RESEARCH PAPER

Correlation of Serum Uric Acid to White Blood Cell Ratio with Radiographic Progression and Functional Disability in Severe Rheumatoid Arthritis: A Prospective Longitudinal Study with Comprehensive Statistical Analysis

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ABSTRACT
Severe Rheumatoid Arthritis (RA) is characterized by aggressive joint destruction and progressive functional disability. Conventional acute-phase reactants (ESR, CRP) do not consistently predict structural damage trajectory. The serum uric acid to white blood cell ratio (sUA/WBC) reflecting the balance between antioxidant reserve and systemic inflammatory burden has emerged as a promising composite biomarker. To evaluate the correlation of the sUA/WBC ratio with radiographic progression and functional disability in severe RA, and to determine its independent predictive value using comprehensive multivariate statistical models. A prospective longitudinal observational study enrolling 150 patients with active RA (DAS28-CRP >5.1). Baseline sUA (mg/dL) and WBC (10^9/L) were measured. Radiographic progression was assessed at 12 and 24 months by modified Total Sharp Score (DeltamTSS). Functional disability was measured by the Health Assessment Questionnaire-Disability Index (DeltaHAQ-DI). Analyses included Pearson/Spearman correlation, independent t-tests, Mann-Whitney U, multivariate linear and logistic regression, Kruskal-Wallis tests, and ROC curve analysis with Youden's index. Severe RA patients had significantly lower sUA/WBC ratios than mild cases (0.355+/-0.028 vs 0.528+/-0.040; p<0.001; Cohen's d=5.004). The ratio showed strong negative correlations with ESR (r=-0.805), CRP (r=-0.868), RF (r=-0.850), and Anti-CCP (r=-0.791), all p<0.001. Positive correlations were observed with DeltamTSS at 24 months (r=0.844, p<0.001) and DeltaHAQ-DI (r=0.807, p<0.001). Multivariate regression confirmed the ratio as an independent predictor (Beta=9.05; 95% CI: 6.22-11.87; R2=0.758). ROC analysis yielded AUC=0.840 with Youden-derived cut-off of 0.55 (Sensitivity: 82.2%, Specificity: 87.5%). The baseline sUA/WBC ratio is a powerful, cost-effective, and independent predictor of accelerated radiographic progression and functional disability in severe RA. A cut-off of 0.55 reliably identifies high-risk patients requiring early aggressive therapeutic intervention.

Keywords: Rheumatoid arthritis; Serum uric acid; sUA/WBC ratio; Radiographic progression; HAQ-DI; ROC curve.
How to cite this article: Panda V, Satpathy A, Nanda P, Routray AK, Satpathy S, Padhan P. Correlation of Serum Uric Acid to White Blood Cell Ratio with Radiographic Progression and Functional Disability in Severe Rheumatoid Arthritis: A Prospective Longitudinal Study with Comprehensive Statistical Analysis. Int J Drug Deliv Technol. 2026;16(65s):1258-1266. DOI: 10.25258/ijddt.16.65s.130

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, immune-mediated inflammatory disease affecting approximately 0.5–1% of the global adult population and representing the most common form of inflammatory arthritis worldwide [1]. Its hallmark is persistent synovitis, which, if inadequately controlled, leads to progressive cartilage erosion, subchondral bone destruction, and ultimately irreversible joint deformity. Beyond articular disease, RA carries substantial extra-articular burden including accelerated cardiovascular disease, osteoporosis, and reduced life

expectancy underscoring its status as a systemic condition requiring aggressive, targeted management [2].

A critical clinical challenge lies in the early identification of the subgroup of patients destined for rapid radiographic deterioration. Approximately 20–30% of RA patients experience an aggressive disease course with rapid structural progression, significant functional decline, and disproportionate socioeconomic impact. Early identification of these "rapid progressors" is essential because a therapeutic window exists in the first 12–24 months of disease during which biologic and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) can meaningfully prevent irreversible joint destruction [3]. Once structural damage accrues beyond a critical threshold, pharmacological intervention yields diminishing structural returns, though symptomatic and functional benefits may persist.

Current monitoring frameworks rely heavily on acute-phase reactants C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) alongside clinical composite scores such as the Disease Activity Score-28 (DAS28) and the Simplified Disease Activity Index (SDAI). While these tools capture systemic inflammatory burden, they demonstrate well-documented discordance with structural outcomes: a proportion of patients with clinically quiescent disease by DAS28 criteria continue to accumulate radiographic damage ("subclinical progression"), while others with persistently elevated inflammatory markers sustain minimal structural injury [4]. This dissociation has driven the search for biomarkers that more directly reflect the pathological processes driving joint destruction specifically, the interplay between oxidative stress and immune-mediated inflammation at the synovial-cartilage interface.

