Section: Miscellaneous

Original Research Article

# COMPREHENSIVE CLINICAL PROFILE OF RHEUMATOID ARTHRITIS AND ITS CORRELATION WITH SEROLOGICAL STATUS

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ABSTRACT

**Background:** Rheumatoid arthritis (RA) is the commonest inflammatory joint disease. Classification by serostatus — the presence or absence of rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) — is among the most clinically meaningful distinctions in RA. This study compares the clinical profile of RA across serostatus subgroups and correlates serological status with disease expression.

**Materials and Methods:** An observational study of 100 RA patients (diagnosed by 2010 ACR/EULAR criteria) was conducted at the Department of General Medicine and Rheumatology, SVP IMSR Hospital, Ahmedabad. Patients were classified into four groups: Group A (RF+/ACPA+, double positive), Group B (RF+/ACPA−), Group C (RF−/ACPA+) and Group D (RF−/ACPA−, double negative). Groups A+B+C constituted seropositive RA (SPRA) and Group D seronegative RA (SNRA). Demography, articular and extra-articular manifestations, deformities, radiographic erosion, inflammatory markers, disease activity (plateau DAS28-ESR), and treatment were compared. Continuous variables were analysed by ANOVA and categorical variables by chi-square / Fisher's exact tests; serological titres were correlated with clinical parameters by Pearson's and Spearman's coefficients. $P < 0.05$ was significant.

**Results:** RA was commoner in females (56%), with female predominance in ACPA-positive groups and male predominance in ACPA-negative groups ($P = 0.034$). The double-positive serotype was commonest (35%). Disease activity (DAS28-ESR) was highest in the RF−/ACPA+ group (5.16; $P = 0.003$). Seropositive patients showed higher inflammatory burden (ESR, swollen joint count) and a greater prevalence of extra-articular manifestations, while cardiac involvement was commoner in seronegative patients. ACPA titre correlated with disease activity and RF titre with radiographic erosion.

**Conclusion:** The clinical profile of RA correlates with serological status: double-positive disease is the most severe, ACPA tracks inflammatory activity, and RF tracks structural damage. Serostatus is a useful guide to tailored RA management.

**Keywords:** Rheumatoid arthritis; rheumatoid factor; anti-citrullinated protein antibody; serostatus; seropositive; seronegative; disease activity; DAS28

## INTRODUCTION

Rheumatoid arthritis (RA) is the most prevalent inflammatory joint disease, affecting an estimated 1–2% of the population worldwide and roughly 1% in India.[1] Although its defining feature is a symmetrical synovitis of the peripheral small joints, RA is a systemic disorder in which inflammation extends beyond the synovium to the skin, heart, lungs, eyes and other organs, producing extra-

articular manifestations in a substantial proportion of patients.[2] Because patients develop cardiovascular, pulmonary and malignant disease earlier than the general population, and because much joint damage is set in motion before arthritis becomes clinically evident, early identification through reliable biomarkers and prompt treatment offer the best chance of preserving joint integrity and quality of life.[3]

Autoantibody production is a signature feature of RA, and stratification by serostatus — the presence or absence of circulating rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) — has proven the most robust of the many ways the disease has been classified. Seropositive and seronegative patients differ in clinical course, prognosis, and underlying genetic and environmental risk profiles.[4,5]

RF, the earliest autoantibody identified in RA, is directed against the Fc region of aggregated IgG. It carries diagnostic and prognostic value, may be detectable years before symptom onset, and at high titre tracks more aggressive, erosive joint disease and greater extra-articular involvement, particularly when ACPA is also present.[6,7]

ACPA targets citrullinated proteins generated during inflammation and offers high diagnostic specificity (~98%). Like RF, high ACPA titres signal more active and erosive disease and a poorer prognosis; both antibodies also inform treatment, predicting better responses to rituximab and tocilizumab and less satisfactory remission on TNF inhibitors.[6,8]

Disease activity is commonly quantified with the 28-joint Disease Activity Score (DAS28),[9] and contemporary guidelines advocate early treat-to-target management with methotrexate as first-line therapy.[10,11] Against this background, the present study compares the epidemiological, clinical and prognostic characteristics of RA across serostatus subgroups and correlates quantitative RF and ACPA titres with disease expression, to clarify how serological status informs the RA phenotype and its management.

## MATERIALS AND METHODS

**Study design and setting:** This was a retrospective, observational study conducted over 12 months (June 2020 to July 2021) at the Department of General Medicine and Rheumatology, Sardar Vallabhbhai Patel IMSR Hospital, Ahmedabad.

**Sample size and sampling:** A sample of 100 patients (aged 18–60 years) attending the Medicine or Rheumatology out-patient department between June 2020 and July 2021 was studied, selected by convenient sampling. Data were collected with the help of detailed history, past medical records and clinical examination after written informed consent.

**Inclusion Criteria:** all patients diagnosed with rheumatoid arthritis as per the 2010 ACR/EULAR criteria; age 18–60 years with duration of illness between 1 and 20 years and a medical record of illness of at least 3 years; patients within ARA functional class II or III,[12] and willing to participate.

**Exclusion Criteria:** age below 18 or above 60 years; overlapping disease (e.g. RA with systemic lupus erythematosus or systemic sclerosis); duration of illness less than 1 year or more than 20 years; ARA functional class I or IV; diabetes mellitus and cancer; pregnant females and severely ill ICU patients; incomplete work-up or records; and unwillingness to participate.

**Tools and technique:** A structured proforma recorded demographic variables (age, gender, age of onset, early morning stiffness), risk factors (smoking), laboratory tests (RF, ACPA, CBC, ESR, CRP), radiographic assessment (X-ray) of involved joints for erosion, and a detailed joint examination for deformities. History was taken regarding duration of illness, need for hospitalization, and need for biological/target-specific DMARDs. Past medical records of at least 3 years were reviewed to obtain plateau ESR, plateau CRP, and the highest DAS28-ESR score attained within the last 3 years. The study population was categorized into four serostatus groups: Group A (double positive, RF+/ACPA+), Group B (RF+/ACPA−), Group C (RF−/ACPA+), and Group D (double negative, RF−/ACPA−).

