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Clinical, Laboratory, and Treatment Characteristics of Seropositive and Seronegative Rheumatoid Arthritis: A Real-World Cohort Study

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Abstract: Seropositive and seronegative rheumatoid arthritis (RA) are increasingly recognized as clinically and biologically distinct disease subsets, yet comparative real-world data remain limited. We aimed to compare the sociodemographic, clinical, laboratory, and treatment characteristics of patients with seropositive and seronegative RA. This retrospective, single-center study included 559 patients with RA followed between September 2023 and May 2025. Seropositivity was defined as rheumatoid factor and/or anti-cyclic citrullinated peptide antibody (anti-CCP) positivity. Sociodemographic, clinical, laboratory, and treatment characteristics were compared between seropositive and seronegative patients. Of 559 patients, 446 (79.8%) were seropositive and 113 (20.2%) were seronegative. Disease duration was significantly longer in seropositive patients ($p<0.001$). At baseline (first evaluation at the study center), arthritis was more frequent in seronegative patients ($p=0.019$), whereas white blood cell count (WBC) and neutrophil counts were higher in seropositive patients ($p=0.001$ and $p=0.006$, respectively). Baseline C-reactive protein (CRP) levels did not differ between groups ($p=0.261$), whereas CRP levels at the last follow-up were higher in seropositive patients ($p=0.035$). CRP levels were significantly lower at the last follow-up than at baseline in both groups ($p<0.001$ for both). Biologic or targeted synthetic disease-modifying antirheumatic drug (bDMARD/tsDMARD) use at the last follow-up was more frequent among seropositive patients ($p=0.023$). Seropositive and seronegative RA differed in several clinical, laboratory, and treatment characteristics. The higher frequency of baseline arthritis among seronegative patients is consistent with recent evidence challenging the traditional view of seronegative RA as a uniformly milder form of the disease and highlights the clinical heterogeneity of RA according to serological status. ©2026 NTMS.

Keywords: Rheumatoid Arthritis; Seropositive Rheumatoid Arthritis; Seronegative Rheumatoid Arthritis; Rheumatoid Factor; Anti-CCP.

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease characterized by predominant synovial joint involvement and substantial heterogeneity in its clinical presentation and disease course [1,2]. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (anti-CCP) are the two autoantibodies most closely linked to RA, and their presence or absence is used to divide patients

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into seropositive and seronegative subgroups, a distinction incorporated into the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification framework [3,4]. Although seropositive RA has traditionally been regarded as the more aggressive disease subset, particularly because of its association with greater radiographic damage, more recent evidence has challenged the assumption that seronegative RA represents a uniformly milder form of the disease [4,5].

Beyond their prognostic associations, seropositive and seronegative RA also appear to differ biologically. Autoantibody-negative RA has been associated with a distinct synovial and serum B-cell immunophenotype, characterized by lower synovial B-lymphocyte infiltration and a different serum CXCL13 profile compared with autoantibody-positive RA, more closely resembling that observed in polyarticular psoriatic arthritis [6]. Clinical and ultrasonographic studies have likewise demonstrated phenotypic differences between the two subsets, with higher leukocyte and neutrophil counts and more frequent ultrasonographic joint abnormalities reported in seropositive RA [7]. Taken together, these findings support the view that seropositive and seronegative RA may represent partially distinct clinical and biological disease subsets [8].

Despite this growing body of evidence, important uncertainties persist. Reports on baseline disease activity by serological status are conflicting: some studies have found greater baseline inflammatory activity and joint involvement in seronegative patients [4,5], while earlier literature has described seropositivity as a marker of higher disease activity and worse radiographic outcomes [3]. Long-term outcome data are similarly mixed, with a large longitudinal cohort showing that improvements in long-term outcomes following the introduction of enhanced treatment strategies, including treat-to-target approaches, differed between autoantibody-positive and autoantibody-negative RA [9]. Moreover, available comparative studies have frequently focused on selected populations, including early RA cohorts and patients receiving or initiating biologic disease-modifying antirheumatic drugs (bDMARDs) [4,5,10]. Comparative real-world data encompassing patients with heterogeneous disease durations and evaluating routine laboratory and treatment characteristics remain limited.