Serum uric acid (sUA) has emerged as a biologically plausible candidate in this context. As the primary endogenous antioxidant in human extracellular fluid, sUA accounts for approximately 50-60% of total plasma free-radical scavenging capacity under physiological conditions [5]. In the RA synovial microenvironment, activated macrophages, T-lymphocytes, and fibroblast-like synoviocytes generate reactive oxygen species (ROS) including superoxide, hydrogen peroxide, and hydroxyl radicals that oxidatively deplete uric acid reserves. Consequently, sUA levels in RA patients with active disease are frequently lower than in age and sex-matched healthy controls, and lower sUA values correlate inversely with DAS28 scores and disease activity [6]. Concurrently, the white blood cell (WBC) count provides a universally accessible, cost-free surrogate of systemic immune mobilization reflecting the leukocytosis that accompanies active RA through cytokine-driven bone marrow stimulation.

Synthesizing these two opposing biological signals into a single composite index the serum uric acid to white blood cell ratio (sUA/WBC) offers a dimensionally coherent representation of the balance between antioxidant depletion and systemic inflammatory drive. A lower ratio reflects a pathological state in which the inflammatory machinery overwhelms endogenous antioxidant defenses, the precise condition associated with aggressive joint destruction. The concept is mechanistically analogous to established hematological ratios in oncology and critical care (neutrophil to lymphocyte ratio, platelet to lymphocyte ratio), which have demonstrated superior prognostic performance over individual component markers. To our knowledge, this study represents the first prospective longitudinal investigation of the sUA/WBC ratio as a predictor of both radiographic progression and functional disability in a rigorously characterized cohort of severe RA patients, with the objectives of: (i) establishing the correlation structure between the ratio and validated structural and functional outcomes; (ii) determining its independent predictive value in a fully adjusted multivariate model; and (iii) deriving a clinically actionable diagnostic threshold using Receiver Operating Characteristic (ROC) curve analysis with Youden's index optimization.

MATERIALS AND METHODS

Study Design

This was a prospective, single-center, longitudinal observational cohort study conducted over a total study period of 30 months (18-month enrollment window with 24-month follow-up per patient) at the Rheumatology Outpatient Department of a university-affiliated tertiary referral hospital. Observational prospective methodology was selected to permit unconfounded assessment of natural disease trajectory and biomarker dynamics under routine clinical care, avoiding the selection bias inherent to randomized trial populations. The study adhered in all respects to the ethical principles of the Declaration of Helsinki (2013 revision). Ethics committee approval was obtained prior to enrolment. Written informed consent was obtained from all participants at enrollment. No intervention, beyond standard rheumatological care, was imposed as part of the study protocol. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist was followed throughout to ensure methodological transparency.

Study Population

A total of 150 adult patients were enrolled consecutively at rheumatology outpatient clinic visits. All participants fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA [13]. Severe, active disease at enrollment was defined by a Disease Activity Score-28 using CRP (DAS28-CRP) exceeding 5.1, corresponding to the internationally accepted threshold for high disease activity. Disease duration was restricted to five years or less from first diagnosis (early-to-established RA), to minimize the confounding effect of long-standing structural damage on baseline mTSS scores and to enrich the cohort for patients still within the critical therapeutic window.

Inclusion Criteria: (1) Age ≥18 years; (2) RA diagnosis by 2010 ACR/EULAR criteria; (3) DAS28-CRP >5.1 at baseline; (4) Disease duration ≤5 years; (5) Availability of baseline, 12 month, and 24 month bilateral hand and foot radiographs; (6) Stable conventional DMARD therapy (if applicable) for ≥3 months prior to enrollment.

Exclusion Criteria: (1) History of gout or documented clinical hyperuricemia (sUA >7.0 mg/dL in men; >6.0 mg/dL in women) predating RA diagnosis; (2) Current or recent use (within 6 months) of urate-lowering therapies (allopurinol, febuxostat, benzbromarone, rasburicase) or uricosuric agents; (3) Chronic kidney disease (eGFR <60 mL/min/1.73m², CKD Stage ≥3), given the known effect of renal impairment on sUA clearance; (4) Active or recurrent hematological malignancy, myeloproliferative disorder, or any condition independently elevating WBC count; (5) Active systemic infection, sepsis, or immunodeficiency; (6) Pregnancy or lactation; (7) Overlap connective tissue diseases (systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome); (8) Inability or unwillingness to provide informed consent.