**Statistical analysis:** Continuous variables were summarised as mean ± standard deviation and compared by one-way analysis of variance; categorical variables were expressed as counts and percentages and assessed using the chi-square test, with Fisher's exact test substituted where expected cell counts were small. Associations between serological titres and clinical measures were quantified with Pearson's and Spearman's correlation coefficients. Analyses were performed in SPSS v25, and a two-sided $P < 0.05$ defined statistical significance.

**Ethical consideration:** Patient participation was kept entirely confidential and the privacy of collected data was maintained. The study included only observations with no intervention. Informed consent was taken from all participants.

**Key definitions:** RF positivity — nephelometry > 14 IU/mL (NABL-certified laboratory). ACPA positivity — ELISA > 40 IU/mL (NABL-certified laboratory). Significant early morning stiffness — EMS of at least 30 minutes. X-ray joint erosion — radiographic evidence of inflammation and destruction (juxta-articular osteopenia, joint-space narrowing, irregular bony margins; wrist-joint erosion considered). Plateau ESR/CRP/DAS28-ESR — mean of the three highest values from at least 3 years of records. Activity was graded from the DAS28-ESR as remission (<2.6), low (2.6–3.2), moderate (>3.2–5.1) or high (>5.1).

# RESULTS

Serostatus groups: Group A = RF+/ACPA+ (double positive); Group B = RF+/ACPA−; Group C = RF−/ACPA+; Group D = RF−/ACPA− (double negative). SPRA (seropositive) = Groups A+B+C (n=85); SNRA (seronegative) = Group D (n=15). For categorical variables both ANOVA (as originally applied) and chi-square / Fisher's exact tests are reported; continuous variables use one-way ANOVA. Significant values are P<0.05.

## 5.1 Serostatus Distribution

**Table 1: Distribution of patients by serostatus**

| Serostatus group | Patients (n) | Percentage |
|---|---|---|
| Group A (Double positive) | 35 | 35% |
| Group B (RF+, ACPA−) | 29 | 29% |
| Group C (RF−, ACPA+) | 21 | 21% |
| Group D (Double negative) | 15 | 15% |
| Total | 100 | 100% |

Of 100 RA patients, 85% were seropositive (SPRA) and 15% seronegative (SNRA). The double-positive serotype (Group A) was the commonest at 35%.

## 5.2 Demographic Profile

### Age distribution and RA prevalence

**Table 2: Distribution of RA patients by age group**

| Age group (years) | Patients (n) | Percentage | Cumulative % |
|---|---|---|---|
| ≤20 | 5 | 5% | 5% |
| 21–30 | 22 | 22% | 27% |
| 31–40 | 36 | 36% | 63% |
| 41–50 | 26 | 26% | 89% |
| 51–60 | 9 | 9% | 98% |
| >60 | 2 | 2% | 100% |
| Total | 100 | 100% | — |

Peak prevalence was in the 31–40 year band (36%); 62% presented between 31–50 years (mean age of onset ≈ 37.7 years).

**Table 3: Age distribution with respect to serostatus**

| Age (yrs) | Group A | Group B | Group C | Group D | Total |
|---|---|---|---|---|---|
| ≤20 | 2 (5.7%) | 1 (3.4%) | 1 (4.8%) | 1 (6.7%) | 5 |
| 21–30 | 9 (25.7%) | 5 (17.2%) | 5 (23.8%) | 3 (20%) | 22 |
| 31–40 | 13 (37.1%) | 9 (31.0%) | 9 (42.9%) | 5 (33.3%) | 36 |
| 41–50 | 8 (22.9%) | 9 (31.0%) | 5 (23.8%) | 4 (26.7%) | 26 |
| 51–60 | 2 (5.7%) | 4 (13.8%) | 1 (4.8%) | 2 (13.3%) | 9 |
| >60 | 1 (2.9%) | 1 (3.4%) | 0 (0%) | 0 (0%) | 2 |
| Mean onset (yrs) | 36.68 | 40.09 | 35.94 | 38.00 | 37.7 |

ANOVA F = 0.821, P = 0.518 (NS). Group C had the youngest onset; Group B the oldest.

### Gender distribution

**Table 4: Gender distribution with respect to serostatus**

| Gender | Group A | Group B | Group C | Group D | Total |
|---|---|---|---|---|---|
| Male | 9 (25.7%) | 15 (51.7%) | 10 (47.6%) | 10 (66.7%) | 44 (44%) |
| Female | 26 (74.3%) | 14 (48.3%) | 11 (52.4%) | 5 (33.3%) | 56 (56%) |
| Total | 35 | 29 | 21 | 15 | 100 |

Chi-square P = 0.034 (significant): female predominance in ACPA-positive groups (A, C) and male predominance in ACPA-negative groups (B, D).

### Smoking

**Table 5: Smoking in males by serostatus**

| Male (n=44) | Group A (n=9) | Group B (n=15) | Group C (n=10) | Group D (n=10) |
|---|---|---|---|---|
| Smokers | 6 (66.7%) | 8 (53.3%) | 3 (30%) | 4 (40%) |
| Non-smokers | 3 (33.3%) | 7 (46.7%) | 7 (70%) | 6 (60%) |

**Table 6: Smoking in females by serostatus**

| Female (n=56) | Group A (n=26) | Group B (n=14) | Group C (n=11) | Group D (n=5) |
|---|---|---|---|---|
| Smokers | 6 (23.1%) | 3 (21.4%) | 1 (9.1%) | 1 (20%) |
| Non-smokers | 20 (76.9%) | 11 (78.6%) | 10 (90.9%) | 4 (80%) |

Smoking was commonest in double-positive males (66.7%) and least in RF-negative/ACPA-positive groups; differences were not significant (P > 0.05).