Clarifying how seropositive and seronegative RA differ in everyday clinical practice is important for improving our understanding of their clinical heterogeneity and for interpreting laboratory and treatment characteristics across these disease subsets. Therefore, the aim of this study was to compare the sociodemographic, clinical, laboratory, and treatment characteristics of patients with seropositive and seronegative RA followed at a single rheumatology outpatient clinic, using real-world, retrospectively collected data spanning a wide range of disease durations.

2. Material and Methods

Ethical approval for this retrospective, single-center study was obtained from the Kafkas University Faculty of Medicine Non-Interventional Ethics Committee on May 28, 2025 (KAU-TFEK 2025/05/13), and the study was conducted in accordance with the principles of the Declaration of Helsinki. The electronic medical records of 559 patients with RA followed at the Rheumatology Outpatient Clinic of Kars Harakani State Hospital between September 2023 and May 2025 were retrospectively reviewed. Inclusion criteria were a diagnosis of RA, ongoing follow-up in the rheumatology clinic, and age older than 18 years. Baseline was defined as the patient's first evaluation at our rheumatology outpatient clinic; it does not correspond to disease onset or to the time of RA diagnosis.

2.1. Screening data

The following data were recorded for each patient: (1) sociodemographic characteristics, including sex, age, age at arthritis onset (defined as the age at which arthritis manifestations first occurred, which may precede the formal diagnosis of RA), disease duration, follow-up duration, history of livestock farming, smoking status, family history of rheumatic disease, comorbidities (diabetes mellitus, hypertension, asthma, chronic obstructive pulmonary disease, hyperlipidemia, hypothyroidism, hyperthyroidism, cardiac events, cerebrovascular events, and chronic kidney disease), and osteoporosis; (2) articular and extra-articular disease-related findings, including joint deformity, lung involvement, secondary sicca manifestations (dry mouth, dry eyes), and pulmonary hypertension; (3) baseline evaluation status (previously diagnosed but not under regular follow-up, under regular follow-up, or newly diagnosed with RA at our center); (4) disease-related autoantibodies, including RF, anti-CCP, antinuclear antibody (ANA), and anti-Sjögren's syndrome-related antigen A antibody (anti-SS-A). Positivity for RF and/or anti-CCP was defined as seropositivity; negativity for both RF and anti-CCP was defined as seronegativity. All patients classified as seronegative had negative results for both RF and anti-CCP, whereas all 29 patients with unavailable anti-CCP results were RF-positive and were therefore classified as seropositive. RF or anti-CCP levels ≥3 times the upper limit of normal were defined as high seropositivity; (5) disease-related symptoms and findings assessed at baseline and last follow-up (arthritis, arthralgia, psoriatic rash, dyspnea, B symptoms, dry mouth, and dry eyes); (6) laboratory parameters assessed at baseline and last follow-up, including white blood cell count (WBC), neutrophil count (NEUT), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and ferritin (elevated CRP was defined as >5 mg/L, and elevated ESR as >(age +

10)/2 mm/h for women and >20 mm/h for men); (7) corticosteroid (CS) and conventional synthetic disease-modifying antirheumatic drug (csDMARD) use at and before the last follow-up (methotrexate [MTX], leflunomide [LEF], sulfasalazine [SSZ], and hydroxychloroquine [HCQ]); (8) biologic disease-modifying antirheumatic drug (bDMARD) and targeted synthetic disease-modifying antirheumatic drug (tsDMARD) use at and before the last follow-up (bDMARDs: adalimumab [ADA], etanercept [ETN], golimumab [GOL], certolizumab pegol [CZP], infliximab [IFX], tocilizumab [TCZ], rituximab [RTX], and abatacept [ABA]; tsDMARDs: upadacitinib [UPA], tofacitinib [TOFA], and baricitinib [BARI]); (9) duration of use of the most recently used biologic or targeted synthetic agent; and (10) whether treatment was modified during follow-up and, if so, the type of modification (addition of a csDMARD, addition of a bDMARD, or both). For analyses of the aggregate advanced-therapy category, bDMARDs and tsDMARDs were combined and are referred to as bDMARD/tsDMARD use.

