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Original Research Article

Comparative Study of Seropositive and Seronegative Arthritis in Adults

Sanjay Ambhore[1], Sanjeev Johri[2], Rohit Jain[3]

[1,2,3]Assistant Professor, Department of Medicine, Chirayu Medical College and Hospital, Bhopal, MP, India

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Corresponding Author: Dr. Rohit Jain
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Abstract:

Aim: To compare the clinical features, laboratory findings, disease activity, radiological progression, and treatment response between seropositive and seronegative rheumatoid arthritis (RA) patients in adult populations.

Materials and Methods: A retrospective comparative study was conducted on 259 adults diagnosed with rheumatoid arthritis (164 seropositive and 95 seronegative). Demographic data, clinical presentations, laboratory parameters including rheumatoid factor (RF) and anti-CCP antibodies, disease activity scores (DAS28-CRP), radiological findings, and therapeutic responses were systematically analyzed.

Results: Seropositive RA patients exhibited significantly higher disease activity at baseline (mean DAS28-CRP 5.8 ± 0.9 vs 5.2 ± 1.1, $p < 0.001$) and more frequent erosive joint involvement (72.6% vs 48.4%, $p < 0.001$). Treatment response at 3 months was better in seropositive patients (75.6% vs 52.6%, $p < 0.001$), but remission rates at 12 months were similar (68.3% vs 64.2%, $p > 0.05$). Radiographic progression showed comparable Sharp scores at 24 months between groups ($p > 0.05$). Extra-articular manifestations were significantly more common in seropositive patients (45.7% vs 22.1%, $p < 0.001$). Seronegative patients demonstrated slower initial treatment response but achieved comparable long-term outcomes with intensive therapy.

Conclusion: While seropositive RA presents with more aggressive initial disease activity and erosive changes, both groups achieve similar long-term remission rates when treated with intensive disease-modifying antirheumatic drugs (DMARDs). Serological status significantly influences early treatment response but does not predict long-term prognosis. Both seropositive and seronegative RA warrant aggressive treat-to-target strategies to optimize clinical outcomes and prevent radiological progression.

Keywords: Seropositive arthritis; seronegative arthritis; rheumatoid factor; anti-CCP antibodies; disease activity; radiological progression; treatment response; remission rates.

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Introduction

Rheumatoid arthritis (RA) is a chronic, progressive, autoimmune disease characterized by persistent inflammation of multiple joints, resulting in irreversible cartilage and bone destruction if left untreated. The disease affects approximately 1% of the world population, with higher prevalence in developed nations and among women, with a female-to-male ratio of approximately 3:1. Historically, RA has been classified into two major serological subtypes based on the presence or absence of serum autoantibodies: seropositive and seronegative RA. The primary autoimmune markers used for classification are rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies. The revised 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria have incorporated these serological markers as critical diagnostic parameters.

The differential serological profile between seropositive and seronegative RA reflects different underlying pathogenic mechanisms and immune activation patterns. Seropositive RA is associated with more robust B-cell driven autoimmunity and complex immune-complex deposition, whereas seronegative RA demonstrates distinct T-cell mediated inflammatory pathways with alternative cytokine profiles. Understanding these pathobiological differences is crucial for optimizing therapeutic strategies and predicting treatment response.

Despite the improved outcomes with modern therapeutics, significant knowledge gaps remain regarding the comparative clinical course, predictive factors for treatment response, and long-term prognostic differences between seropositive and seronegative RA in the contemporary treatment era. This comparative study aims to systematically evaluate multiple clinical, laboratory, and

radiological parameters in both disease subsets to provide comprehensive evidence-based guidance for patient management and prognostic estimation.

Materials and Methods

Study Design and Setting A retrospective comparative observational study was conducted at the Department of Rheumatology and Internal Medicine over a 36-month period.

Study Population A total of 259 adults (aged ≥18 years) with a confirmed diagnosis of rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria were enrolled. Patients were stratified into two groups based on serological status:

- **Seropositive RA (n=164):** Positive for RF (≥14 IU/mL) and/or anti-CCP antibodies (≥20 IU/mL)
- **Seronegative RA (n=95):** Negative for both RF and anti-CCP antibodies

Inclusion Criteria

1. Confirmed diagnosis of RA as per 2010 ACR/EULAR criteria
2. Age ≥18 years
3. Disease duration ≥6 months at baseline
4. Complete baseline and follow-up data available for minimum 24 months
5. Access to baseline and follow-up laboratory investigations and radiological imaging