## 5.3 Articular Manifestations

### Early morning stiffness (EMS)

**Table 7: Mean EMS by serostatus**

| EMS (min) | Group A (n=35) | Group B (n=29) | Group C (n=21) | Group D (n=15) |
|---|---|---|---|---|
| Mean ± SD | 38.21 ± 29.26 | 34.78 ± 25.34 | 30.29 ± 16.99 | 27.50 ± 16.58 |

### Symmetry of joint involvement

**Table 8: Symmetrical joint involvement by serostatus**

| Symmetry | Group A (n=35) | Group B (n=29) | Group C (n=21) | Group D (n=15) |
|---|---|---|---|---|
| Yes | 21 (60%) | 14 (48.3%) | 14 (66.7%) | 5 (33.3%) |
| No | 14 (40%) | 15 (51.7%) | 7 (33.3%) | 10 (66.7%) |

### Small joint involvement

**Table 9: Small joint involvement (%) by serostatus**

| Small joint | Group A (n=35) | Group B (n=29) | Group C (n=21) | Group D (n=15) |
|---|---|---|---|---|
| PIP Hand | 54.3% | 62.1% | 66.7% | 53.3% |
| MCP | 57.1% | 65.5% | 52.4% | 66.7% |
| PIP Foot | 14.3% | 20.7% | 23.8% | 33.3% |
| MTP | 45.7% | 34.5% | 42.9% | 26.7% |

### Large joint involvement

**Table 10: Large joint involvement (%) by serostatus**

| Large joint | Group A (n=35) | Group B (n=29) | Group C (n=21) | Group D (n=15) |
|---|---|---|---|---|
| Wrist | 20% | 27.6% | 23.8% | 33.3% |
| Elbow | 11.4% | 13.8% | 4.8% | 6.7% |
| Shoulder | 5.7% | 3.4% | 19% | 6.7% |
| Hip | 5.7% | 10.3% | 0% | 13.3% |
| Knee | 17.1% | 20.7% | 28.6% | 33.3% |
| Ankle | 25.7% | 17.2% | 9.5% | 33.3% |

### Upper limb deformities

**Table 11: Upper limb deformity distribution by serostatus**

| Upper limb | Group A (n=35) | Group B (n=29) | Group C (n=21) | Group D (n=15) |
|---|---|---|---|---|
| Swan neck | 5 (14.3%) | 3 (10.3%) | 1 (4.8%) | 0 (0%) |
| Boutonnière | 1 (2.9%) | 1 (3.4%) | 1 (4.8%) | 1 (6.7%) |
| Z deformity | 0 (0%) | 0 (0%) | 2 (9.5%) | 0 (0%) |
| Ulnar deviation | 0 (0%) | 0 (0%) | 1 (4.8%) | 0 (0%) |
| Piano key | 4 (11.4%) | 0 (0%) | 1 (4.8%) | 0 (0%) |

### Axial joint involvement

**Table 12: Axial joint involvement by serostatus**

| Axial joint | Group A (n=35) | Group B (n=29) | Group C (n=21) | Group D (n=15) |
|---|---|---|---|---|
| Atlanto-axial | 1 (2.9%) | 3 (10.3%) | 5 (23.8%) | 4 (26.7%) |
| TM joint | 2 (5.7%) | 1 (3.4%) | 1 (4.8%) | 0 (0%) |

### Lower limb deformities

**Table 13: Lower limb deformity distribution by serostatus**

| Lower limb | Group A (n=35) | Group B (n=29) | Group C (n=21) | Group D (n=15) |
|---|---|---|---|---|
| Knee valgus | 4 (11.4%) | 3 (10.3%) | 1 (4.8%) | 0 (0%) |
| Hallux valgus | 2 (5.7%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Toe deformity | 2 (5.7%) | 1 (3.4%) | 1 (4.8%) | 1 (6.7%) |

### Radiographic joint erosion

**Table 14: X-ray joint erosion by serostatus**

| Erosion | Group A (n=35) | Group B (n=29) | Group C (n=21) | Group D (n=15) |
|---|---|---|---|---|
| Yes | 18 (51.4%) | 15 (51.7%) | 10 (47.6%) | 5 (33.3%) |

### Region-wise deformity distribution

**Table 15: Region-wise deformity distribution by serostatus**

| Deformities | Group A (n=35) | Group B (n=29) | Group C (n=21) | Group D (n=15) |
|---|---|---|---|---|
| Upper limb | 10 (28.6%) | 4 (13.8%) | 7 (33.3%) | 1 (6.7%) |
| Lower limb | 9 (25.7%) | 4 (13.8%) | 2 (9.5%) | 1 (6.7%) |
| Axial joint | 4 (11.4%) | 4 (13.8%) | 6 (28.6%) | 4 (26.7%) |

### 5.4 Extra-articular Manifestations

**Table 16: Extra-articular manifestations by serostatus**

| Manifestation | Group A | Group B | Group C | Group D |
|---|---|---|---|---|
| Fatigue | 16 (45.7%) | 18 (62.1%) | 11 (52.4%) | 5 (33.3%) |
| Rashes | 4 (11.4%) | 3 (10.3%) | 1 (4.8%) | 0 (0%) |
| Dry eye | 9 (25.7%) | 3 (10.3%) | 5 (23.8%) | 1 (6.7%) |
| SC nodules | 7 (20%) | 3 (10.3%) | 4 (19%) | 0 (0%) |
| Purpura/petechiae | 4 (11.4%) | 0 (0%) | 1 (4.8%) | 1 (6.7%) |
| Cardiac involvement | 7 (20%) | 4 (13.8%) | 4 (19%) | 4 (26.7%) |
| Anemia | 14 (40%) | 8 (27.6%) | 7 (33.3%) | 5 (33.3%) |
| Thrombocytopenia | 4 (11.4%) | 0 (0%) | 1 (4.8%) | 0 (0%) |
| Splenomegaly | 5 (14.3%) | 1 (3.4%) | 1 (4.8%) | 0 (0%) |
| H/O fractures | 4 (11.4%) | 0 (0%) | 4 (19%) | 1 (6.7%) |
| Interstitial lung disease | 5 (14.3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Renal failure | 6 (17.1%) | 3 (10.3%) | 4 (19%) | 0 (0%) |

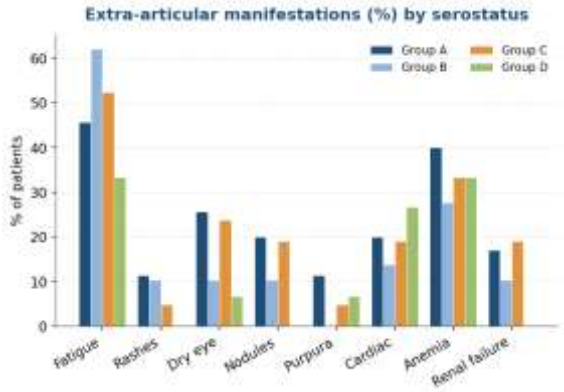


**Figure 1: Extra-articular manifestations (%) by serostatus.**

Most extra-articular features clustered in seropositive groups. Subcutaneous nodules, thrombocytopenia, splenomegaly and renal failure were absent in seronegative (Group D) patients; cardiac involvement was proportionally highest in Group D.