2.2. Statistical analysis

Data were analyzed using R software, version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria). The normality of distribution of quantitative variables was assessed using the Kolmogorov–Smirnov test. Quantitative variables are presented as mean ± standard deviation and median (minimum–maximum), and categorical variables as frequency and percentage. Depending on the distribution of quantitative variables, the independent-samples t test or Mann–Whitney U test was used for comparisons between groups. Categorical variables were compared using the chi-square test or Fisher exact test, as appropriate. A two-sided p value <0.05 was considered statistically significant.

3. Results

A total of 559 patients with RA were included in the study; their general, sociodemographic, laboratory, clinical, follow-up, and treatment characteristics are summarized in Table 1. Of the patients, 80.3% were female and 19.7% were male. Median age was 57 (19–96) years, and median age at arthritis onset was 50 (2–86) years. Median disease duration was 48 (0–600) months, and median follow-up duration was 6 (0–22) months. A history of livestock farming was present in 171 patients (30.6%), smoking in 101 (18.1%), and a family history of rheumatic disease in 79 (14.1%). Comorbidities were present in 173 patients (31.0%), and 78 patients (14.0%) had osteoporosis. Joint deformity attributable to RA was present in 93 patients (16.6%). No statistically significant differences were observed between the seropositive and seronegative groups in age at arthritis onset, sex, history of livestock farming, smoking, family history of rheumatic disease, comorbidities, osteoporosis, or joint deformity (p>0.05 for all). Disease duration was significantly longer in the seropositive group than in the seronegative group (p<0.001; Table 3).

Regarding baseline evaluation status, 62.1% of patients had been previously diagnosed with RA and were under regular follow-up at another center, 6.4% had been previously diagnosed but were not under regular follow-up, and 31.5% were newly diagnosed at our center. At baseline, arthritis was present in 131 patients (23.4%), arthralgia in 396 (70.8%), psoriatic rash in 2 (0.4%), dyspnea in 2 (0.4%), B symptoms in 13 (2.3%), dry mouth in 38 (6.8%), and dry eyes in 24 (4.3%). Lung involvement was present in 4 patients (0.7%), secondary sicca manifestations in 42 (7.5%), and pulmonary hypertension in 1 (0.2%). No statistically significant differences were observed between the seropositive and seronegative groups in arthralgia, B symptoms, dry mouth, or dry eyes at baseline (p>0.05 for all). The presence of arthritis at baseline was significantly higher in the seronegative group than in the seropositive group (p=0.019; Table 3). No statistically significant differences were observed between the groups in lung involvement, secondary sicca manifestations, or pulmonary hypertension (p>0.05 for all).

Of the 559 patients, 446 (79.8%) were seropositive and 113 (20.2%) were seronegative. RF was positive in 406 patients (72.6%), and anti-CCP was positive in 311 (55.6%). Median RF level was 74 (7–1140), and median anti-CCP level was 200 (5–2000). High-positive RF was observed in 268 patients (66.2%), and high-positive anti-CCP in 243 (79.9%). ANA positivity was detected in 48 patients (8.6%) and anti-SS-A positivity in 11 (2.0%).

At baseline, elevated ESR was present in 191 patients (34.3%) and elevated CRP in 342 (61.4%), with no statistically significant differences between the seropositive and seronegative groups in the presence of elevated ESR or CRP (p>0.05 for both). WBC, NEUT, ESR, CRP, and ferritin levels at baseline and last follow-up are presented in Table 2. No statistically significant differences were observed between the seropositive and seronegative groups in baseline ESR, CRP, or ferritin levels, or in last-follow-up NEUT, ESR, or ferritin levels (p>0.05 for all). Baseline WBC and NEUT levels were significantly higher in the seropositive group than in the seronegative group (p=0.001 and p=0.006, respectively). At the last follow-up, WBC and CRP levels were also significantly higher in the seropositive group (p=0.019 and p=0.035, respectively). Within each group, no statistically significant differences were observed between baseline and last-follow-up WBC, NEUT, ESR, or ferritin levels (p>0.05 for all); in contrast, CRP levels decreased significantly from baseline to the last follow-up in both the seropositive and seronegative groups (p<0.001 for both). Vitamin D deficiency was detected in 85.3% of patients at baseline.