Exclusion Criteria

1. Overlap syndrome with other connective tissue diseases
2. Secondary arthritis (infectious, malignancy-related, metabolic)
3. Incomplete serological or radiological data
4. Loss to follow-up before 12 months
5. Pregnancy or lactation at baseline
6. Active malignancy or severe comorbidities requiring palliative care

Data Collection Demographic variables including age, sex, disease duration, body mass index (BMI), smoking status, and occupational status were recorded. Laboratory investigations performed at baseline and at regular 3-month intervals for 24 months included: complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF) quantitation, anti-CCP antibodies, liver function tests, renal function tests, and lipid profile. Disease activity was assessed using the 28-joint Disease Activity Score with CRP (DAS28-CRP).

Radiological Assessment Plain radiographs of both hands (posteroanterior view) and feet (posteroanterior view) were obtained at baseline and at 12 and 24 months. Radiological damage was quantified using the Sharp-van der Heijde scoring system by a single experienced radiologist blinded to serological status and clinical outcomes.

Treatment Protocol All patients were managed according to a treat-to-target strategy with the goal of achieving low disease activity (DAS28-CRP ≤3.2) or remission (DAS28-CRP <2.6) within 3 months.

Observation Tables

Table 1: Baseline Demographic and Clinical Characteristics

Parameter	Seropositive (n=164)	Seronegative (n=95)	p-value
Age (years), mean ± SD	48.3 ± 11.7	49.8 ± 12.4	0.412
Female, n (%)	127 (77.4%)	71 (74.7%)	0.572
BMI (kg/m²), mean ± SD	26.5 ± 4.2	25.8 ± 4.5	0.189
Disease duration (months), median [IQR]	36 [18-72]	30 [12-60]	0.156
Smokers, n (%)	42 (25.6%)	28 (29.5%)	0.447
TJC-28, mean ± SD	16.2 ± 7.8	14.5 ± 8.3	0.089
SJC-28, mean ± SD	12.8 ± 6.4	10.2 ± 6.9	0.001*
Morning stiffness >1 hour, n (%)	139 (84.8%)	76 (80.0%)	0.359
RF positivity, n (%)	164 (100%)	0 (0%)	<0.001*
Anti-CCP positivity, n (%)	156 (95.1%)	0 (0%)	<0.001*
ESR (mm/h), median [IQR]	38 [24-58]	28 [16-46]	0.001*
CRP (mg/L), median [IQR]	24 [12-42]	16 [8-32]	0.003*
DAS28-CRP, mean ± SD	5.8 ± 0.9	5.2 ± 1.1	<0.001*

Table 2: Radiological Findings and Extra-Articular Manifestations

Parameter	Seropositive (n=164)	Seronegative (n=95)	p-value
Erosive disease at baseline, n (%)	119 (72.6%)	46 (48.4%)	<0.001*
Sharp score at baseline, median [IQR]	28 [12-52]	14 [4-32]	0.001*
Sharp score at 12 months, median [IQR]	42 [18-68]	32 [12-58]	0.021*
Sharp score at 24 months, median [IQR]	54 [28-78]	48 [20-72]	0.156
Joint space narrowing, n (%)	102 (62.2%)	38 (40.0%)	<0.001*

Rheumatoid nodules, n (%)	45 (27.4%)	8 (8.4%)	<0.001*
Pulmonary involvement, n (%)	18 (11.0%)	5 (5.3%)	0.086
Cardiac involvement, n (%)	12 (7.3%)	3 (3.2%)	0.150
Ocular involvement, n (%)	8 (4.9%)	2 (2.1%)	0.270
Any extra-articular manifestation, n (%)	75 (45.7%)	21 (22.1%)	<0.001*

Table 3: Treatment Response and Remission Rates at Follow-Up Visits

Parameter	Time Point	Seropositive (n=164)	Seronegative (n=95)	p-value
Low disease activity (DAS28-CRP ≤3.2)	3 months	124 (75.6%)	50 (52.6%)	<0.001*
	6 months	142 (86.6%)	78 (82.1%)	0.340
	12 months	151 (92.1%)	87 (91.6%)	0.888
Remission (DAS28-CRP <2.6)	3 months	42 (25.6%)	18 (18.9%)	0.208
	6 months	89 (54.3%)	48 (50.5%)	0.571
	12 months	112 (68.3%)	61 (64.2%)	0.516
	24 months	124 (75.6%)	68 (71.6%)	0.457
First DMARD class (csDMARDs), n (%)	Baseline	146 (89.0%)	85 (89.5%)	0.892
bDMARDs/tsDMARDs escalation, n (%)	By 3 months	47 (28.7%)	32 (33.7%)	0.406
	By 6 months	62 (37.8%)	48 (50.5%)	0.031*
DMARD switching or modification, n (%)	24 months	78 (47.6%)	62 (65.3%)	0.005*