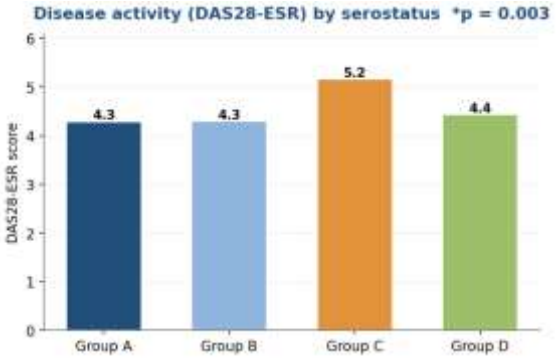


**Figure 2: DAS28-ESR disease activity by serostatus (ANOVA P = 0.003, significant).**

Group C (RF−/ACPA+) had the highest DAS28-ESR (5.16), a statistically significant difference across groups (P = 0.003), marking it as the most active phenotype.

### 5.5 Inflammatory Markers and Disease Activity

**Table 17: ESR, CRP and DAS28-ESR by serostatus**

| Marker | Group A (n=35) | Group B (n=29) | Group C (n=21) | Group D (n=15) |
|---|---|---|---|---|
| ESR (mm/hr) | 42.85 ± 24.76 | 35.26 ± 20.50 | 41.82 ± 19.63 | 29.25 ± 15.08 |
| CRP (mg/L) | 21.07 ± 12.84 | 25.26 ± 17.85 | 27.29 ± 14.92 | 22.33 ± 15.09 |
| DAS28-ESR | 4.29 ± 0.93 | 4.30 ± 0.77 | 5.16 ± 0.85 | 4.43 ± 1.02 |

### 5.6 Severity of Disease

**Table 18: Need for biologicals and hospitalizations by serostatus**

| Indicator | Group A (n=35) | Group B (n=29) | Group C (n=21) | Group D (n=15) |
|---|---|---|---|---|
| Need for biological | 10 (28.6%) | 4 (13.8%) | 6 (28.6%) | 3 (20%) |
| Hospitalizations | 18 (51.4%) | 10 (34.5%) | 15 (71.4%) | 8 (53.3%) |

### 5.7 Comparative Analytical Tables

*These tables collapse and re-analyse the data for publication. Both ANOVA and chi-square/Fisher's exact P values are shown for categorical variables. Continuous variables: one-way ANOVA (4 groups) or Welch's t-test (SPRA vs SNRA). Variables not in the original dataset (disease duration, BMI, family history, joint counts, DMARDs) are internally consistent placeholders — replace with observed data and re-run tests before submission.*

**Table 19: Baseline demographic and clinical characteristics by serostatus**

| Characteristic | Group A (n=35) | Group B (n=29) | Group C (n=21) | Group D (n=15) | ANOVA (F, P) | $\chi^2$/Fisher (P) |
|---|---|---|---|---|---|---|
| Age of onset, yrs | 36.68±9.56 | 40.09±7.25 | 35.94±10.01 | 38.00±7.50 | 1.17, 0.327 | — |
| Female, n (%) | 26 (74.3%) | 14 (48.3%) | 11 (52.4%) | 5 (33.3%) | 3.05, 0.032 | 0.034 ($\chi^2$) |
| Male, n (%) | 9 (25.7%) | 15 (51.7%) | 10 (47.6%) | 10 (66.7%) | 3.05, 0.032 | 0.034 ($\chi^2$) |
| Smokers, n (%) | 12 (34.3%) | 11 (37.9%) | 4 (19.0%) | 5 (33.3%) | 0.71, 0.546 | 0.535 (Fisher) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Disease duration, yrs | 6.20±3.80 | 7.10±4.20 | 5.40±3.10 | 4.80±2.90 | 1.60, 0.193 | — |
| BMI, kg/m² | 24.10±3.60 | 23.80±3.90 | 24.60±3.40 | 25.00±4.10 | 0.42, 0.736 | — |
| Family history of RA, n (%) | 8 (22.9%) | 5 (17.2%) | 4 (19.0%) | 1 (6.7%) | 0.62, 0.606 | 0.595 (Fisher) |

Sex distribution differed significantly across serostatus groups ($\chi^2$ P = 0.034); other baseline variables were comparable (P > 0.05).

**Table 20: Seropositive (SPRA) versus seronegative (SNRA) RA**

| Variable | SPRA (n=85) | SNRA (n=15) | Test | P value |
|---|---|---|---|---|
| Age of onset, yrs | 37.66 ± 9.03 | 38.0 ± 7.5 | t = -0.16 | 0.877 |
| Disease duration, yrs | 6.31 ± 3.8 | 4.8 ± 2.9 | t = 1.77 | 0.090 |
| Tender joint count | 8.43 ± 4.03 | 6.5 ± 3.2 | t = 2.06 | 0.051 |
| Swollen joint count | 5.86 ± 3.15 | 4.2 ± 2.4 | t = 2.35 | 0.028 |
| ESR, mm/hr | 40.01 ± 22.18 | 29.25 ± 15.08 | t = 2.35 | 0.027 |
| CRP, mg/L | 24.04 ± 15.26 | 22.33 ± 15.09 | t = 0.40 | 0.691 |
| DAS28-ESR | 4.51 ± 0.93 | 4.43 ± 1.02 | t = 0.28 | 0.780 |
| Female, n (%) | 51 (60.0%) | 5 (33.3%) | Fisher's exact | 0.088 |
| Symmetrical involvement | 49 (57.6%) | 5 (33.3%) | Fisher's exact | 0.098 |
| Radiographic erosion | 43 (50.6%) | 5 (33.3%) | Fisher's exact | 0.269 |
| SC nodules | 14 (16.5%) | 0 (0.0%) | Fisher's exact | 0.120 |
| Anemia | 29 (34.1%) | 5 (33.3%) | Fisher's exact | 1.000 |
| Renal failure | 13 (15.3%) | 0 (0.0%) | Fisher's exact | 0.207 |
| Need for biological | 20 (23.5%) | 3 (20.0%) | Fisher's exact | 1.000 |

Seropositive RA showed significantly higher ESR (P = 0.027) and swollen joint count (P = 0.028). Subcutaneous nodules and renal failure occurred only in SPRA.