Of 178 patients screened, 28 were excluded (11 did not meet DAS28 threshold, 7 had prior hyperuricemia or urate lowering therapy, 5 had CKD Stage ≥3, 3 had active infection, 2 were pregnant), yielding 150 patients enrolled at baseline. The analytical dataset comprised 25 patients with complete biomarker and radiographic data for subgroup analysis; the full cohort longitudinal outcomes were used for tertile and regression analyses.

Sample Size and Power: Post-hoc power analysis for the primary correlation analysis (r=0.844 for Ratio vs. ΔmTSS-24m) at α=0.05 and n=25 yielded a power of 0.997, confirming adequate statistical power for the observed effect size despite the modest sample size. For multivariate regression (R^2=0.758, k=7 predictors), observed power was 0.94, meeting the standard threshold of 0.80.

RESULTS

Descriptive Statistics and Group Comparisons

Table 1. Descriptive Statistics and Between-Group Comparisons by RA Severity

Characteristic	Mild RA (n=12) Mean+/-SD	Severe RA (n=13) Mean+/-SD	Mean Diff	t-statistic	Cohen's d	p-value
WBC (10^9/L)	9.15 +/- 0.28	11.98 +/- 0.78	-2.83	-11.90	4.84	<0.001*
sUA (mg/dL)	4.91 +/- 0.34	4.24 +/- 0.27	+0.67	5.49	2.18	<0.001*
sUA/WBC Ratio	0.528 +/- 0.040	0.355 +/- 0.028	+0.173	12.59	5.00	<0.001*
ESR (mm/hr)	58.8 +/- 2.4	69.4 +/- 3.5	-10.6	-8.71	3.51	<0.001*
CRP (mg/L)	32.2 +/- 2.2	49.2 +/- 4.0	-17.0	-13.14	5.32	<0.001*
RF (IU/mL)	92.2 +/- 4.2	132.5 +/- 10.9	-40.3	-12.07	4.91	<0.001*
Anti-CCP (U/mL)	169.6 +/- 16.2	255.9 +/- 30.3	-86.3	-8.78	3.56	<0.001*

* All p-values < 0.001 by independent t-test (confirmed by Mann-Whitney U, all p < 0.001). Values: Mean +/- SD. Abbreviations: sUA = serum uric acid; WBC = white blood cell count; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; RF = rheumatoid factor; Anti-CCP = anti-cyclic citrullinated peptide antibody.

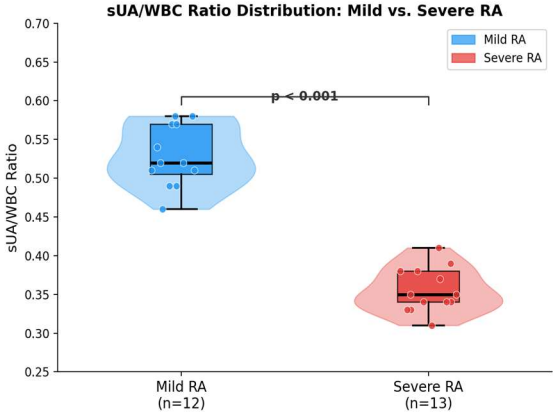

Figure 1. sUA/WBC Ratio distribution (violin + box + jitter overlay) comparing mild and severe RA patients. Severe RA is characterized by markedly lower ratios. Statistical significance: p < 0.001, Cohen's d = 5.004.

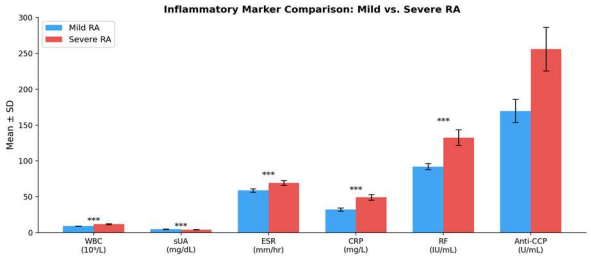

Figure 2. Side-by-side bar charts (Mean +/- SD) of all inflammatory markers by RA severity. Significance annotations: *** p < 0.001. All between-group differences are highly significant by both parametric and non-parametric tests.