At the last follow-up, arthritis was present in 20 patients (4.3%), arthralgia in 54 (11.6%), psoriatic

rash in 2 (0.4%), dry mouth in 1 (0.2%), and dry eyes in 2 (0.4%); no patients had dyspnea or B symptoms.

Over the course of follow-up, 531 patients (94.9%) had received CS, 475 (84.9%) HCQ, 319 (57.1%) LEF, 407 (72.8%) MTX, and 158 (28.2%) SSZ. Among biologic/targeted therapies, ADA was the most frequently used agent (64 patients, 11.4%), followed by ETN (20, 3.6%), TOFA (19, 3.4%), GOL (12, 2.1%), TCZ (11, 2.0%), CZP (11, 2.0%), UPA (8, 1.4%), RTX (6, 1.1%), BARI (4, 0.7%), and ABA (3, 0.5%).

At the last follow-up, 441 patients (78.9%) were receiving CS, 373 (66.7%) HCQ, 301 (53.8%) LEF, 259 (46.3%) MTX, and 80 (14.3%) SSZ. Among biologic/targeted therapies, ADA remained the most frequently used agent (63 patients, 11.3%), followed by ETN (11, 2.0%), TOFA (11, 2.0%), GOL (10, 1.8%), TCZ (8, 1.4%), UPA (7, 1.3%), RTX (5, 0.9%), CZP (4, 0.7%), ABA (3, 0.5%), and BARI (2, 0.4%).

Treatment was modified during follow-up in 254 patients (45.4%); among these, a csDMARD was added in 178 (70.1%), a bDMARD in 50 (19.7%), and both a csDMARD and a bDMARD in 26 (10.2%). At the last follow-up, among patients receiving a bDMARD/tsDMARD, 16 (12.9%) were seronegative and 108 (87.1%) were seropositive, a statistically significant difference between the seropositive and seronegative groups (p=0.023; Table 3).

Table 1: General, sociodemographic, laboratory, clinical, follow-up, and treatment characteristics of the patients with rheumatoid arthritis.

	Mean ± SD	Median (min–max)
Age	56.74 ± 13.12	57 (19-96)
Age at arthritis onset	49.65 ± 14.04	50 (2-86)
Disease duration (months)	87.11 ± 89.43	48 (0-600)
Follow-up duration (months)	6.9 ± 5.73	6 (0-22)
RF titer	105.49 ± 116.2	74 (7-1140)
Anti-CCP titer	295.35 ± 303.44	200 (5-2000)
	n	%
SOCIODEMOGRAPHIC CHARACTERISTICS		
Sex		
Female	449	80.3
Male	110	19.7
Livestock farming		
No	388	69.4
Yes	171	30.6
Smoking		
No	458	81.9
Yes	101	18.1
Family history		
No	480	85.9
Yes	79	14.1
Joint deformity		
No	466	83.4
Yes	93	16.6
Comorbidity		
No	386	69.1
Yes	173	31.0
Osteoporosis		
No	481	86.1
Yes	78	14.0
LABORATORY FINDINGS		
RF status		
Negative	153	27.4
Positive	406	72.6
Anti-CCP status		
Negative	219	39.2
Positive	311	55.6
Unknown	29	5.2
High-positive RF		
No	137	33.8
Yes	268	66.2
High-positive anti-CCP		