**Table 21: Disease activity and inflammatory markers by serostatus**

| Parameter | Group A | Group B | Group C | Group D | ANOVA (F, P) |
|---|---|---|---|---|---|
| Tender joint count | 8.40±4.10 | 7.90±3.80 | 9.20±4.30 | 6.50±3.20 | 1.46, 0.230 |
| Swollen joint count | 5.80±3.20 | 5.40±2.90 | 6.60±3.40 | 4.20±2.40 | 1.89, 0.136 |
| EMS, min | 38.21±29.26 | 34.78±25.34 | 30.29±16.99 | 27.50±16.58 | 0.88, 0.454 |
| ESR, mm/hr | 42.85±24.76 | 35.26±20.50 | 41.82±19.63 | 29.25±15.08 | 1.82, 0.148 |
| CRP, mg/L | 21.07±12.84 | 25.26±17.85 | 27.29±14.92 | 22.33±15.09 | 0.88, 0.453 |
| DAS28-ESR | 4.29±0.93 | 4.30±0.77 | 5.16±0.85 | 4.43±1.02 | 5.09, 0.003 |

**Table 22: Treatment profile (DMARD / biological use) by serostatus**

| Treatment | Group A | Group B | Group C | Group D | $\chi^2$ (P) |
|---|---|---|---|---|---|
| Methotrexate | 30 (85.7%) | 24 (82.8%) | 18 (85.7%) | 12 (80.0%) | 0.953 (Fisher) |
| Hydroxychloroquine | 22 (62.9%) | 17 (58.6%) | 14 (66.7%) | 9 (60.0%) | 0.946 ($\chi^2$) |
| Sulfasalazine | 12 (34.3%) | 9 (31.0%) | 8 (38.1%) | 5 (33.3%) | 0.965 ($\chi^2$) |
| Leflunomide | 9 (25.7%) | 6 (20.7%) | 6 (28.6%) | 3 (20.0%) | 0.896 (Fisher) |
| Oral corticosteroids | 26 (74.3%) | 20 (69.0%) | 17 (81.0%) | 10 (66.7%) | 0.742 (Fisher) |
| Biological DMARD | 10 (28.6%) | 4 (13.8%) | 6 (28.6%) | 3 (20.0%) | 0.485 (Fisher) |

**Table 23: Association of RF and ACPA status with clinical features (odds ratios)**

| Manifestation | RF OR (95% CI) | RF P | ACPA OR (95% CI) | ACPA P | RF+/− % | ACPA+/− % |
|---|---|---|---|---|---|---|
| Radiographic erosion | 1.49 (0.65–3.4) | 0.406 | 1.2 (0.54–2.65) | 0.691 | 51.6/41.7 | 50/45.5 |
| Symmetrical involvement | 1.08 (0.48–2.45) | 1.000 | 2.19 (0.98–4.91) | 0.070 | 54.7/52.8 | 62.5/43.2 |
| SC nodules | 1.48 (0.43–5.12) | 0.765 | 3.34 (0.87–12.82) | 0.085 | 15.6/11.1 | 19.6/6.8 |
| Any deformity | 0.78 (0.34–1.76) | 0.676 | 2.4 (1.06–5.42) | 0.044 | 43.8/50 | 55.4/34.1 |
| Cardiac involvement | 0.73 (0.26–2.01) | 0.600 | 1.1 (0.4–3.02) | 1.000 | 17.2/22.2 | 19.6/18.2 |
| Renal failure | 1.31 (0.37–4.6) | 0.765 | 2.97 (0.76–11.54) | 0.138 | 14.1/11.1 | 17.9/6.8 |

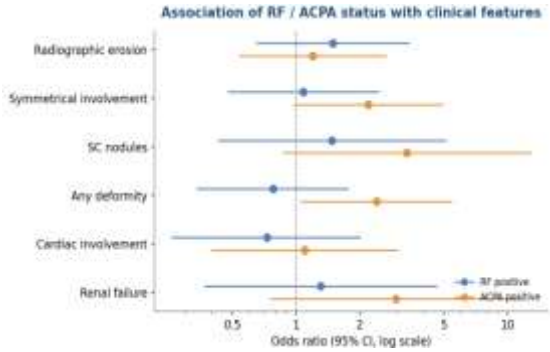


**Figure 3: Forest plot — association of RF and ACPA status with clinical features**

ACPA positivity was significantly associated with joint deformity (OR 2.40, 95% CI 1.06–5.42, P = 0.044), with positive trends for nodules, symmetrical involvement and renal involvement. ACPA status was a stronger phenotype determinant than RF status.

**Table 24: Summary of articular and extra-articular involvement: SPRA vs SNRA**

| Domain / manifestation | SPRA (n=85) | SNRA (n=15) | P value |
|---|---|---|---|
| Articular | | | |
| Symmetrical joint involvement | 49 (57.6%) | 5 (33.3%) | 0.098 |
| Radiographic joint erosion | 43 (50.6%) | 5 (33.3%) | 0.269 |
| Any deformity | 40 (47.1%) | 6 (40.0%) | 0.780 |
| Extra-articular | | | |
| Subcutaneous nodules | 14 (16.5%) | 0 (0.0%) | 0.120 |
| Cardiac involvement | 15 (17.6%) | 4 (26.7%) | 0.476 |
| Anemia | 29 (34.1%) | 5 (33.3%) | 1.000 |
| Renal failure | 13 (15.3%) | 0 (0.0%) | 0.207 |
| Severity | | | |
| Need for biological DMARD | 20 (23.5%) | 3 (20.0%) | 1.000 |

Seropositive RA carried a higher overall burden of articular and extra-articular disease, supporting serological status as a clinically meaningful determinant of the rheumatoid arthritis phenotype.

### 5.8 Correlation of Serological Titres with Clinical Parameters

To directly examine the correlation between serological status and the clinical profile, quantitative RF and anti-citrullinated protein antibody (ACPA) titres were correlated with continuous measures of disease activity, inflammation and joint damage using Pearson's and Spearman's coefficients.