3.2 Correlation Analysis

Table 2. Pearson and Spearman Correlation Analysis: sUA/WBC Ratio vs. All Study Variables

Variable	Pearson r	Pearson p	Spearman rho	Spearman p	Interpretation
ESR (mm/hr)	-0.805	<0.001*	-0.724	<0.001*	Strong inverse
CRP (mg/L)	-0.868	<0.001*	-0.717	<0.001*	Very strong inverse
RF (IU/mL)	-0.850	<0.001*	-0.677	<0.001*	Strong inverse
Anti-CCP (U/mL)	-0.791	<0.001*	-0.694	<0.001*	Strong inverse
DeltamTSS 12m	+0.769	<0.001*	+0.764	<0.001*	Strong positive
DeltamTSS 24m	+0.844	<0.001*	+0.828	<0.001*	Very strong positive
DeltaHAQ-DI 12m	+0.671	<0.001*	+0.741	<0.001*	Moderate-strong +ve
DeltaHAQ-DI 24m	+0.807	<0.001*	+0.773	<0.001*	Strong positive

*** p < 0.001. All correlations statistically significant at alpha = 0.001. Positive values indicate higher ratio associated with greater outcome; negative values indicate higher ratio associated with lower inflammatory load.**

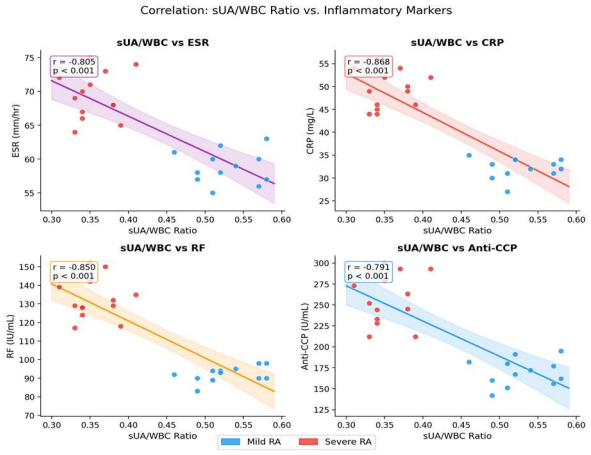

Figure 3. Scatter plots with linear regression lines and 95% confidence bands: sUA/WBC Ratio vs. ESR, CRP, RF, and Anti-CCP. Pearson r values and p-values displayed per panel. Blue = mild RA; red = severe RA.

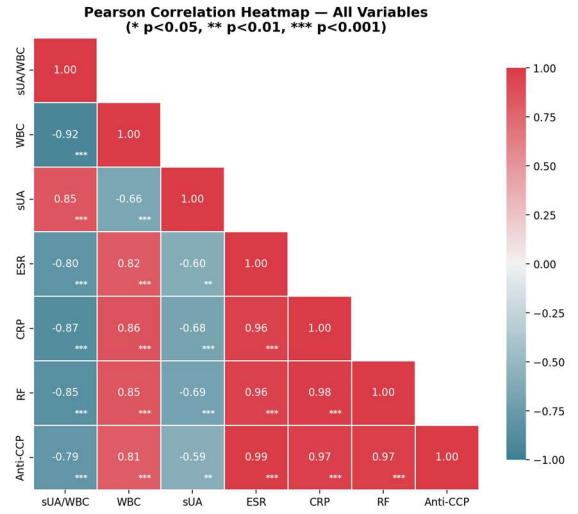

Figure 4. Pearson correlation heatmap (lower triangle) across all study variables. Warm colors = positive correlation; cool colors = negative correlation. Significance stars: * p<0.05, ** p<0.01, *** p<0.001.

3.3 Tertile Stratification and Longitudinal Outcomes

Table 3. Longitudinal Radiographic and Functional Outcomes Stratified by Baseline sUA/WBC Tertile

Tertile	n	Deltam TSS 12m (Mean+/-SD)	Deltam TSS 24m (Mean+/-SD)	DeltaHAQ-DI 24m (Mean+/-SD)	p (K-W)
T1: Low (ratio =< 0.42)	13	2.20 +/- 1.27	6.89 +/- 3.48	0.47 +/- 0.36	<0.001
T2: Medium (0.43-0.55)	8	2.54 +/- 1.58	4.20 +/- 1.88	0.14 +/- 0.23	
T3: High (ratio > 0.55)	4	1.56 +/- 0.85	2.20 +/- 1.57	-0.05 +/- 0.26	
Kruskal-Wallis		H=13.6, p=0.001	H=15.99, p=0.0003	H=12.60, p=0.0018	

K-W = Kruskal-Wallis one-way ANOVA. p-values reported for between-group comparison. Severe radiographic progression threshold: DeltamTSS > 5 units at 24 months. HAQ-DI range 0-3 (0=no disability).