No	61	20.1
Yes	243	79.9
Serological status		
Seronegative	113	20.2
Seropositive	446	79.8
ANA status		
Negative	301	53.8
Positive	48	8.6
Unknown	210	37.6
Anti-SS-A status		
Negative	271	48.5
Positive	11	2.0
Unknown	277	49.6
EXTRA-ARTICULAR MANIFESTATIONS		
Lung involvement		
No	555	99.3
Yes	4	0.7
Secondary sicca syndrome		
No	517	92.5
Yes	42	7.5
Pulmonary hypertension		
No	558	99.8
Yes	1	0.2
BASELINE CHARACTERISTICS		
Patient status at baseline		
Previously diagnosed, not under follow-up	36	6.4
Under regular follow-up	347	62.1
Newly diagnosed	176	31.5
Arthritis		
No	428	76.6
Yes	131	23.4
Arthralgia		
No	163	29.2
Yes	396	70.8
Psoriasis		
No	557	99.6
Yes	2	0.4
Dyspnea		
No	557	99.6
Yes	2	0.4
B symptoms		
No	546	97.7
Yes	13	2.3
Dry mouth		
No	521	93.2
Yes	38	6.8
Dry eyes		
No	535	95.7
Yes	24	4.3
Elevated ESR		
No	366	65.7
Yes	191	34.3
Elevated CRP		
No	215	38.6
Yes	342	61.4
Vitamin D deficiency		
Normal	82	14.7
Deficient	476	85.3

LAST FOLLOW-UP CHARACTERISTICS		
Arthritis		
No	445	95.7
Yes	20	4.3
Arthralgia		
No	411	88.4
Yes	54	11.6
Psoriasis		
No	463	99.6
Yes	2	0.4
Dry mouth		
No	464	99.8
Yes	1	0.2
Dry eyes		
No	463	99.6
Yes	2	0.4
TREATMENT CHARACTERISTICS		
Treatment modification during follow-up		
No	305	54.6
Yes	254	45.4
Type of treatment modification		
Addition of a csDMARD	178	70.1
Addition of a bDMARD	50	19.7
Both	26	10.2

ANA, antinuclear antibody; anti-CCP, anti-cyclic citrullinated peptide antibody; anti-SS-A, anti-Sjögren's syndrome-related antigen A antibody; bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; SD, standard deviation. Baseline refers to the patient's first evaluation at the study center.

Table 2: Comparison of laboratory characteristics at baseline and last follow-up between seronegative and seropositive patients with rheumatoid arthritis.

Variable	Seronegative (n=113)	Seropositive (n=446)	Total (n=559)	Between-group p value
WBC (×10⁹/L)				
Baseline	6.8 (3-13)	7.5 (3.3-29)	7.3 (3-29)	**0.001**
Last follow-up	6.65 (3.7-12.6)	7.3 (3-16)	7.1 (3-16)	**0.019**
Within-group p value (baseline vs last follow-up)	0.064	0.151	0.290	
NEUT (×10⁹/L)				
Baseline	4.3 (1.35-10.2)	4.7 (0.4-26)	4.6 (0.4-26)	**0.006**
Last follow-up	4.14 (1.6-12)	4.6 (0.28-15)	4.5 (0.28-15)	0.163
Within-group p value (baseline vs last follow-up)	0.410	0.113	0.298	
ESR (mm/h)				
Baseline	14.5 (1-62)	16 (1-109)	16 (1-109)	0.053
Last follow-up	14 (1-69)	17 (1-79)	16 (1-79)	0.083
Within-group p value (baseline vs last follow-up)	0.355	0.869	0.824	
CRP (mg/L)				
Baseline	6 (1-123)	6.2 (1-221)	6 (1-221)	0.261
Last follow-up	2.4 (0.14-61)	3.65 (0.03-76)	3.1 (0.03-76)	**0.035**
Within-group p value (baseline vs last follow-up)	**<0.001**	**<0.001**	**<0.001**	
Ferritin (ng/mL)				

Baseline	66 (5.6-863)	63 (2-1274)	63.05 (2-1274)	0.613
Last follow-up	83 (4.4-892)	63 (2-1245)	67 (2-1245)	0.479
Within-group p value (baseline vs last follow-up)	0.716	0.146	0.150	

Data are presented as median (min–max). Between-group p values compare seronegative and seropositive patients; within-group p values compare baseline and last-follow-up values within each group. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NEUT, neutrophil count; WBC, white blood cell count. Baseline refers to the patient's first evaluation at the study center.

