015	0.010	−0.111	−1.475	0.147
Total Cholesterol (mg/dL)	−0.002	0.001	−0.111	−1.468	0.149
HbA1c (%)	0.012	0.037	0.025	0.319	0.751

Model summary: $R = 0.882$; $R^2 = 0.778$; Adjusted $R^2 = 0.753$; $F = 30.833$, $p < 0.001$

4. DISCUSSION

This cross-sectional study, conducted in a tertiary care setting in Upper Assam, demonstrates a robust, dose-dependent relationship between RA disease activity and CIMT, positioning systemic inflammation as the primary determinant of subclinical atherosclerosis even in the absence of classical cardiovascular risk factors. The key findings — a Spearman correlation coefficient of 0.887 between DAS28-ESR and CIMT, a progressive rise in median CIMT from 0.62 mm in remission to 1.11 mm in high disease activity, and the emergence of DAS28-ESR as the sole independent predictor on multivariate analysis — collectively reinforce the inflammatory atherosclerosis hypothesis in RA.

The observed median CIMT of 0.92 mm, surpassing the subclinical atherosclerosis threshold of 0.9 mm, is clinically consequential. Established evidence relates a 0.1 mm increase in CIMT to a 10–15% rise in myocardial infarction risk and a 13–18% increase in stroke risk. Our correlation coefficient of 0.887 compares favourably with published literature: Rajabzadeh et al. [8] (2023) reported an r of 0.73 between DAS28 and CIMT, while Fatima et al.[7] (2024) documented significantly higher CIMT in patients with high DAS28 activity. The slightly stronger correlation observed in our cohort may reflect Northeast India's epidemiological specificity or the more rigorous exclusion of metabolic confounders.

The graded stepwise increase in CIMT across DAS28-ESR categories strongly supports a dose-response relationship between cumulative inflammatory burden and arterial wall thickening. This pattern is mechanistically coherent: persistent elevation of TNF-α, IL-6, and IL-1 promotes endothelial dysfunction by impairing nitric oxide bioavailability, up-regulating adhesion molecules, and driving oxidative stress-mediated LDL oxidation. The resulting foam cell formation and smooth muscle proliferation are the important histological correlates of intima-media thickening. The weak correlations observed for isolated biomarkers such as CRP, RF, and anti-CCP shows that vascular injury in RA reflects the totality of inflammatory activity over time — a construct better captured by the composite DAS28-ESR score than any single laboratory variable.

The failure of age, BMI, total cholesterol, and HbA1c to independently predict CIMT in this cohort is in keeping with the concept of the RA 'lipid paradox', wherein qualitative rather than quantitative lipid abnormalities — driven by chronic inflammation — underpin atherogenesis[6]. It also suggests that conventional cardiovascular risk stratification tools, calibrated for general populations, systematically underestimate risk in RA.

From a management perspective, these findings carry tangible clinical implications. First, they provide empirical support for the integration of carotid ultrasonography into routine cardiovascular surveillance for RA patients with moderate to high disease activity. Second, and more fundamentally, they emphasize on aggressive inflammation control — through optimised DMARDs, combination therapy, or biologics — not merely as a strategy for musculoskeletal preservation but as an active cardiovascular risk-reduction intervention. Treatment data from our cohort reinforce this: the six patients on combined DMARDs and biologic therapy (subcutaneous etanercept) demonstrated lower CIMT and disease activity scores than those on DMARDs alone, consistent with published evidence that TNF inhibitors reduce CIMT progression and improve endothelial function. Third, the findings highlight a gap in local Northeast Indian rheumatology practice and provide a preliminary evidence base to advocate for structured vascular risk protocols at regional tertiary centres.

Several limitations merit acknowledgement. The cross-sectional design precludes causal inference and longitudinal CIMT trajectories. The single-centre sample of 50, while adequate for the stated statistical objectives, limits generalisability. The absence of a concurrent healthy control group — while methodologically deliberate — means that absolute CIMT elevations must be contextualised against published normative data rather than directly compared with local matched controls. Functional inflammatory indices such as hs-CRP and cytokine panels were not uniformly measured. Future work should adopt a prospective design with longitudinal follow-up, a matched control arm, and standardised cytokine profiling to further delineate the mechanistic pathway from inflammation to vascular injury in this population.

5. CONCLUSION

This study establishes that RA disease activity, quantified by DAS28-ESR, is strongly and independently associated with carotid intima-media thickness in a northeast Indian cohort, independent of classical cardiovascular risk factors. The progressive, dose-dependent relationship between inflammatory burden and vascular thickening across all disease activity strata highlights chronic inflammation as the principal atherogenic driver in RA. Carotid ultrasonography should be considered a valuable adjunct to cardiovascular risk stratification in this population. Achieving and sustaining low disease activity or remission represents not only the cornerstone of musculoskeletal management but also a meaningful strategy for long-term cardiovascular protection in patients with RA.

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