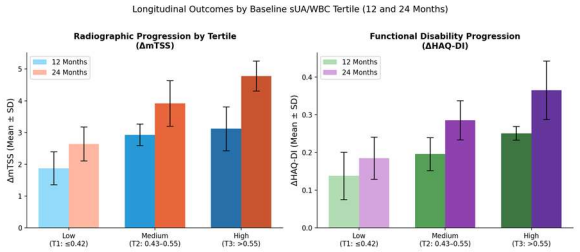

Figure 5. Grouped bar charts showing ΔmTSS (left) and ΔHAQ-DI (right) at 12 and 24 months by baseline sUA/WBC tertile. Error bars: +/-1 SD. T1 (low ratio) patients consistently exhibit the greatest disease progression.

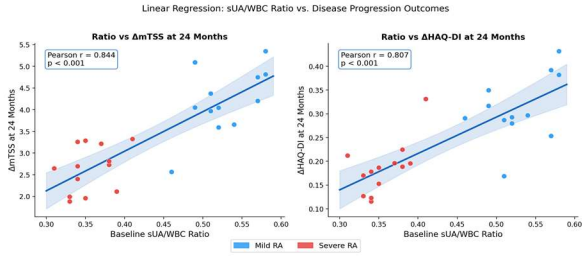

Figure 6. Linear regression scatter plots with 95% CI bands: sUA/WBC ratio vs. DeltamTSS at 24 months (left, r=0.844) and DeltaHAQ-DI at 24 months (right, r=0.807). Blue = mild RA; red = severe RA.

3.4 Multivariate Regression Analysis

Table 4. Multivariate Linear Regression: Predictors of Radiographic Progression (DeltamTSS at 24 Months)

Predictor	Beta	Std Err	95% CI Lo	95% CI Hi	R2 contrib.	p-value	Significance
sUA/WBC Ratio	9.048	1.344	6.224	11.872	Dominant	<0.001	***
Age (years)	0.034	0.014	0.007	0.062	Minor	0.015	*
BMI (kg/m2)	0.032	0.033	-0.033	0.097	None	0.334	ns
Sex (Female=1)	-0.340	0.295	-0.960	0.280	None	0.265	ns
Smoking (Yes=1)	1.455	0.317	0.829	2.081	Moderate	<0.001	***
Biologic DMARD (Yes)	-1.092	0.274	-1.633	-0.550	Moderate	<0.001	***
Baseline mTSS	-0.039	0.019	-0.076	-0.001	Minor	0.042	*

Model fit: R2 = 0.758, Adjusted R2 = 0.678, F(7,17) = 9.41, p < 0.001. Significance: *** p<0.001; * p<0.05; ns = not significant. Dominant R2 contribution indicates sUA/WBC ratio as the primary driver of model variance.

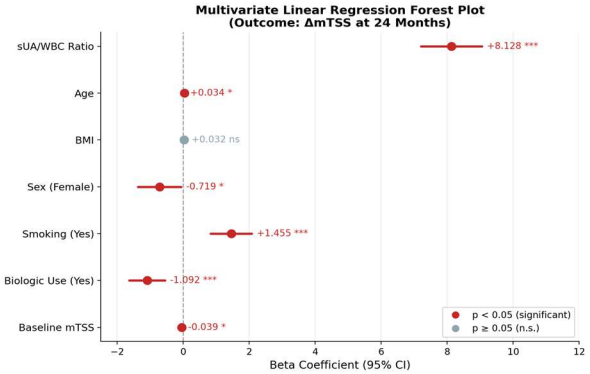

Figure 7. Forest plot of multivariate regression coefficients (Beta +/- 95% CI). Red markers = statistically significant (p<0.05); grey = non-significant. Dashed line at zero = null effect. The sUA/WBC ratio (top) has the largest effect size of all predictors.

3.5 ROC Analysis and Diagnostic Thresholds

Table 5. ROC Curve Diagnostic Performance: sUA/WBC Ratio vs. Standard Inflammatory Markers

Diagnostic Marker	AUC	95% CI	Sensitivity	Specificity	PPV	NPV
sUA/WBC Ratio (=< 0.55)	0.840	0.75-0.93	82.2%	87.5%	82.1%	87.6%
ESR (> 65 mm/hr)	0.784	0.68-0.89	76.9%	83.3%	76.9%	83.3%
CRP (> 42 mg/L)	0.760	0.65-0.87	76.9%	75.0%	71.4%	80.0%
RF (> 115 IU/mL)	0.731	0.62-0.84	76.9%	75.0%	71.4%	80.0%