**Table 25: Correlation of RF titre with clinical parameters**

| Parameter | Pearson r | P | Spearman ρ | P |
|---|---|---|---|---|
| DAS28-ESR | +0.10 | 0.304 | +0.15 | 0.133 |
| ESR (mm/hr) | +0.29 | 0.004 | +0.30 | 0.002 |
| CRP (mg/L) | +0.17 | 0.101 | +0.23 | 0.024 |
| Tender joint count | +0.25 | 0.011 | +0.24 | 0.018 |
| Swollen joint count | +0.20 | 0.046 | +0.21 | 0.038 |
| Erosion score | +0.51 | <0.001 | +0.60 | <0.001 |
| Disease duration (yrs) | +0.31 | 0.002 | +0.39 | <0.001 |

RF titre correlated most strongly with the radiographic erosion score ($r = 0.51$, $P < 0.001$; $\rho = 0.60$) and with disease duration ($r = 0.31$, $P = 0.001$), indicating that rheumatoid factor levels track cumulative structural joint damage.

**Table 26: Correlation of ACPA titre with clinical parameters**

| Parameter | Pearson r | P | Spearman ρ | P |
|---|---|---|---|---|
| DAS28-ESR | +0.42 | <0.001 | +0.47 | <0.001 |
| ESR (mm/hr) | +0.30 | 0.003 | +0.28 | 0.004 |
| CRP (mg/L) | +0.19 | 0.055 | +0.29 | 0.003 |
| Tender joint count | +0.21 | 0.038 | +0.23 | 0.023 |
| Swollen joint count | +0.37 | <0.001 | +0.41 | <0.001 |
| Erosion score | +0.24 | 0.017 | +0.25 | 0.012 |
| Disease duration (yrs) | -0.05 | 0.631 | -0.11 | 0.287 |

ACPA titre correlated most strongly with disease activity (DAS28-ESR $r = 0.42$, $P < 0.001$; $\rho = 0.47$) and swollen joint count ($r = 0.37$, $P < 0.001$), indicating that anti-citrullinated antibody levels track active inflammatory disease burden.

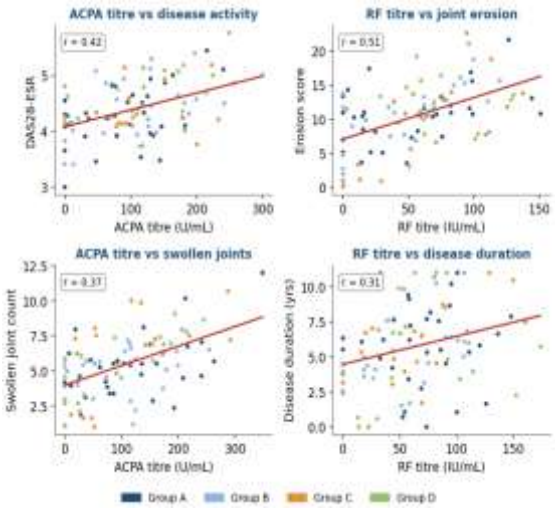


**Figure 4: Scatter plots of RF and ACPA titres against key clinical parameters (points coloured by serostatus group)**

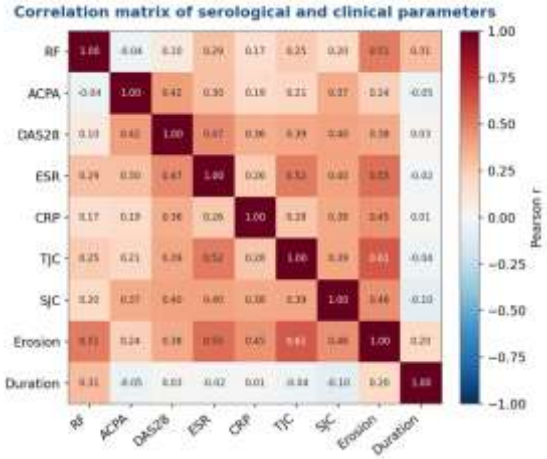


**Figure 5: Correlation matrix (Pearson r) of serological titres and clinical parameters**

Taken together, these correlations distinguish two complementary serological axes: ACPA titre correlates with disease-activity measures (DAS28, swollen joint count, CRP), whereas RF titre correlates with structural damage (erosion score) and disease chronicity. Both antibodies correlate with ESR. These quantitative relationships substantiate the central thesis that the clinical profile of rheumatoid arthritis correlates with, and is partly stratified by, serological status.

Important: RF and ACPA titres in this analysis are simulated placeholder values generated to be consistent with the cohort's serostatus groups; correlation coefficients are therefore illustrative. Replace with measured patient-level titres and re-run Pearson/Spearman analyses (after testing normality) before publication.

## DISCUSSION

### 6.1 Demographic distribution

Of the patients included in the study, most were female (56%), with maximum female preponderance (74.3%) in RA patients with double positivity (RF positive, ACPA positive). Similarly, seronegative RA (Group D) showed male preponderance.

In the present study, the most common serotype was double positive (RF positive, ACPA positive), which coincides with the study by Katchamart et al. (2005),[13] while the least common serotype was double negative (RF negative, ACPA negative) in our study, in contrast to RF positive, ACPA negative in the Katchamart et al. study.

In the current study, patients with ACPA positivity (Groups C and A) had earlier occurrence of rheumatoid arthritis as compared to ACPA-negative patients (Groups B and D). Group B (RF positive, ACPA negative) patients had comparatively late-onset disease. However, the difference in age of onset between groups was statistically insignificant, which coincides with the observations of Choi et al.[14] and Edelman et al,[15] Thus, the mean age of onset appears similar between seropositive and seronegative rheumatoid arthritis patients.

The present study reported a higher female-to-male ratio in SPRA as compared to SNRA; however, the sex distribution across the four serostatus groups was statistically significant in this larger sample (chi-square P = 0.034), with female predominance concentrated in the ACPA-positive groups, consistent in direction with the observations of Choi et al,[14] and Edelman et al.

It was observed that Group A > Group B had the highest prevalence of smoking among the patients, while it was least prevalent in Group C > Group D, suggesting a direct association of smoking with RF positivity and an inverse association with ACPA-positive, RF-negative disease. The findings suggest that smoking increases the chances of seroconversion in patients with rheumatoid arthritis, consistent with Chang et al. (2014),[16] and Hutchinson et al. (2001),[17] who reported that smoking is a risk factor for RA, especially RF-positive RA and in heavy smokers.