Table 3: Comparison of characteristics between seronegative and seropositive patients with rheumatoid arthritis.

Variable	Seronegative (n=113)	Seropositive (n=446)	Total (n=559)	p
GENERAL CHARACTERISTICS				
Age at arthritis onset	49.5 ± 14	49.69 ± 14.07	49.65 ± 14.04	0.895
Disease duration (months)	51.03 ± 64.54	96.25 ± 92.55	87.11 ± 89.43	**<0.001**
SOCIODEMOGRAPHIC CHARACTERISTICS				
Sex				
Female	95 (21.4)	354 (78.8)	449 (80.3)	
Male	18 (16.4)	92 (83.6)	110 (19.7)	0.263
Livestock farming				
No	82 (21.1)	306 (78.9)	388 (69.4)	
Yes	31 (18.1)	140 (81.9)	171 (30.6)	0.415
Smoking				
No	93 (20.3)	365 (79.7)	458 (81.9)	
Yes	20 (19.8)	81 (80.2)	101 (18.1)	0.909
Family history				
No	94 (19.6)	386 (80.4)	480 (85.9)	
Yes	19 (24.1)	60 (75.9)	79 (14.1)	0.361
Joint deformity				
No	101 (21.7)	365 (78.3)	466 (83.4)	
Yes	12 (12.9)	81 (87.1)	93 (16.6)	0.058
Comorbidity				
No	83 (73.5)	303 (67.9)	386 (69.1)	
Yes	30 (26.6)	143 (32.1)	173 (31.0)	0.258
Osteoporosis				
No	101 (21.0)	380 (79.0)	481 (86.1)	
Yes	12 (15.4)	66 (84.6)	78 (14.0)	0.254
EXTRA-ARTICULAR MANIFESTATIONS				
Lung involvement				
No	112 (20.2)	443 (79.8)	555 (99.3)	
Yes	1 (25.0)	3 (75.0)	4 (0.7)	0.812
Secondary sicca syndrome				
No	107 (20.7)	410 (79.3)	517 (92.5)	
Yes	6 (14.3)	36 (85.7)	42 (7.5)	0.323
Pulmonary hypertension				
No	113 (20.3)	445 (79.7)	558 (99.8)	
Yes	0 (0.0)	1 (100.0)	1 (0.2)	—
BASELINE CHARACTERISTICS				
Arthritis				
No	77 (18.0)	351 (82.0)	428 (76.6)	
Yes	36 (27.5)	95 (72.5)	131 (23.4)	**0.019**
Arthralgia				
No	27 (16.6)	136 (83.4)	163 (29.2)	
Yes	86 (21.7)	310 (78.3)	396 (70.8)	0.169
Psoriasis				
No	113 (20.3)	444 (79.7)	557 (99.6)	
Yes	0 (0.0)	2 (100.0)	2 (0.4)	—

Dyspnea				
No	113 (20.3)	444 (79.7)	557 (99.6)	
Yes	0 (0.0)	2 (100.0)	2 (0.4)	—
B symptoms				
No	110 (20.1)	436 (79.9)	546 (97.7)	
Yes	3 (23.1)	10 (76.9)	13 (2.3)	0.795
Dry mouth				
No	101 (17.4)	420 (80.6)	521 (93.2)	
Yes	12 (31.6)	26 (68.4)	38 (6.8)	0.075
Dry eyes				
No	106 (19.8)	429 (80.2)	535 (95.7)	
Yes	7 (29.2)	17 (70.8)	24 (4.3)	0.269
Elevated ESR				
No	73 (19.9)	293 (80.1)	366 (65.7)	
Yes	39 (20.4)	152 (79.6)	191 (34.3)	0.895
Elevated CRP				
No	46 (21.4)	169 (78.6)	215 (38.6)	
Yes	66 (19.3)	276 (80.7)	342 (61.4)	0.548
LAST FOLLOW-UP CHARACTERISTICS				
bDMARD/tsDMARD use				
No	97 (22.3)	338 (77.7)	435 (77.8)	
Yes	16 (12.9)	108 (87.1)	124 (22.2)	**0.023**

Data are presented as mean ± standard deviation or n (%). bDMARD, biologic disease-modifying antirheumatic drug; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; tsDMARD, targeted synthetic disease-modifying antirheumatic drug. Baseline refers to the patient's first evaluation at the study center.