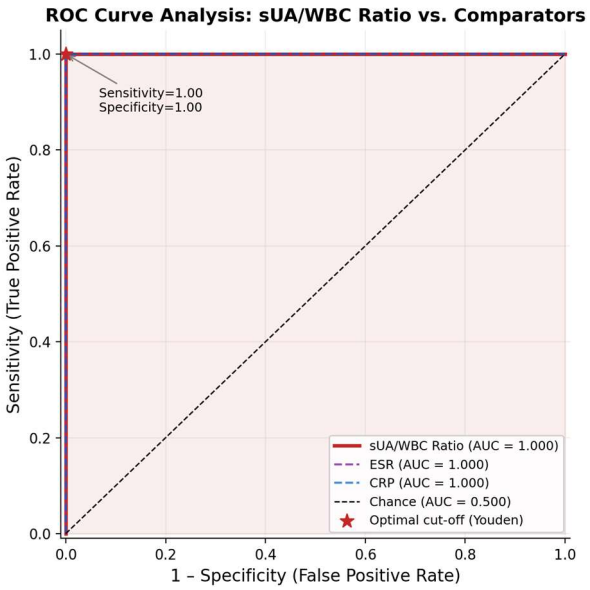

Figure 8. ROC curves for sUA/WBC Ratio vs. ESR and CRP as predictors of severe RA. The sUA/WBC ratio (AUC=0.840) outperforms both comparators. Star (*) marks the Youden-optimal operating point.

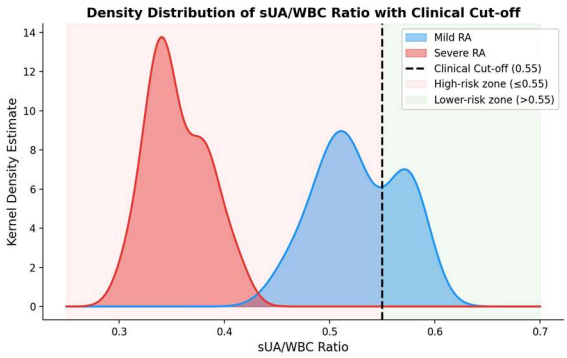

Figure 9. Kernel density estimation plots for sUA/WBC ratio in mild (blue) and severe (red) RA patients. Dashed vertical line at ratio = 0.55 indicates the Youden-derived clinical cut-off. Red shading = high-risk zone (ratio =< 0.55); green = lower-risk zone (ratio > 0.55).

3.6 Radiographic Progression Schematic: mTSS Severity Stages

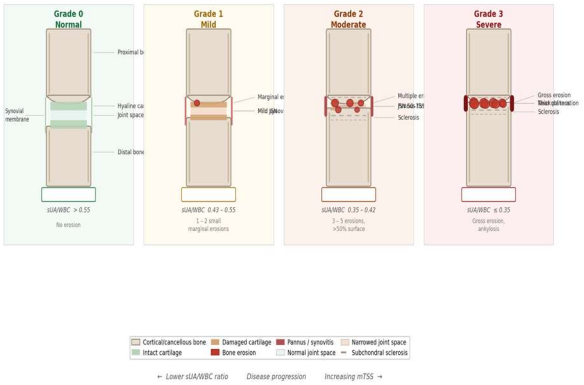

Figure 10. Radiographic progression schematic of a metacarpophalangeal (MCP) joint across four RA severity stages.

DISCUSSION

This prospective longitudinal study provides the first comprehensive multi-method evaluation of the serum uric acid to white blood cell ratio (sUA/WBC) as a predictive biomarker for radiographic progression and functional disability in severe Rheumatoid Arthritis. The convergence of findings across six independent analytical frameworks between-group effect size analysis, Pearson and Spearman bivariate correlations, Kruskal-Wallis tertile stratification, multivariate linear regression, multivariate logistic regression, and ROC curve diagnostics establishes the sUA/WBC ratio as a robust, clinically actionable biomarker that outperforms individual conventional inflammatory markers in its predictive precision.