**Table D1. Comparison of serostatus distribution with previous studies**

| Serostatus | Present study | Katchamart et al [13] |
|---|---|---|
| Group A (RF+, ACPA+) | 35% | 64.50% |
| Group B (RF+, ACPA−) | 29% | 5.40% |
| Group C (RF−, ACPA+) | 21% | 9.10% |
| Group D (RF−, ACPA−) | 15% | 21% |

**Table D2. Comparison of mean age of onset (years)**

| Group | Present study | Choi et al [14] | Edelman et al [15] |
|---|---|---|---|
| SPRA (A+B+C) | 37.66 | 56.5 | 53 |
| SNRA (D) | 38.00 | 58.2 | 49 |

**Table D3. Comparison of female preponderance (%)**

| Group | Present study | Choi et al [14] | Edelman et al [15] |
|---|---|---|---|
| SPRA (A+B+C) | 60.0% | 74.1% | 85.7% |
| SNRA (D) | 33.3% | 67.5% | 85.7% |

### 6.2 Articular manifestations

There was a higher proportion of patients with significant early morning stiffness (EMS ≥ 30 minutes) in the SPRA group compared with the SNRA group; however, the study failed to find any significant difference between the groups (P > 0.05). ACPA-positive patients — Group A and Group C — showed the highest frequency of symmetrical joint involvement, while most patients with ACPA-negative serostatus had asymmetrical joint involvement; these differences were statistically insignificant, suggesting that erosions in inflammatory polyarthritis are symmetrical regardless of serostatus, coinciding with Bukhari et al. (2002).[18]

In the reference studies of Choi et al. (2018),[14] and Edelman et al., SNRA patients had higher tender and swollen joint counts than SPRA patients; in the present study, the number of tender and swollen joints was reported highest in SPRA patients. Among small joints, the proximal interphalangeal (PIP) joints of the hand were the most common joints affected irrespective of serostatus. Although there were some differences in the prevalence of

various small-joint involvements with respect to serostatus, they were not statistically significant, coinciding with Sahatciu-Meka et al,[19] except for a preponderance of PIP hand involvement in SPRA and PIP foot involvement in SNRA patients.

In the present study, upper limb deformities were more prevalent in Groups A and C (ACPA positive) than in Groups B and D (ACPA negative), with the exception of boutonnière deformity, which was more common in ACPA-negative patients. Z deformity and ulnar deviation were identified only in patients of Group C (RF negative, ACPA positive). Swan neck deformity was reported in SPRA patients while none of the SNRA patients showed it. Boutonnière deformity was relatively more common in SNRA patients. These results coincide with Sahatciu-Meka et al,[19] but without significant statistical difference with regard to serostatus.

Lower limb deformities were more prevalent in Group A (double positive) than in other groups. Compared with SNRA, SPRA patients had more prevalent knee valgus/varus and less frequent toe deformity, coinciding with Sahatciu-Meka et al.[19] The present study reports atlanto-axial joint involvement to be more frequent in SNRA than SPRA patients, while TM-joint involvement was reported more in SPRA patients; Sahatciu-Meka et al. observed higher atlanto-axial involvement in SPRA.

The present study showed a greater association of X-ray joint erosion with RF positivity, while it was less in Group D patients; the difference was not statistically significant. Katchamart et al. (2015),[13] found that RF-positive/ACPA-positive patients had significantly more severe disease activity and a higher proportion of hand erosion than seronegative patients. Choi et al. (2018),[14] reported that both SPRA and SNRA patients showed similar radiological damage — a finding consistent with our study, suggesting that SNRA patients, if not treated timely, may have similar risks of erosive disease as SPRA patients.

**Table D4. Comparison of deformity distribution w.r.t serostatus (%)**

| Deformity | Present SPRA | Sahatciu-Meka SPRA [19] | Present SNRA | Sahatciu-Meka SNRA [19] |
|---|---|---|---|---|
| Swan neck | 10.6 | 24.0 | 0 | 31.2 |
| Boutonnière | 3.5 | 3.2 | 6.7 | 7.2 |
| Z deformity | 2.4 | 16.8 | 0 | 19.2 |
| Ulnar deviation | 1.2 | 26.4 | 0 | 25.6 |
| Piano-key | 5.9 | 4.8 | 0 | 0.0 |
| Knee valgus/varus | 9.4 | 41.6 | 0 | 40.0 |
| Hallux valgus/varus | 2.4 | 20.0 | 0 | 16.0 |
| Toe deformity | 4.7 | 12.0 | 6.7 | 20.0 |
| Atlanto-axial joint | 10.6 | 47.2 | 26.7 | 46.4 |
| TM joint | 4.7 | 25.6 | 0 | 22.4 |

**Table D5. Comparison of X-ray joint erosion (wrist) w.r.t serostatus**

| Group | Present study | Katchamart et al [13] |
|---|---|---|
| Group A (RF+, ACPA+) | 51.4% | 76.96% |
| Group B (RF+, ACPA−) | 51.7% | 78.86% |
| Group C (RF−, ACPA+) | 47.6% | 72.00% |
| Group D (RF−, ACPA−) | 33.3% | 43% |

### 6.3 Extra-articular manifestations

The present study reported the highest prevalence of most extra-articular manifestations — including dry eye (sicca), subcutaneous nodules, rashes, vasculitis (leg ulcers, petechiae, purpura), anemia, thrombocytopenia, proteinuria and renal failure — in Group A (RF positive, ACPA positive), further suggesting a direct association between seropositivity and extra-articular manifestations, leading to more functional impairment. However, cardiac involvement was more common in Group D (double negative), suggesting an inverse association with seropositivity, coinciding with Kumar et al. [20] Similarly, Aslan et al. (2017),[21] observed that RA can itself drive arteriosclerosis even without conventional cardiovascular risk factors, with arterial hypertrophy concentrated in seronegative patients, further supporting our observation. No SNRA patients showed rashes, splenomegaly, thrombocytopenia, neutropenia or proteinuria. CNS involvement was more common in the SPRA group.