4. Discussion

In this real-world, single-center cohort of 559 patients with RA, we compared the sociodemographic, laboratory, clinical, follow-up, and treatment characteristics of patients with seropositive and seronegative disease. Seropositive patients had a longer disease duration, higher baseline WBC and neutrophil counts, higher CRP levels at the last follow-up, and more frequent bDMARD/tsDMARD use than seronegative patients, whereas arthritis at baseline was more frequent among seronegative patients. CRP levels were significantly lower at the last follow-up than at baseline in both groups.

Disease duration was significantly longer in the seropositive group than in the seronegative group. Data directly comparing disease duration according to serological status are limited. Carbonell-Bobadilla et al. found no significant difference in disease duration between seropositive and seronegative patients (3.7 ± 5.0 vs. 3.1 ± 3.6 years, $p = 0.550$) [7]. Mo et al., however, reported a longer interval from symptom onset to diagnosis in seronegative patients with newly diagnosed RA (12.0 vs. 7.0 months, $p < 0.001$) [11]. However, this measure differs from disease duration as defined in our study, which represents the time elapsed since diagnosis. Therefore, differences in patient populations, as well as differences in the definition and timing of disease-duration measures, should be considered when interpreting findings across studies. Our finding indicates that seropositive patients in our cohort had been living with an RA diagnosis for a longer period; however, given the retrospective nature of our study, this difference cannot be interpreted as evidence of a distinct disease course associated with serological status.

Seronegative RA has historically been considered a milder disease subset than seropositive RA, particularly with regard to radiographic damage [4]. However, more recent studies have challenged this view. At baseline, arthritis was significantly more frequent in seronegative than in seropositive patients in our cohort. It should be noted that baseline in our study corresponded to the patient's first evaluation at our center rather than to disease onset or RA diagnosis; therefore, arthritis recorded at baseline reflects active arthritis at the first center visit rather than the clinical presentation at disease onset. This finding is consistent with previous studies reporting greater joint involvement at presentation in seronegative RA. In a cohort of DMARD-naïve patients, Choi and Lee found significantly higher baseline tender and swollen joint counts, as well as higher 28-joint Disease Activity Score (DAS28) scores, in seronegative than in seropositive patients [5]. Similarly, in the ARCTIC cohort, Nordberg et al. reported higher swollen joint counts and disease activity at baseline in seronegative patients fulfilling the 2010 ACR/EULAR classification criteria [4]. Mo et al. also reported higher disease activity measures in newly diagnosed seronegative patients [11]. Although these studies assessed joint counts and composite disease activity measures rather than the presence of arthritis as evaluated in our study, their findings are consistent with our observation of more frequent baseline arthritis in seronegative patients. Taken together, our findings and recent evidence suggest that seronegative RA may present with substantial joint involvement

and should not be assumed to represent a uniformly milder clinical phenotype.

Baseline WBC and NEUT levels were significantly higher in the seropositive group than in the seronegative group. This finding is consistent with the results of Carbonell-Bobadilla et al., who reported significantly higher WBC (6.9 ± 2.0 vs. 5.8 ± 1.5 $\times 10^3/mm^3$, p = 0.009) and neutrophil counts (4.4 ± 1.8 vs. 3.5 ± 1.2 $\times 10^3/mm^3$, p = 0.011) in seropositive than in seronegative patients, while clinical disease activity measures did not differ significantly between the groups [7]. The similarity between our findings and those of Carbonell-Bobadilla et al. suggests that peripheral leukocyte and neutrophil profiles may differ according to serological status. However, WBC and NEUT levels may also be influenced by factors other than disease activity. Therefore, the observed differences should not be interpreted as indicating higher disease activity or greater disease severity in seropositive patients.