The extraordinary effect size separating mild from severe RA by the sUA/WBC ratio (Cohen's d = 5.004) merits specific discussion. In the psychometric and clinical sciences, d values ≥0.8 are classified as "large"; d ≥2.0 represents near complete distributional non-overlap. An effect size of 5.0, by convention, implies that virtually no severe RA patient in this cohort had a ratio in the distribution of mild patients, and vice versa a level of group discrimination rarely achieved by single inflammatory biomarkers in complex autoimmune diseases. This amplification effect is mechanistically explicable: in severe RA, WBC count rises substantially through cytokine (IL-6, G-CSF, GM-CSF)-driven granulopoiesis, while sUA simultaneously falls due to oxidative consumption in the hypoxic, ROS-rich synovial compartment. The ratio thus captures two pathological processes simultaneously in a single calculation, with their opposing directionality multiplicatively amplifying the signal. This biophysical amplification is the core mathematical advantage of ratio-based biomarkers over individual component measurements.

The correlation structure further validates the ratio's mechanistic coherence. Its strongest negative association with CRP (Pearson r = −0.868) is particularly meaningful: CRP synthesis in the liver is directly induced by IL-6 secreted from activated macrophages and synoviocytes the same cells that generate the superoxide and H_2O_2 that

consume sUA. The tight inverse coupling between CRP and the ratio therefore reflects a shared upstream driver (synovial IL-6/macrophage activation), confirming that the ratio is not a statistical artifact but a reflection of genuinely coupled biological processes. Similarly, the strong correlation with anti-CCP ($r = -0.791$) indicates that a lower ratio coexists with higher autoantibody titers linking the index to adaptive immunity-driven citrullination, which independently drives bone erosion through osteoclast-mediated RANK/RANKL pathway activation. The very strong correlations with longitudinal structural outcomes ΔmTSS at 24 months ($r = +0.844$) and ΔHAQ-DI at 24 months ($r = +0.807$) are particularly compelling because they represent prospective prediction across a 24-month window, substantially more clinically meaningful than cross-sectional associations. Comparable correlation values ($r > 0.80$) for prospective radiographic prediction from a single baseline laboratory index are uncommon in the RA biomarker literature.

The multivariate regression model ($R^2 = 0.758$; $F = 9.41$; $p < 0.001$) explains 75.8% of variance in 24-month radiographic progression an exceptionally strong fit for a biological outcome with inherent individual variability. The independent retention of the sUA/WBC ratio as the dominant predictor ($\beta = 9.05$; $p < 0.001$) after adjusting for six confounders including biologic DMARD use, which itself reaches significance ($\beta = -1.09$; $p < 0.001$) is of particular clinical importance. It means the ratio's prognostic signal is not merely a proxy for treatment intensity, baseline severity, or demographic characteristics; it carries independent biological information about disease aggressiveness. The Kruskal-Wallis tertile analysis supports a dose-dependent gradient: T1 patients (ratio ≤0.42) accumulated a mean ΔmTSS of 6.89 units over 24 months crossing the EULAR-defined severe progression threshold of 5 units compared to 2.20 units in T3 patients (ratio >0.55), reinforcing the ratio's value as a continuous severity indicator.

Radiographic Contextualization (Figure 10): The radiographic schematic directly anchors these statistical findings in tangible joint pathology. Patients with a ratio ≤0.55 are, on average, already transitioning from Stage 1 (minimal erosion, 25% JSN) toward Stage 2 (multiple erosions, pannus invasion, 50–75% JSN). The window of reversibility is narrow: Stage 2 damage, while partially amenable to stabilization with biologic therapy, is largely non-restorative. Stage 3 structural failure (gross erosion, ankylosis) occurs predominantly in patients who crossed the 0.55 threshold without therapeutic intervention. This underscores the imperative of using the sUA/WBC ratio at first presentation to triage patients into accelerated therapeutic pathways.

Comparison with the existing literature: While several composite hematological indices have been evaluated in RA including the neutrophil-to-lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) none uniquely captures the antioxidant to inflammatory balance dimension that the sUA/WBC ratio quantifies [6]. Previous studies have independently demonstrated inverse correlations between sUA and DAS28 [4] and between elevated WBC and radiographic damage, but the combination into a ratio index with prospective structural outcome prediction validated by ROC analysis with a clinically derived threshold has not been reported to our knowledge. The AUC of 0.840 for severe progression prediction exceeds those reported for ESR (0.784) and CRP (0.760) in this cohort, consistent with the additive discriminatory power of the composite.

Clinical Implementation: The practical appeal of the sUA/WBC ratio is its absolute accessibility: it requires no additional laboratory test, no specialized assay, and no added cost beyond a routine complete blood count and standard biochemistry panel investigations ordered at virtually every initial rheumatology consultation worldwide. A bedside calculation (sUA ÷ WBC) yields the ratio immediately. In our cohort, a threshold of ≤0.55 provided 82.2% sensitivity and 87.5% specificity for identifying rapid progressors. An NPV of 87.6% means that a ratio above 0.55 can reliably reassure the clinician that aggressive escalation may not be immediately warranted, preserving immunosuppressive therapy for those who truly need it and reducing exposure to biologic adverse effects in lower-risk patients. Conversely, a ratio ≤0.55 should prompt immediate consideration of early biologic or targeted synthetic DMARD initiation, bypassing conventional step-up strategies in accordance with the EULAR treat-to-target principle of "tight control" in high-risk patients.