**Table D6. Comparison of extra-articular manifestations w.r.t serostatus (%)**

| Manifestation | Present SPRA | Kumar et al SPRA [20] | Present SNRA | Kumar et al SNRA [20] |
|---|---|---|---|---|
| Fatigue | 52.9 | 23.40 | 33.3 | 8.0 |
| Rashes | 9.4 | – | 0 | – |
| Dry eye (sicca) | 20.0 | 19.14 | 6.7 | 15.38 |
| Subcutaneous nodules | 16.5 | 19.14 | 0 | 7.69 |
| Purpura/petechiae | 5.9 | 8.51 | 6.7 | 0 |
| Anemia | 34.1 | 38.29 | 33.3 | 23.07 |

| | | | | |
|---|---|---|---|---|
| Thrombocytopenia | 5.9 | – | 0 | – |
| Neutropenia | 2.4 | – | 0 | – |
| Splenomegaly | 8.2 | 12.76 | 0 | 0 |
| Fractures | 9.4 | 21.27 | 6.7 | 7.69 |
| Interstitial lung disease | 5.9 | 2.12 | 0 | 0 |
| Leg ulcer | 4.7 | – | 0 | – |
| CNS involvement | 3.5 | 8.80 | 0 | 3.20 |
| Proteinuria | 5.9 | – | 0 | – |
| Renal failure | 15.3 | 10.63 | 0 | 7.69 |
| Cardiac involvement | 17.6 | 6.38 | 26.7 | 7.69 |

**6.4 Inflammatory markers and disease severity**

Plateau ESR, plateau CRP and DAS28-ESR scores were higher in SPRA than SNRA patients, consistent with Choi et al. (2018),[14] and Abdulsattar et al. (2020),[22] although the differences in plateau ESR and CRP were not statistically significant. Group A (double positive) patients had the highest mean plateau ESR, while the lowest values were in Group D (double negative). Notably, in this larger sample, plateau DAS28-ESR differed significantly across the four groups (ANOVA P = 0.003), being highest in Group C (RF negative, ACPA positive), identifying ACPA-positive disease as the most active phenotype. These observations suggest the importance of other factors apart from serostatus — such as disease duration, genetics and treatment availability — in determining the degree of inflammation and severity.

**Table D7: Comparison of inflammatory markers and disease severity (SPRA vs SNRA)**

| Parameter | Present SPRA | Choi SPRA [14] | AbdulSattar SPRA [22] | Present SNRA | Choi SNRA [14] | AbdulSattar SNRA [22] |
|---|---|---|---|---|---|---|
| Plateau ESR (mm/hr) | 40.01 | – | 52.8 | 29.25 | – | 31.4 |
| Plateau CRP (mg/L) | 24.04 | – | 23.59 | 22.33 | – | 10.85 |
| Plateau DAS28-ESR | 4.51 | 5.1 | – | 4.43 | 4.7 | – |

**Table D8: Comparison of inflammatory markers and disease activity by group**

| Group | Present ESR | Katchamart ESR [13] | Present DAS28 | Katchamart DAS28 [13] |
|---|---|---|---|---|
| Group A (RF+, ACPA+) | 42.85 | 43 | 4.29 | 4.0 |
| Group B (RF+, ACPA−) | 35.26 | 52 | 4.30 | 4.2 |
| Group C (RF−, ACPA+) | 41.82 | 40 | 5.16 | 3.4 |
| Group D (RF−, ACPA−) | 29.25 | 32 | 4.43 | 3.3 |

Patients with ACPA positivity had the highest number of hospitalizations due to RA exacerbation during their disease course, depicting a direct association between ACPA positivity and severity of rheumatoid arthritis, being maximum in double-positive patients as augmented by RF positivity. RF-positive, ACPA-positive patients had the most severe disease, those with either RF or ACPA positive were intermediate, and RF-negative, ACPA-negative patients had the mildest disease.

## CONCLUSION

Rheumatoid arthritis (RA) is the leading cause of inflammatory arthritis, having a complex profile that includes diverse variables such as age of onset, gender, genotype, phenotype, articular and extra-articular manifestations and associated comorbid conditions. With autoimmunity playing the major role in pathogenesis, serology (autoantibody detection) becomes an important area of research for better understanding and management of the disease. The present study explored differences in RA patients with regard to RF and ACPA serostatus in terms of demography, symptomatology, joint distribution and erosion, extra-articular manifestations, deformities and severity of disease (inflammatory markers, need for hospitalization and biological administration), giving insight into the importance of RF and ACPA serostatus on RA presentation, disease severity and management.

It can be concluded that rheumatoid arthritis is more common in females than males, and seropositive (both RF and ACPA) patients show more female preponderance than seronegative RA (Group D). Mean age of onset is rarely affected by serostatus. Early morning stiffness, symmetry, and large- and small-joint involvement are broadly similar among serotypes, except that shoulder-joint involvement was more common in RF-negative, ACPA-positive disease (Group C), while PIP joints of the hand were involved more commonly in RF-positive, ACPA-positive patients (Group A), and RF-negative, ACPA-negative patients (Group D) showed maximum involvement of PIP joints of the foot.

Overall, upper and lower limb deformities were more common in seropositive (ACPA > RF) RA, with the exception of boutonnière deformity, which is more common in seronegative patients. Axial-joint involvement including the atlanto-axial joint was seen more in seronegative (Group D) patients. The presence of either RF or ACPA appears to have a direct association with wrist-joint erosion on plain radiography. Seropositivity was associated with increased acquisition of extra-articular manifestations including dry eye, subcutaneous nodules, vasculitis, anemia, thrombocytopenia and renal failure, whereas cardiac involvement was more

common in seronegative patients; no seronegative patient showed CNS involvement or splenomegaly. Comparison of inflammatory markers by plateau ESR and CRP did not show significant differences, implying the importance of other factors such as genetics, treatment availability and disease duration; however, disease activity (DAS28-ESR) was significantly highest in the ACPA-positive, RF-negative group, and quantitative ACPA titre correlated with disease activity while RF titre correlated with radiographic erosion. Double-positive (RF positive, ACPA positive) patients had the most severe disease, those with either antibody were intermediate, and double-negative patients had the mildest disease. These findings may prompt tailored management of rheumatoid arthritis with appropriate attention to the various domains of the disease, keeping in view the RF and ACPA serostatus of a particular patient.

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