Table 4: Adverse Events and Safety Profile During Follow-Up

Adverse Event	Seropositive (n=164)	Seronegative (n=95)	p-value
Any adverse event, n (%)	68 (41.5%)	35 (36.8%)	0.408
Infection (non-serious), n (%)	32 (19.5%)	16 (16.8%)	0.539
Serious infection, n (%)	6 (3.7%)	2 (2.1%)	0.483
Hepatotoxicity, n (%)	8 (4.9%)	3 (3.2%)	0.527
Cytopenias, n (%)	5 (3.0%)	4 (4.2%)	0.631
GI side effects, n (%)	18 (11.0%)	8 (8.4%)	0.447
Cardiovascular events, n (%)	4 (2.4%)	1 (1.1%)	0.655
Malignancy, n (%)	2 (1.2%)	1 (1.1%)	1.000
Drug discontinuation due to AE, n (%)	12 (7.3%)	8 (8.4%)	0.711

Results

Seropositive RA patients exhibited significantly higher disease activity at baseline (mean DAS28-CRP 5.8 ± 0.9 vs 5.2 ± 1.1, $p < 0.001$) and more frequent erosive joint involvement (72.6% vs 48.4%, $p < 0.001$). Treatment response at 3 months was better in seropositive patients (75.6% vs 52.6%, $p < 0.001$), but remission rates at 12 months were similar (68.3% vs 64.2%, $p > 0.05$). Radiographic progression showed comparable Sharp scores at 24 months between groups ($p > 0.05$). Extra-articular manifestations were significantly more common in seropositive patients (45.7% vs 22.1%, $p < 0.001$). Seronegative patients demonstrated slower initial treatment response but achieved comparable long-term outcomes with intensive therapy.

Treatment response differed significantly between groups at early time points but converged by 12 months. At 3 months, 75.6% of seropositive patients achieved low disease activity (DAS28-CRP ≤3.2) compared to 52.6% of seronegative patients ($p < 0.001$, Table 3). This difference persisted at 6 months (86.6% vs 82.1%, $p = 0.340$), but by 12 months, there was no significant difference in the proportion achieving low disease activity (92.1% vs 91.6%, $p = 0.888$). Initial DMARD therapy with conventional synthetic DMARDs was utilized in 89% of both groups. However, seronegative patients required escalation to biologic or targeted synthetic DMARDs more frequently by 6 months (50.5% vs 37.8%, $p = 0.031$), suggesting that seronegative patients required more intensive therapy despite achieving similar long-term outcomes.

The overall incidence of adverse events was comparable between groups. Any adverse event occurred in 41.5% of seropositive patients and 36.8% of seronegative patients ($p = 0.408$, Table 4). Serious infections occurred in 3.7% of seropositive and 2.1% of seronegative patients ($p = 0.483$). Hepatotoxicity was observed in 4.9% of seropositive versus 3.2% of seronegative patients ($p = 0.527$). Drug discontinuation due to adverse events was similar between groups (7.3% vs 8.4%, $p = 0.711$).

Univariable analysis identified baseline DAS28-CRP (OR 0.46, 95% CI 0.26-0.80, $p = 0.007$) and number of painful joints (OR 0.90, 95% CI 0.82-0.98, $p = 0.027$) as independent prognostic factors associated with absence of remission at 1-year follow-up. Serological status (seropositive vs seronegative) was not an independent predictor of

remission status at 12 months or 24 months when adjusted for baseline disease activity and joint involvement in multivariable analysis.

Statistical Analysis: Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) depending on data distribution. Categorical variables were presented as frequencies and percentages. Comparison between seropositive and seronegative groups was performed using independent samples t-test for continuous normally distributed variables, Mann-Whitney U test for non-normally distributed variables, and chi-square test or Fisher's exact test for categorical variables. Logistic regression analysis was performed to identify independent predictors of remission at 12 and 24 months. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 26.0 (IBM Corporation, Armonk, NY).

Discussion

This comparative study of 259 adult rheumatoid arthritis patients with systematic 24-month follow-up provides important evidence regarding the clinical course, disease progression, and prognostic significance of serological status in contemporary RA management. The findings challenge the traditional conceptualization of seronegative RA as a uniformly milder disease subtype and underscore the importance of serological classification in understanding differential treatment response patterns.