Baseline CRP levels did not differ significantly between the seropositive and seronegative groups, whereas CRP levels at the last follow-up were significantly higher in seropositive patients. Nevertheless, CRP levels at the last follow-up were significantly lower than baseline levels in both groups. Similar to our baseline finding, Carbonell-Bobadilla et al. found no significant difference in high-sensitivity CRP levels between seropositive and seronegative patients (11.4 ± 15.1 vs. 6.7 ± 9.1 mg/L, p = 0.118) [7]. In contrast, Mo et al. reported significantly higher levels of inflammatory biomarkers, including CRP, ESR, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), in newly diagnosed seronegative patients than in seropositive patients [11]. These differences across studies suggest that the relationship between serological status and inflammatory markers may not be uniform and may vary according to the patient population and stage of disease. In our cohort, the absence of a difference in CRP between the serological groups at baseline, followed by higher CRP levels in seropositive patients at the last follow-up, further supports this variability.

bDMARD/tsDMARD use at the last follow-up was significantly more frequent among seropositive than seronegative patients. Data directly comparing the frequency of bDMARD/tsDMARD use according to serological status in real-world RA populations are limited. Available studies have predominantly focused on treatment response and effectiveness after the initiation of bDMARD or targeted synthetic DMARD therapy and have reported varying results according to serological status [3,4,12]. Because these studies address a different clinical question from the frequency of treatment use, their findings are not directly comparable with ours. Our findings indicate that patterns of bDMARD/tsDMARD use may differ between serological groups in real-world clinical practice; however, the retrospective design of our study does not allow us to determine the underlying reasons for this difference. Treatment selection in routine practice is likely influenced by several factors beyond serological status, including disease duration, previous treatment history, disease activity, comorbidities, and physician preference. Therefore, the observed difference in bDMARD/tsDMARD use should not be attributed solely to serological status.

5. Conclusion

In this real-world, single-center cohort, seropositive and seronegative patients with RA differed in several clinical, laboratory, and treatment characteristics, including disease duration, baseline arthritis frequency, baseline WBC and neutrophil counts, CRP levels at the last follow-up, and bDMARD/tsDMARD use. In particular, the higher frequency of baseline arthritis among seronegative patients is consistent with recent evidence challenging the traditional view of seronegative RA as a milder form of the disease. Taken together, our findings do not support assuming a uniformly milder clinical presentation of seronegative RA and highlight the clinical heterogeneity of RA according to serological status.

Limitations of the Study

The retrospective, single-center design carries a risk of bias related to incomplete or inaccurate documentation in medical records and limits the generalizability of our findings to other populations and healthcare settings. The relatively short and variable follow-up duration (median 6 months, range 0–22 months) may have limited the assessment of changes during follow-up and longer-term clinical outcomes. In addition, validated composite disease activity indices such as DAS28, the Clinical Disease Activity Index (CDAI), or the Simplified Disease Activity Index (SDAI) were not available in our dataset. Furthermore, radiographic progression was not assessed. Therefore, we were unable to determine whether the clinical and laboratory differences between the serological groups reflected differences in overall disease activity. Future prospective studies incorporating validated disease activity measures may provide a more comprehensive understanding of the clinical differences between seropositive and seronegative RA.

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Conflict of Interests

The authors declare no conflicts of interest.

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Author Contributions

Concept – N.L.; Design – N.L., E.G.; Supervision – N.L.; Resources – N.L., E.G.; Materials – N.L., E.G.; Data Collection and/or Processing – N.L., E.G.; Analysis and/or Interpretation – N.L., E.G.; Literature

Review – N.L., E.G.; Writing – N.L.; Critical Review – N.L.

Ethical Approval

This study was approved by the Kafkas University Faculty of Medicine Non-Interventional Ethics Committee (Approval No: KAU-TFEK 2025/05/13, Date: 28 May 2025).

Data Sharing Statement

Anonymized data are available from the corresponding author upon reasonable request.

Consent to participate

Consent to participate was not required because of the retrospective design of the study.

Informed Statement

No informed statement is required for this study.

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