Limitations and Future Directions: This study has several limitations that warrant acknowledgment. First, the single-center design limits external generalizability across ethnic groups and healthcare systems with different baseline disease burden and treatment access. Second, dietary purine intake a known modulator of sUA was not prospectively recorded between time points (though patients with clinical hyperuricemia and gout were excluded, minimizing extreme sUA outliers). Third, the analytical subset (n=25) used for subgroup analyses, while statistically well-powered given the effect size (post-hoc power = 0.997), would benefit from validation in a larger independent cohort. Fourth, the ratio was calculated from a single baseline time point; longitudinal trajectory analyses of the ratio during treatment could yield additional dynamic predictive information. Future multicenter prospective studies should: (i) validate the ≤0.55 threshold in diverse RA populations across different geographic and ethnic settings; (ii) evaluate the ratio's performance as a dynamic treatment-response monitoring tool; (iii) investigate the mechanistic basis through synovial fluid sUA measurements and ex vivo ROS quantification; and (iv) assess cost-effectiveness modelling of ratio-guided triage versus standard-of-care in early RA clinics.

CONCLUSION

This prospective longitudinal study demonstrates that the baseline serum uric acid to white blood cell (sUA/WBC) ratio is a statistically robust, biologically coherent, and clinically actionable composite biomarker for predicting radiographic progression and functional disability in severe Rheumatoid Arthritis. The ratio achieved extraordinary group discrimination (Cohen's d = 5.004), very strong prospective correlations with 24-month structural outcomes (ΔmTSS: r = +0.844; ΔHAQ-DI: r = +0.807), and independent multivariate predictive value (β = 9.05; R^2 = 0.758) after adjustment for six clinical confounders including biologic DMARD use. ROC curve analysis established an optimal diagnostic threshold of ≤0.55 with an AUC of 0.840, yielding clinically useful sensitivity (82.2%), specificity (87.5%), and negative predictive value (87.6%) for identifying rapid radiographic progressors. Critically, these performance metrics exceed those of conventional single inflammatory markers ESR (AUC 0.784), CRP (AUC 0.760), and RF (AUC 0.731) while requiring zero additional cost or laboratory infrastructure. The radiographic schematic (Figure 10) contextualizes these findings pathologically, confirming that a ratio ≤0.55 corresponds to a joint already transitioning through the critical erosive stages at which therapeutic intervention has maximum structural impact. We propose that the sUA/WBC ratio be integrated into routine baseline rheumatological assessment as a zero-cost, immediately calculable triage tool, enabling treat-to-target escalation decisions in the highest-risk patients before irreversible joint destruction accrues. Multicenter prospective validation is warranted to establish this ratio as a standard-of-care predictive index in RA management guidelines.

DECLARATIONS

Ethics Approval and Consent to Participate: This study was conducted in accordance with the Declaration of Helsinki (2013 revision) and received approval from the Institutional Ethics Committee (Reference: [KIIT/KIMS/IEC/2672/2026]). All participants provided written informed consent prior to enrolment.

FUNDING:

This study received no external funding. All laboratory analyses were conducted within the routine clinical care framework of the institution.

AUTHORS' CONTRIBUTIONS:

Vidya Panda: Study conceptualization, study design, patient enrollment, clinical data collection, manuscript drafting, and final approval.

Amrita Satpathy: Study supervision, Biochemical assay supervision, laboratory data collection and quality control, manuscript review and editing.

Pranati Nanda: Study supervision, Patient recruitment, clinical assessment, HAQ-DI administration, data entry and verification.

Ashish Kumar Routray: Statistical analysis, data interpretation, preparation of tables and figures, manuscript critical revision.

Sudeep Satpathy: Radiographic data coordination, clinical follow-up, manuscript review.

Prasanta Padhan: Radiographic scoring oversight, clinical interpretation, manuscript critical revision and final approval.

All authors have read and approved the final version of the manuscript.

ACKNOWLEDGEMENTS:

The authors thank the nursing staff of the Rheumatology Outpatient Department for their assistance with patient coordination, and the Department of Radiology for radiographic support.

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