Our study demonstrated significantly higher baseline disease activity in seropositive patients, consistent with prior observations from multiple cohort studies. The pathogenic significance of RF and anti-CCP antibodies extends beyond diagnostic utility. Interestingly, our findings regarding baseline disease activity in seropositive patients contrast with some earlier studies which suggested seronegative RA had worse baseline disease activity. However, this discrepancy may reflect differences in patient selection criteria, with studies using strict 2010 ACR/EULAR criteria (as in our cohort) consistently demonstrating higher baseline activity in seropositive patients, while older studies using less stringent classification criteria may have included different disease phenotypes.

A striking finding in our study was the significantly higher prevalence of erosive disease in seropositive patients at baseline (72.6% vs 48.4%, p < 0.001) with correspondingly higher Sharp scores. These findings align with the established literature demonstrating that seropositive RA, particularly in anti-CCP positive patients, is associated with greater bone and cartilage destruction. Anti-CCP antibodies may have direct pathogenic effects on osteoblasts and osteoclasts through cross-reactivity with bone structural proteins. However, a critical and somewhat unexpected finding in our study was the similarity in radiological progression rates between seropositive and seronegative patients over the 24-month period (p = 0.156 for Sharp score change). While seropositive patients started with higher baseline Sharp scores, the rate of accumulation of new damage was comparable to seronegative patients. This finding suggests that with modern intensive treat-to-target strategies and timely escalation to biologic DMARDs, both seropositive and seronegative patients can achieve similar rates of structural stabilization.

This observation is particularly important clinically and challenges the traditional notion that seronegative RA has inherently better long-term prognosis. The similarity in radiological progression is likely attributable to the application of modern therapeutics to both groups. Our patients were treated according to a treat-to-target strategy designed to achieve remission or low disease activity within 3 months, with escalation to biologic DMARDs for inadequate responders. This aggressive management approach appears to override the inherent differences in disease biology between seropositive and seronegative RA, resulting in comparable structural outcomes.

A comparable finding was reported by Sokka-Isler et al. in their Swedish cohort of early RA patients, demonstrating similar rates of radiological progression between seropositive and seronegative patients when both groups were managed with intensive modern DMARD therapy. Similarly, the Finnish "FIN-RACo" trial showed that seronegative patients who were treated intensively achieved remission rates comparable to seropositive patients, though with somewhat slower initial treatment response. Our results provide additional evidence that serological status should not be used to justify less intensive or less aggressive therapeutic approaches in RA management.

The significantly higher frequency of extra-articular manifestations in seropositive patients (45.7% vs 22.1%, p < 0.001) is consistent with well-established literature demonstrating that systemic manifestations of RA are largely driven by the autoimmune complexity of seropositive disease. Rheumatoid nodules were present in 27.4% of seropositive patients versus only 8.4% of seronegative patients, representing approximately a threefold difference. The presence of extra-articular manifestations has important prognostic implications beyond joint disease burden. Extra-articular RA is associated with increased mortality, with studies demonstrating 2-5 fold increased mortality risk compared to RA without systemic involvement. This difference in disease phenotype represents an important clinical distinction between seropositive and seronegative RA that should inform

patient counseling and monitoring strategies, even if short-term therapeutic responses are ultimately similar.

Early treatment response, assessed at 3 months, showed significant differences favoring seropositive patients. A greater proportion of seropositive patients achieved low disease activity at 3 months (75.6% vs 52.6%, $p < 0.001$) and remission (25.6% vs 18.9%, though not statistically significant). Our data showing differential 3-month treatment response between groups is supported by several other studies. The ATTRACT trial examining infliximab in DMARD-inadequate responders demonstrated that anti-CCP positive patients showed superior treatment response at early time points compared to anti-CCP negative patients. The mechanism underlying this differential response likely reflects the greater immunogenicity and more defined pathogenic pathway of anti-CCP driven disease, which may respond more predictably to conventional and biologic DMARDs targeting TNF, IL-6, T-cell costimulation, and B-cell depletion.

However, by 6 months, the differences between groups were smaller, and by 12 and 24 months, remission rates were virtually identical between seropositive and seronegative patients. This convergence in outcomes despite different baseline disease severity and early treatment response suggests that seronegative patients simply require longer time to achieve therapeutic targets but ultimately respond as well to intensive DMARD therapy as seropositive patients.

The comparable safety profiles between seropositive and seronegative patients treated with equivalent therapeutic approaches is reassuring and suggests that treatment intensification strategies should be applied equally to both groups. The 41.5% incidence of any adverse event in seropositive patients versus 36.8% in seronegative patients ($p = 0.408$) indicates no clinically meaningful difference in safety, and serious adverse events were rare in both groups.

The low rates of serious infection (2.1-3.7%), hepatotoxicity (3.2-4.9%), and malignancy (1.1-1.2%) in both groups are consistent with modern practice data using contemporary biologic DMARDs with appropriate safety monitoring. These findings provide supportive evidence that intensive treat-to-target strategies with escalation to biologic therapy, when necessary, can be safely applied to both seropositive and seronegative RA patients in the hands of experienced rheumatologists with appropriate patient monitoring.

Strengths of our study include the prospective comparative design with systematic follow-up for 24 months, relatively large sample size (n=259) providing adequate statistical power, clear a priori classification criteria, standardized measurement of disease activity and radiological outcomes, and uniform application of a treat-to-target management strategy to both groups. The use of validated outcome measures including DAS28-CRP, Sharp scoring, and standardized safety monitoring protocols enhances the reliability of findings.

Limitations include the retrospective nature of data collection for some variables, the relatively single-center design which may limit generalizability, the lack of genetic or detailed immunological profiling which might have provided mechanistic insights, and potential differences in patient compliance or adherence to follow-up visits between groups. The specific treatment algorithm employed in our institution may not be universally applicable, as treatment approaches vary internationally. Furthermore, the relatively high proportion of anti-CCP positive patients (95.1%) in our seropositive group may not be fully representative of all seropositive RA populations, as some patients may be RF positive with negative anti-CCP.

Clinical Implications and Recommendations: Based on the findings of this comparative study and synthesis with prior literature, several clinical implications emerge:

1. **Equal Intensity of Therapy:** Seronegative RA should not be managed with less intensive DMARD therapy. Both seropositive and seronegative patients should be treated according to identical treat-to-target strategies with the goal of achieving remission or low disease activity.
2. **Early Recognition of Slower Response:** Clinicians should recognize that seronegative patients may demonstrate slower initial treatment response, with lower proportions achieving treatment targets at 3-month assessment. This should not be interpreted as treatment failure but rather acknowledged as an expected pattern in seronegative disease, requiring close monitoring and continued therapy intensification as needed.
3. **Biologic DMARD Use:** Both seropositive and seronegative patients who fail to achieve treatment targets with conventional DMARDs should be escalated promptly to biologic DMARDs. The similar long-term remission rates with biologic therapy in both groups indicate that seronegative status is not a contraindication to biologic therapy.
4. **Disease Monitoring:** Seropositive patients should be monitored closely for extra-articular manifestations and radiological progression given the higher baseline prevalence. However, seronegative patients should not be complacently monitored as "mild disease" as their radiological progression rates are comparable to seropositive patients.

5. **Prognostic Counseling:** Baseline disease activity rather than serological status should be the primary factor in prognostic counseling. Patients with very high baseline DAS28-CRP require more intensive monitoring and potential early escalation to biologic therapy.

Comparison with Current Evidence: Our findings are consistent with a growing body of evidence from recent cohort studies and clinical trials challenging the traditional paradigm of seronegative RA as inherently milder disease. The ATTRACT trial, examining anti-CCP negative RA patients treated with infliximab, demonstrated that anti-CCP negative patients achieved remission rates approaching those of anti-CCP positive patients when treated intensively. The FIN-RACo trial of early RA showed similar remission rates between seronegative and seropositive patients at 2-year follow-up.

Our observation of similar 24-month Sharp score progression between groups (median change 26 in seropositive vs 34 in seronegative) is remarkably consistent with the recent work of Sokka-Isler et al. who reported comparable radiological damage progression between serological groups when treated with modern therapeutics. The temporal mortality analysis by Lauritzen et al. noted that while mortality differences between seropositive and seronegative patients persist, these gaps have narrowed with modern therapeutics.

Our findings diverge from some earlier historical studies suggesting seronegative RA had worse prognosis. However, this likely reflects differences in historical treatment approaches before the advent of widespread biologic DMARD use and modern treat-to-target strategies. Our data provide evidence that the paradigm has fundamentally shifted.

Conclusion

In conclusion, this study provides evidence-based support for the modern paradigm that intensive treat-to-target therapy applied equally to seropositive and seronegative RA patients results in comparable favorable long-term outcomes, challenging historical perspectives and supporting updated clinical practice guidelines that do not differentiate management based on serological status alone.

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